was extracted (CH_2Cl_2, 3 × 60 ml) and the extract was concentrated. The residue was partitioned between 2 *N* HCl and ether. The 2 *N* HCl fraction was basified (20% KOH) and reextracted (ether). Removal of the ether gave an oil (3.34 g, 52%), which was essentially **14** (R = CH_3) from nmr spectroscopy. This was characterized as the biscyclamate: mp 126–128°; ν_{max} 3240 (m), 1584 (m), 1290 (s), 1270 (s) 1208 (s), 1170 (s), 1030 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr (free base) δ 7.10 (q, 4), 3.64 (s, 2), 2.24 (s, 3), 2.04 (s, 3).

Anal. Calcd for $C_{14}H_{22}N_2 \cdot 2C_6H_{13}NO_3S$: C, 54.15; H, 8.39; N, 9.72. Found: C, 53.89; H, 8.66; N, 9.60.

Attempted Catalytic Reduction of 6 (R = H) to 5.—Compound **6** (R = H) (2.07 g, 0.011 mol) was hydrogenated (room temperature and pressure) in ethanol over PtO_2 (100 mg). Hydrogen was consumed (410 ml), the reaction mixture was filtered through Celite, and the ethanol was removed. The residue was an oil (0.02 g), identical (nmr, ir) with 2-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**) prepared by $NaBH_4$ reduction of **1** (*n* = 2). The dihydrochloride melting point (263–265°) was identical with that of material above.

Attempted Reduction of 6 (R = H) to 5.—Compound **6** (R = H) (3.74 g, 0.02 mol) was dissolved in dry THF (30 ml) and added to a well-stirred slurry of $LiAlH_4$ (1.9 g) in THF (100 ml) under nitrogen. The mixture was refluxed overnight. The excess reagent was decomposed with saturated sodium potassium tartrate and the mixture was filtered through Celite. The filtrate was diluted with ether, well washed (saturated salt solution), dried ($MgSO_4$), and concentrated to yield an oil (3.31 g) identical (ir, nmr) with the starting material **6** (R = H).

Mercuric Acetate–EDTA Oxidation of Compound 9.—Compound **9** (700 mg, 0.0035 mol) was added to a solution of mercuric acetate (1.14 g, 0.0035 mol) and EDTA disodium salt (1.3 g, 0.0035 mol) in 2% aqueous acetic acid (50 ml). After 2 days at room temperature, the mixture was made basic (20% KOH) and extracted (ether). The ether was washed (saturated NaCl solution), dried ($MgSO_4$), and removed. The resulting oil (420 mg) was distilled in a hot box (0.05 mm). The distilled material (380 mg) was examined: ν_{max} 1650 cm^{-1} (m), 1620 (m); nmr δ 8.34 (d, ~0.25), 6.18 (d, ~0.5), 5.34 (d, ~0.5); mass spectrum *m/e* 216, 200, 187, 157, 129; 200 → 157 is loss of $\cdot CH_2{=}NCH_2$, linked by a metastable peak at 123.2; 157 → 129 is loss of C_2H_4 linked by a metastable peak at 106.0.

Registry No.—**1** (*n* = 1), 37384-28-4; **1** (*n* = 2), 37384-29-5; **3** (*n* = 1), 37394-04-0; **3** (*n* = 2), 21139-96-8; **4**, 5596-87-2; **5**, 37393-84-3; **6** (R = H, biscyclamate), 37393-83-2; **7**, 37413-11-9; **8**, 37393-85-4; **10**, 37393-86-5; **13** (R = H), 37393-87-6; **14** (R = H, biscyclamate), 37393-88-7; **14** (R = CH_3, biscyclamate), 37393-89-8.

Acknowledgment.—We wish to acknowledge the support and encouragement of Dr. George deStevens and helpful discussions of the spectral data with Mr. L. Dorfman, whose staff we thank for the microanalyses and spectra.

A Novel Approach to the Synthesis of Nitrogen Analogs of the Tetrahydrocannabinols

MARK CUSHMAN[1] AND NEAL CASTAGNOLI, JR.*

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94122

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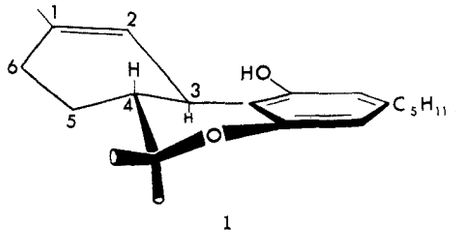
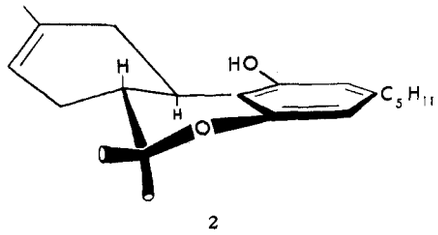
An approach to the synthesis of nitrogen analogs of the tetrahydrocannabinols which preserves the integrity of the trans ring fusion and a natural location of the double bond is reported in the present study. The condensation of *o*-anisylidenemethylamine (**10**) and glutaric anhydride yielded *trans*- and *cis*-1-methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidones (**11** and **12**). Subsequent O-demethylation and cyclodehydration of the trans diastereomer provided the tricyclic lactone **16**, which was converted into the corresponding *gem*-dimethyl alcohol **18**. Cyclodehydration of **18** gave the key tricyclic intermediate **23**, which was also obtained independently *via* the methyl ester **13** of **11**. Treatment of the trans ester **13** with CH_3MgBr yielded the tertiary alcohol **24**, which on treatment with BBr_3 gave the trans bromide **25**. Dehydrohalogenation of **25** provided a mixture of olefins **26** and **27**, which could be cyclized to the key intermediate **23** in CF_3COOH. Configurational and conformational assignments were made by nmr spectroscopy. Subsequent methylations and reductions of **23** provided the corresponding carbinolamines, enamines, and amines.

It has been shown that the biologically active constituents of *Cannabis* are Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC) **1**[2] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol



1

($\Delta^{1(6)}$-THC) **2**.[3] The absolute configurations of Δ^1-THC and $\Delta^{1(6)}$-THC at C-3 and C-4 are R.[4]



2
(monoterpenoid numbering)

In view of the generally recognized psychotropic activity of the THC's,[5] a striking structural feature of these molecules is the absence of nitrogen. However, a number of THC nitrogen analogs have been reported. Thus far, the synthesis of most of these nitrogen analogs has been based on the early work of Adams and Todd and their collaborators,[6] who con-

(1) NDEA Predoctoral Fellow and American Foundation for Pharmaceutical Education Fellow.

(2) Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, **86**, 1646 (1964).

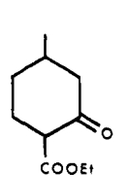
(3) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).

(4) R. Mechoulam and Y. Gaoni, *Tetrahedron Lett.*, 1109 (1967).

(5) L. E. Hollister, *Ann. N. Y. Acad. Sci.*, **191**, 132 (1971).

(6) R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62**, 2405 (1940); R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1121 (1940).

densed ethyl 5-methylcyclohexanone-2-carboxylate (**3**) with olivetol (**4**) in the presence of phosphorus oxychloride to give the benzopyrone **5**. Treatment of **5** with methylmagnesium iodide provided the unnatural and less physiologically active Δ^3-THC **6**. By con-



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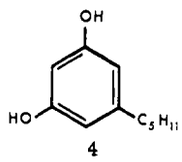

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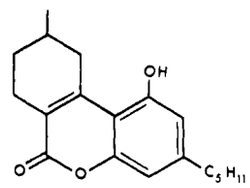

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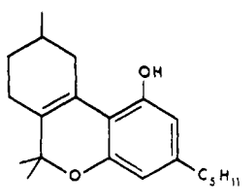
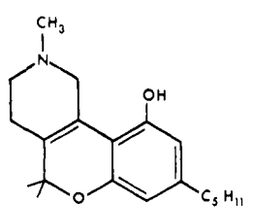


6

densation of appropriately substituted piperidones with olivetol under similar conditions followed by Grignard methylation, aza analogs **7**,[7] **8**,[8] and **9**[9a] have been prepared.[9b]



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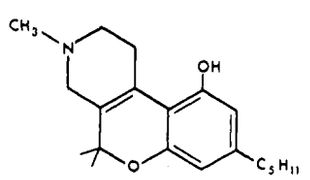

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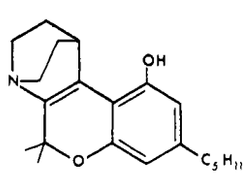
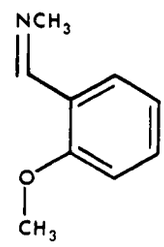


9

Anker and Cook synthesized compound **8** in 1946 and reported it to have no analgesic activity.[8] Razdan, *et al.*, repeated the synthesis of compound **8** and reported in 1968 that it is an active CNS agent similar to compound **7**,[10] reported by Pars, *et al.*[7] Both compounds were found to depress spontaneous activity and produce analgesia in mice.[11] The pharmacologic activity of these nitrogen analogs encouraged the synthesis of the quinuclidine derivative **9**, which was also reported to be an active CNS agent.[11]

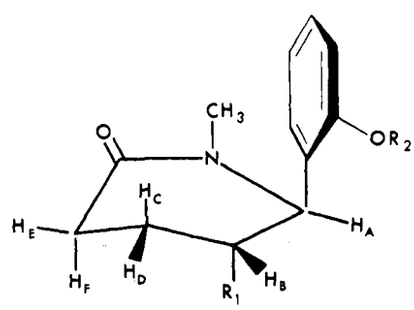
Since the unnatural Δ^3 isomer **6** is considerably less potent in animals[12] and in man[13] than the trans isomers **1** and **2**, it may be concluded that the stereochemistry of the terpene ring is an important factor in terms of any physiological response. Therefore, we have undertaken a new approach to the synthesis of nitrogen analogs of the THC's in which the integrity of the trans ring fusion and a natural location of the double bond are preserved. An additional factor which should be considered in the design of a synthetic route to these compounds is its potential versatility toward structural modification, since the preparation of a series of structurally related compounds should prove of value in the elucidation of parameters associated with the biological activity. With these considerations in mind, we chose *dl-trans*-1,5,5-trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (**23**) as our first objective.

The condensation of *o*-anisylidenemethylamine (**10**)



10

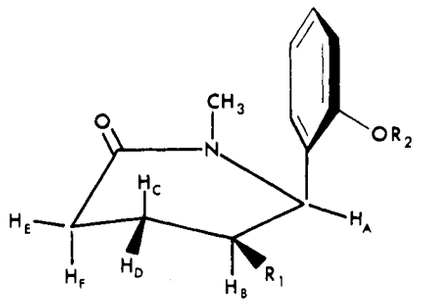
and glutaric anhydride in refluxing xylene proceeded smoothly to yield a diastereomeric mixture of piperidones **11** and **12**, which could be separated by fractional crystallization. These trans and cis diastereomers were converted into their methyl esters **13** and **14** by treatment with diazomethane. By analogy with the condensation of Schiff bases and succinic anhydrides,[14,15] the major diastereomer would be expected to have the trans configuration while that of the minor diastereomer would be cis. In addition, the aromatic ring in both trans and cis diastereomers may be expected to occupy the axial conformation in



11, R_1 = COOH, R_2 = CH_3
13, R_1 = $COOCH_3$, R_2 = CH_3
15, R_1 = COOH, R_2 = H
18, R_1 = $C(CH_3)_2OH$, R_2 = H
24, R_1 = $C(CH_3)_2OH$, R_2 = CH_3
25, R_1 = $C(CH_3)_2Br$, R_2 = H
26, R_1 = $C(CH_3)=CH_2$, R_2 = H

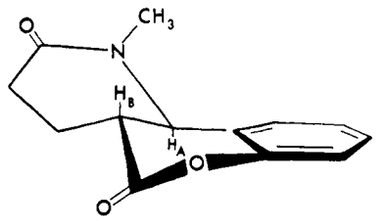
view of the planar amide linkage containing two trigonal atoms and with reference to the work which has been done on A strain in cyclohexenes.[16] These expectations regarding the configurations and conformations of these compounds were verified by nmr as follows. The signal for the methoxycarbonyl pro-

(7) H. G. Pars, F. E. Granchelli, J. K. Keller, and R. K. Razdan, *J. Amer. Chem. Soc.*, **88**, 3664 (1966).
(8) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 58 (1946).
(9) (a) R. E. Lyle, R. K. Razdan, F. E. Granchelli, and H. G. Pars, U. S. Patent 3,493,579 (1970). (b) Benzodiazepine and benzopyranopyrimidine analogs of **6** have also been reported: W. Greb, D. Bieniek, and F. Korte, *Tetrahedron Lett.*, 545 (1972).
(10) R. K. Razdan, V. V. Kane, H. G. Pars, J. L. Kucera, D. H. Reid, L. S. Harris, W. L. Dewey, and J. F. Howes, Minutes, 30th Meeting Committee on Problems of Drug Dependence, NAS-NRC (1968).
(11) H. G. Pars and R. K. Razdan, *Ann. N. Y. Acad. Sci.*, **191**, 15 (1971).
(12) R. Adams, *Bull. N. Y. Acad. Med.*, **18**, 715 (1942).
(13) L. E. Hollister, *Nature (London)*, **227**, 968 (1970).
(14) N. Castagnoli, Jr., *J. Org. Chem.*, **34**, 3187 (1969).
(15) M. Cushman and N. Castagnoli, Jr., *ibid.*, **36**, 3404 (1971).
(16) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).



12, R_1 = COOH, R_2 = CH_3
14, R_1 = $COOCH_3$, R_2 = CH_3

tons of the methyl ester of the major trans diastereomer **13** appears at δ 3.75 ppm whereas the corresponding signal of the minor diastereomer **14** appears at δ 3.56 ppm. Inspection of Dreiding models reveals that the methoxycarbonyl protons of the equatorial ester group of **14** may experience the shielding effect of the aromatic π cloud whereas those of the axial ester group of **13** may not. Further support of these assignments is provided by the coupling constant of H_A in **11** (J = 2.5 Hz) in comparison with the coupling constant of H_A in **12** (J = 5 Hz). This is as expected since in comparable systems the coupling constants for diequatorial protons are invariably significantly smaller than those of axial–equatorial protons.[17] Finally, the trans lactone **16**, a key intermediate in our overall

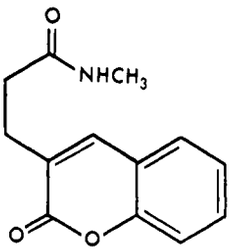


16

synthetic plan (see below), exists as a rigid diequatorial conformer. This conversion from the diaxial arrangement in the ring open system, *e.g.*, **11** to diequatorial **16** was accompanied by a change in coupling constant for H_A from 2.5 Hz for **11** to **13** Hz for **16**. It is firmly established that the nmr spectra of compounds containing six-membered rings show coupling constants for diaxial protons in the range of 8–13 Hz and diequatorial protons in the range 1–5 Hz.[17]

The relative amounts of **11** and **12** present in the crude reaction product could be estimated by integration of the O–CH_3 singlets in the nmr spectrum. Based on these values, the mixture contained 88% of the trans diastereomer and 12% of the cis. In order to determine the thermodynamic equilibrium for the methyl esters **13** and **14**, each diastereomer was heated in MeOH in the presence of an equivalent of CH_3O^-. The mixture obtained in this way starting from either pure trans or pure cis contained 92% of the trans isomer and 8% of the cis, determined by integration of methoxycarbonyl proton signals in nmr spectra. Comparable results were obtained by pyrolysis of the trans acid **11**.

The next step in our approach to the model aza analogs of THC involved formation of the tricyclic compound **16**. Attempted conversion[18] of the methyl ether **11** into **16** *via* the phenol intermediate **15** with HI in acetic acid gave unexpectedly the coumarin **17**.

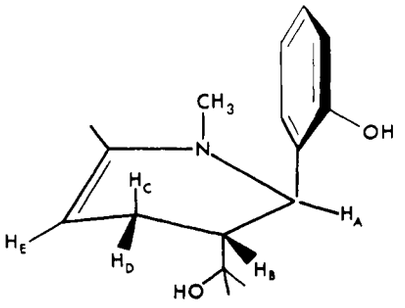


17

The ir spectrum of the solid reveals strong lactone and amide carbonyl bands as well as an N–H band at 3280 cm^{-1} which shifts to 2425 cm^{-1} after deuterium exchange with D_2O, consistent with the proposed secondary amide structure.[19] The nmr chemical shift value (δ 7.65 ppm) of the olefinic proton singlet agrees well with the δ 7.72 ppm value reported for the corresponding doublet in coumarin.[20] The remaining nmr signals as well as the mass spectral, uv, and microanalytical data also support this structure (see Experimental Section for details).

Synthesis of the desired tricyclic lactone **16** was finally accomplished by a two-step sequence. The methyl ether **11** was converted into the phenol **15** by treatment with boron tribromide in methylene dichloride.[21] The phenol underwent cyclodehydration smoothly to compound **16** in the presence of dicyclohexylcarbodiimide. Attempted thermal cyclization of phenol **15** to **16** gave instead the same coumarin **17** isolated by HI treatment of compound **11**. Since both **11** and **16** could not be converted into **17** by heating, it would appear that compound **15** is an obligatory intermediate in the formation of the coumarin.

Treatment of **16** with excess methylmagnesium bromide in tetrahydrofuran at 0° provided the lactam **18** as the sole isolable product. When the lactone **16** was treated with methylmagnesium bromide in refluxing xylene for 6 hr, glpc analysis showed the isolated product to be a 3:1 mixture of two components which could be separated by column chromatography on neutral alumina. Although the chemical ionization mass spectrum and elemental analysis of the major component could be interpreted in terms of the enamine **19**, the nmr spectrum could not be



19

(17) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 288.

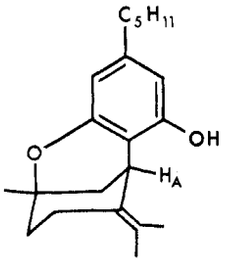
(18) R. Adams and R. B. Carlin, *J. Amer. Chem. Soc.*, **65**, 360 (1943).

(19) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 207.

(20) Varian High Resolution NMR Spectra Catalog, No. 225.

(21) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).

rationalized on the basis of this structure. In particular, the signal for the C–CH_3 α to nitrogen appeared at δ 1.26 ppm as a sharp singlet, which is at a higher field than expected for an olefinic methyl signal. Furthermore, the olefinic proton H_E of **19** should appear near δ 4.4 ppm.[22] The only signal in this area appeared as a singlet at δ 4.18 ppm which may be assigned to a benzylic proton. A review of the THC literature revealed that a compound originally thought to be $\Delta^{1(6)}$-3,4-*cis*-THC was reassigned structure **20** on the basis of its nmr spectrum.[23] Consideration of the arguments for this reassignment led to the realization that the corresponding structure **21** was consistent



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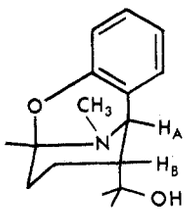
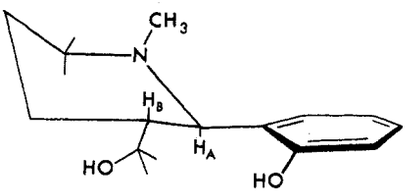


21

with our spectral data. The chemical shift value of the benzylic proton H_A of **21** of δ 4.18 compares favorably with the δ 4.19 reported for the allylic benzylic proton H_A of **20**. The δ 1.26 value for the *C*-methyl α to nitrogen in **21** also compares favorably with the δ 1.36 for the corresponding methyl group of **20**.

The second minor component of the reaction mixture proved to be the product resulting from the addition of four methyl groups to **16** yielding the diequatorially substituted ($J_{A,B}$ = 10.5 Hz) amine **22**. Mixtures of



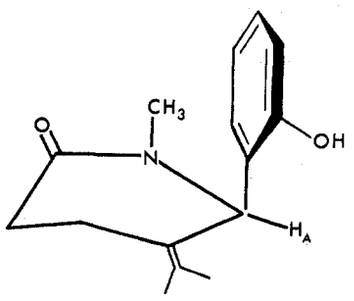
22

21 and **22** could be converted completely into **22** by repeated subjection of the mixture to the Grignard conditions in refluxing xylene.

The tricyclic amide **23** was obtained in 40% yield by cyclization of the tertiary alcohol **18** in CF_3COOH. As in the conversion of **15** into **16**, this reaction was accompanied by a conformational conversion from a diaxial to a rigid diequatorial ring system, as indicated by a change in the coupling constant $J_{A,B}$ from 2.5 to 9.5 Hz.

An alternative route to the tricyclic amide **23** was also established. Treatment of the trans ester **13** with methylmagnesium bromide in tetrahydrofuran provided the corresponding tertiary alcohol **24**, which was converted with boron tribromide into the trans bromide **25**. Dehydrohalogenation of this bromide **25** gave a mixture of the olefins **26** and **27**, which were shown by nmr to be present in a 19:1 ratio, respectively.

In addition to the above two olefins, concentration of the aqueous HBr solution of this reaction mixture gave a crystalline solid material which proved to be the amide hydrobromide **28**.[24] Comparison of the



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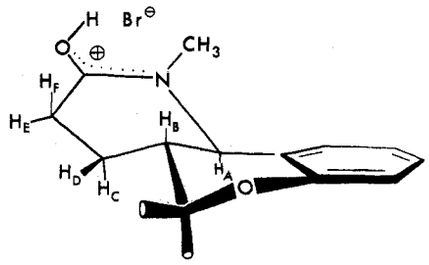

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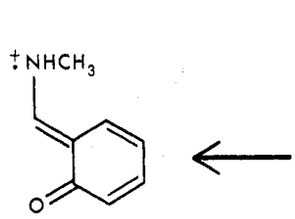
nmr spectrum in $CDCl_3$ of this material with that of the corresponding amide **23** reveals downfield shifts for the *N*-methyl group and all protons in the nitrogen-containing heterocyclic ring. Furthermore, the magnitude of this effect is greatest for the protons nearest the positive charge. Treatment of the nmr samples with a few drops of Py-d_5 or D_2O instantaneously generated the spectrum of the amide **23**. Except for the appearance of HBr, the electron impact mass spectrum of the hydrobromide **28** was identical with that of the amide **23**. The empirical formula of the base peak in both spectra was established as C_8H_9NO by high resolution, which is consistent with structure **29**. Radical



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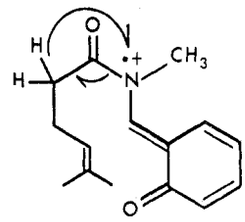


23a

ion **29** may be formed by ring opening of the pyran[25] followed by α cleavage of the amide **23a** with loss of a carbene.[26] The ir spectrum of hydrobromide **28** contained a broad absorption at 1650 cm^{-1}, near the $\nu_{C=O}$ (1660 cm^{-1}) of amide **23**. The amide **23** was obtained after extraction of $CHCl_3$ suspensions of **28** with water.

The 19:1 mixture of olefins **26** and **27** was treated with boiling CF_3COOH for 35 min and the nonphenolic material isolated in 70% yield. Integration of the NCH_3 groups at δ 3.15 and 3.35 ppm of the crude isolate indicated that the trans amide **23** and cis amide **30**

(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

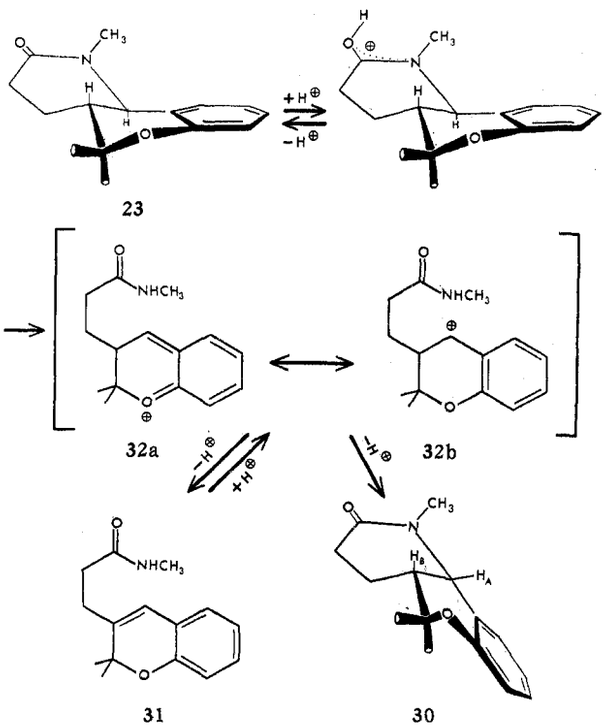
(23) Y. Gaoni and R. Mechoulam, *ibid.*, **88**, 5673 (1966).

(24) Houben-Weyl, "Die Methoden der organischen Chemie," 11/2, Georg Thieme, Leipzig, 1958, p 568.

(25) B. Wilhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron*, **20**, 1185 (1964).

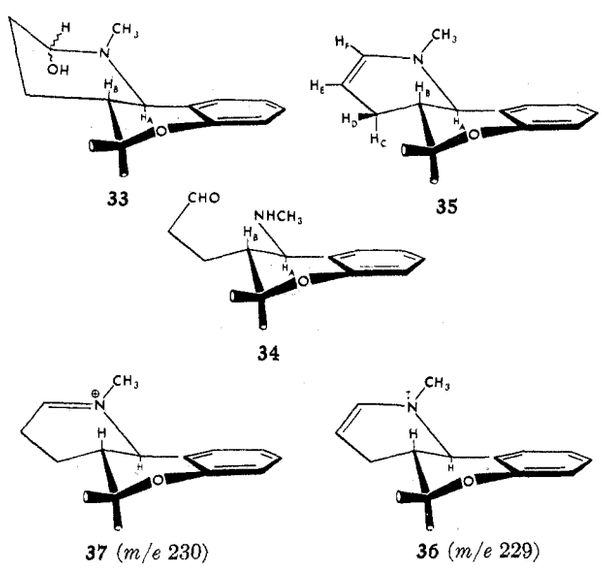
(26) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 340–346.

were present in a 17:3 ratio, respectively. During separation of **23** and **30** by fractional crystallization, a trace impurity was detected by glpc on SE-30 which cocrystallized and cosublimed with the desired trans amide **23**. Column chromatography led to the separation of the trans and cis amides **23** and **30** from the impurity. As had been observed with the coumarin **17**, the *N*-methyl doublet (J = 5 Hz) in the nmr spectrum of the "impurity" collapsed to a singlet after addition of D_2O, suggesting the chromene **31**. Although the appearance of the signal for the four methylene protons as a sharp singlet was somewhat surprising, examples of other unsymmetrically 1,2-disubstituted ethylenes in which the four methylene protons appear as a singlet have been reported.[27] The ir characteristics of **31** were similar to those observed for the coumarin **17**. When the CF_3COOH reaction period was extended to 24 hr, the cis amide **30** ($J_{A,B}$ = 5 Hz) was the only isolable product, and none of **23** or **31** could be detected. Since the chromene **31** is a symmetrical molecule, our attention was directed to the possibility that it is an intermediate in the epimerization of **23** to **30**. Therefore a solution of **31** in CF_3COOH was heated at the boiling point and the reaction progress followed by nmr. Essentially complete conversion of the chromene **31** to the cis amide **30** was observed within 3 hr. Evidently the epimerization of **23** to **30** proceeds by cleavage of the benzylic carbon–nitrogen bond to form intermediate **32a** ↔ **32b**, which then deprotonates to generate the chromene



31 or cyclizes to the cis amide **30**. Similar results were also observed on treatment of the tertiary alcohol **18** with boiling CF_3COOH.

The carbinolamine **33** was isolated as a stable solid in 63% yield after reduction of the amide **23** with a large excess of lithium aluminum hydride in tetrahydrofuran. The corresponding amino aldehyde **34** and enamine **35** structures can be excluded due to the lack of any aldehyde or enamine double bond absorbance in the solid state ir spectrum. Broad multiplets were observed in the nmr spectrum for the methine and methylene protons. The nmr spectrum recorded 16 hr after dissolution of the carbinolamine **33** showed substantial conversion (>60%) into the enamine **35**. The signal for the benzylic proton H_A appeared as a distinct doublet ($J_{A,B}$ = 10 Hz) at δ 4.00 ppm. The signal for the olefinic proton H_F has been assigned to a doublet ($J_{E,F}$ = 7 Hz) at δ 6.19 ppm and the signal for the remaining proton H_E corresponds to a multiplet at δ 4.95 ppm.[28] This change in the nmr spectrum was paralleled by the appearance of the enamine double bond (1650 cm^{-1}) in the ir spectrum.[22,29,30] This



facile dehydration was also evident in the chemical ionization mass spectrum of the carbinolamine **33** which showed no ion at m/e 248 corresponding to protonated **33**, but did show the iminium ion **37** (m/e 230) as the base peak along with the enamine radical ion **36** (m/e 229, 47%).

Treatment of the trans amide **23** with an excess of methylmagnesium bromide in boiling tetrahydrofuran yielded the carbinolamine **38** as a stable solid in 86% yield. As with carbinolamine **33**, the corresponding amino aldehyde and enamine structures could be ruled out due to lack of any aldehyde or enamine double bond absorbance in the solid state ir spectrum. In contrast to carbinolamine **33**, the nmr and ir spectra recorded at 10-min intervals after dissolution of carbinolamine **38** indicated essentially complete conversion into the enamine **39** plus water within 1 hr. The olefinic proton in the nmr spectrum of the enamine **39** appeared as a multiplet at δ 4.87 ppm and the ir spectrum displayed an absorbance at 1650 cm^{-1}, corresponding to an enamine double bond.[22] The enamine **39** could be isolated and characterized as an oil after

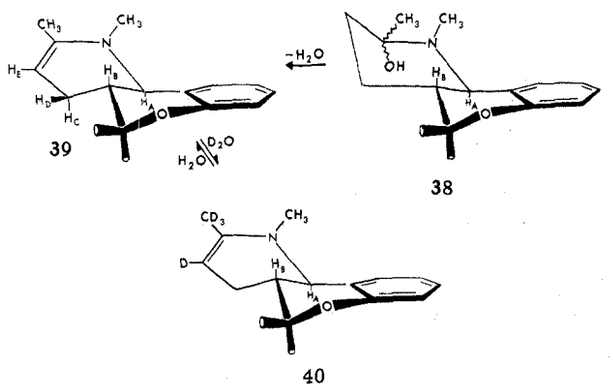
(27) Varian High Resolution NMR Spectra Catalog No. 106 and 129.

(28) H. Diekmann, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964).

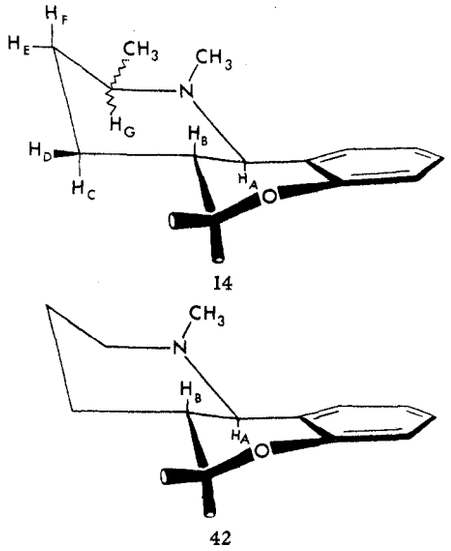
(29) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954).

(30) N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).

dehydration of the carbinolamine **38**. Unlike other members in this series, the signal for proton H_A appeared as a multiplet instead of the expected doublet, presumably due to virtual long-range coupling.[31] Addition of D_2O to $CDCl_3$ solutions of enamine **39** resulted in disappearance of the olefinic proton H_E and the olefinic methyl group in the nmr spectrum yielding the deuterated enamine **40**[32,33] ($t_{1/2}$ for exchange approximately 15 min). In order to establish that an exchange process had occurred rather than decomposition, the reversibility of the reaction was tested by back-exchange of deuterium in **40** with H_2O. Addition of H_2O to $CDCl_3$ solutions of **40** resulted in regeneration of the nmr spectrum of **39**.



Proton H_A in the amine **41**, obtained by catalytic reduction of **38**, appeared as a doublet ($J_{A,B}$ = 11 Hz). The presence of a single diastereomer was indicated by the sharp melting point, the presence of single signals for the N–CH_3 and C–CH_3 groups in the nmr spectrum, and observation of a single peak on glpc. The relative configuration at C-2 was not assigned. Compound **42** was obtained by diborane reduction of amide **23**.



Experimental Section[34]

o-**Anisylidenemethylamine** (**10**).—*o*-Anisaldehyde (136.15 g, 1 mol) and methylamine (34.17 g, 1.1 mol) were stirred for 5 hr at room temp in 200 ml of C_6H_6 in the presence of molecular sieves (3A, 200 g). Following filtration and washing of the sieves with benzene, the solvent was removed and the residue distilled at 70° (0.2 mm) to give the Schiff base as a pale yellow oil (132.47 g, 89%): nmr δ 8.68 (q, J = 1.5 Hz, imino H), 7.92–6.91 (m, Ar), 3.77 (s, OCH_3), 3.48 (d, J = 1.5 Hz, NCH_3).

Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.38; N, 9.41.

trans-**1-Methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidone** (**11**).—*o*-Anisylidenemethylamine (74.60 g, 0.5 mol) and glutaric anhydride (57.05 g, 0.5 mol) were heated in refluxing xylene (100 ml) for 24 hr. Crystallization of a light yellow solid (109.92 g, 83%), mp 155–173°, was induced by scratching the hot solution. Analytically pure trans acid (71.68 g, 55%) was obtained from the diastereomeric mixture by fractional crystallization from 2-butanone (1 l.): mp 182–183; ir (KBr) 3400 (broad), 2900, 1715 (carboxylic acid $\nu_{C=O}$), 1605 (lactam $\nu_{C=O}$); nmr δ 11.99 (s, COOH, exchangeable with D_2O), 7.14 (m, Ar), 5.37 (d, J = 2.5 Hz, H_A), 3.86 (s, OCH_3), 3.02 (m, H_B), 2.89 (s, NCH_3), 2.65 (m, $H_{E,F}$) 2.01 (m, $H_{C,D}$).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.47; N, 5.46.

cis-**1-Methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidone** (**12**).—The filtrate left after separation of the above trans isomer was concentrated to a volume of 150 ml. After standing overnight, the white solid (7.03 g), mp 170–204°, was collected. The pure cis acid (**12**) (0.73 g, 0.6%) was obtained after three recrystallizations from EtOH: mp 215–216°; ir (KBr) 3385 (b, OH), 2890, 1710 (carboxylic acid $\nu_{C=O}$), 1595 (lactam $\nu_{C=O}$); nmr δ 10.27 (s, COOH, exchangeable with D_2O), 7.08 (Ar), 5.36 (d, J = 5 Hz, H_A), 3.62 (s, OCH_3), 3.24 (m, H_B), 2.81 (s, NCH_3), 2.19 (m, CH_2–CH_2).

Anal. Calcd for $C_{14}H_{17}NO$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.11; H, 6.53; N, 5.40.

trans-**1-Methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone** (**13**).—An excess of CH_2N_2 in EtOH–Et_2O was added to the piperidone **11** (52.66 g, 0.2 mol). Evaporation of solvent from the resulting solution left the methyl ester as a glassy residue which crystallized from Et_2O–pentane (100:55 ml) as a colorless solid (45.52 g), mp 77–78°. An additional 4.06 g, mp 77–78°, was obtained after concentrating the filtrate to a volume of 50 ml to give a total yield of analytically pure solid of 49.58 g, 89%: mp 77–78°; ir (KBr) 2900, 1735 (ester $\nu_{C=O}$), 1640 (lactam $\nu_{C=O}$); nmr δ 7.14 (m, Ar), 5.28 (d, J = 3 Hz, H_A), 3.86 (s, OCH_3), 3.75 (s, $COOCH_3$), 2.99 (m, H_B), 2.84 (s, NCH_3), 2.51 (m, $H_{E,F}$), 2.00 (m, $H_{C,D}$).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.02; H, 6.89; N, 4.98.

cis-**1-Methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone** (**14**).—Evaporation of solvent from the filtrate after crystallization of the trans acid **11** left a solid residue (38.24 g), mp 170–210°. An excess of CH_2N_2 in EtOH–Et_2O was added. Evaporation of solvent from the solution left a quantitative yield of diastereomeric esters **13** and **14** as an oil in a ratio of 3:1 (by nmr). The cis ester (0.13 g, 0.1%) was isolated by fractional crystallization once from Et_2O and twice from Me_2CO: mp 122–124°; ir (KBr) 2935, 1735 (ester $\nu_{C=O}$), 1650 (amide $\nu_{C=O}$); nmr δ 7.07 (m, Ar), 5.25 (d, J = 5 Hz, H_A), 3.78 (s, OCH_3), 3.56 (s, $COOCH_3$), 2.79 (s, NCH_3), 3.34–1.72 (m, $H_{B\to F}$).

(31) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1968, pp 130, 131.

(32) W. H. Daly, J. G. Underwood, and S. C. Kuo, *Tetrahedron Lett.*, 4375 (1971).

(33) P. Beak and J. Bonham, *J. Amer. Chem. Soc.*, **87**, 3365 (1965).

(34) All reactions were performed under a nitrogen atmosphere, and solvents were evaporated on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-4H-100 100-MHz instrument and, except where noted, in $CDCl_3$ solvent. Chemical shift values are reported in parts per million relative to TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Glpc analyses were performed on Varian Aerograph Model 2100 gas chromatograph equipped with a flame ionization detector using a 1/8 in. × 6 ft column of 3% SE-30 on Chromosorb W, 100–120 mesh. The electron impact mass spectra were recorded on an AE1 MS-12 instrument at 70 eV and the chemical ionization mass spectra were recorded on an AE1 MS-901 spectrometer modified for chemical ionization. Details of the instrumental modification will be published elsewhere. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley. The uv spectrum was recorded on a Cary 15 spectrophotometer.

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.16; H, 6.87; N, 5.08.

trans-**1-Methyl-5-carboxy-6-(*o*-hydroxyphenyl)-2-piperidone (15).**—A solution of BBr_3 (25 g, 100 mmol) in CH_2Cl_2 (200 ml) was added dropwise to a solution of the piperidone **11** (8.69 g, 33 mmol) in CH_2Cl_2 (225 ml) at room temperature. After stirring 48 hr H_2O (150 ml) and Et_2O (600 ml) were added. The two phases were stirred for 2.5 hr before the organic phase was separated. The aqueous phase was extracted with Et_2O (350 ml), and the combined organic phases were dried ($MgSO_4$) and concentrated to 25 ml (bath at room temperature) and the resulting suspension left at 1° overnight. A white solid (6.04 g, 73%), mp 197–199°, separated and was recrystallized twice from 50% aqueous EtOH to provide the analytical sample: mp 202–202.5°; ir (KBr) 3650-2500 (b, OH), 1735 (carboxylic acid $\nu_{C=O}$), 1580 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 8:3) 10.01 ppm (s, COOH + OH, exchangeable with D_2O), 6.95 (m, Ar), 5.63 (d, J = 3 Hz, H_A), 3.28 (m, H_B), 2.95 (s, NCH_3), 2.65 (m, $H_{E,F}$), 2.10 (m, $H_{C,D}$).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.60; H, 6.17; N, 5.58.

trans-**1-Methyl-2,5-dioxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (16).**—A mixture of the piperidone **15** (20.00 g, 80.2 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (16.54 g, 80.2 mmol) were heated in refluxing THF (175 ml) with stirring for 2 hr. The suspension was then stirred at room temperature for 21 hr. The *N*,*N*′-dicyclohexylurea was filtered off and the THF evaporated from the filtrate to give a quantitative yield (18.54 g) of the lactone, mp 149–152°. Crystallization from C_6H_6 gave the analytical sample: mp 150–152°; ir (KBr) 1765 (lactone $\nu_{C=O}$), 1645 (lactam $\nu_{C=O}$); nmr δ 7.26 (m, Ar), 4.57 (d, J = 13 Hz, H_A), 3.24 (s, NCH_3), 2.88–1.73 (m, $H_{B\rightarrow F}$).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.51; H, 5.97; N, 6.16.

3-(*N*-Methyl-β-propionamido)coumarin (17). A.—A mixture of Ac_2O (6 ml), 57% aqueous HI (6 ml), red phosphorus (1.00 g), and **11** (1.32 g, 5 mmol) was heated under reflux for 3.5 hr. After cooling to room temperature, the red phosphorus was removed by filtration and the filtrate in 5% aqueous $NaHCO_3$ (100 ml) was extracted with $CHCl_3$ (100 ml). The $CHCl_3$ layer was separated and washed with 5% aqueous $NaHCO_3$ (100 ml). Evaporation of the dried ($MgSO_4$) $CHCl_3$ solution left the coumarin (0.48 g, 41%) as a white powder, mp 155–156°, which was crystallized from EtOH to provide the analytical sample: mp 156–156.5°; ir (KBr) 3280 (ν_{N-H}, shifted to 2425 cm^{-1} after deuterium exchange), 2910, 1710 (lactone $\nu_{C=O}$), 1635 (amide $\nu_{C=O}$), 1605, 1570 (amide II band), ($CDCl_3$) 3450 (ν_{N-H}, shifted to 2555 cm^{-1} after deuterium exchange), 2930, 1715 (lactone $\nu_{C=O}$), 1665 (amide $\nu_{C=O}$), 1615, 1530 (amide II band); nmr δ 7.65 (s, C=CH), 7.15 (m, Ar), 6.58 (s, NH, exchangeable with D_2O, $t_{1/2}$ for exchange 10 min), 2.91 (t, J = 7 Hz, CH_2), 2.77 (d, N-CH_3, J = 5 Hz, collapsed to a singlet after deuterium exchange of N–H), 2.58 (t, J = 7 Hz, CH_2); electron impact mass spectrum m/e (rel intensity) 231 (25), 200 (32), 173 (100), 159 (18), 154 (19), 125 (30); high-resolution mass spectrum, calcd (for $C_{13}H_{13}NO_3$) m/e 231.0895, found 231.0896; uv max (C_2H_5OH) 307 nm (ε 6940) and 274 (11,300).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.37; H, 5.83; N, 5.89.

B.—*trans*-1-Methyl-5-carboxy-6-(*o*-hydroxyphenyl)-2-piperidone (**15**) (200.0 mg, 0.80 mmol) was heated neat at 204–206° for 0.5 hr. Trituration of the resulting oil with Me_2CO (1 ml) gave the coumarin in 80% crude yield. The analytical sample was recrystallized twice from 2-butanone and once from EtOH. The identity of the coumarin with that obtained above was established by superimposable nmr, ir, and mixture melting point behavior.

Epimerization Studies. A.—*trans*-1-Methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidone (**11**) (131.6 mg, 0.5 mmol) was heated neat at 204–206° for 0.5 hr. Treatment of the oily product (132.1 mg) with an excess of CH_2N_2 in EtOH–Et_2O followed by evaporation of solvent from the resulting solution provided a quantitative yield of the trans and cis esters **13** and **14**, respectively, as an oil. The esters were identified as *trans*- and *cis*-1-methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone (**13** and **14**) by comparison of the nmr spectrum with those of the previously isolated esters. Integration of the methoxycarbonyl proton signals showed the ratio of trans/cis was 92:8.

B.—A solution of the piperidone **13** (27.7 mg, 0.1 mmol) and CH_3ONa (5.4 mg, 0.1 mmol) in dry MeOH (1 ml) was heated under reflux for 5 hr. The solution was cooled to room temperature and CH_2Cl_2 (10 ml) and H_2O (10 ml) were added. The separated CH_2Cl_2 layer was dried ($MgSO_4$) and the solvent evaporated, leaving a quantitative yield of esters as an oil. The esters were identified as *trans*- and *cis*-1-methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone (**13** and **14**, respectively) by comparison of the nmr spectrum with those of the previously isolated esters. Integration of the methoxycarbonyl proton signals showed that the ratio of trans/cis esters was 92:8.

C.—Exactly the same results were obtained when *cis*-1-methyl-5-methoxycarbonyl-6-(*o*-methoxyphenyl)-2-piperidone (**14**) was treated as in method B above (*i.e.*, the ratio of trans/cis esters was 92:8).

trans-**1-Methyl-5-dimethylcarbinol-6-(*o*-hydroxyphenyl)-2-piperidone (18).**—A solution of CH_3MgBr (2 ml of a 3 *M* solution in Et_2O, 6 mmol) was added dropwise to an ice-cold, stirred solution of the tricyclic intermediate **16** (231.3 mg, 1 mmol) in THF (5 ml). After stirring for 0.5 hr at 0°, saturated aqueous NH_4Cl (5 ml) was added dropwise, the organic phase separated and the aqueous phase washed with Et_2O (5 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Crystallization of the glassy residue from EtOH–Et_2O (1 + 2 ml) gave a solid (139.1 mg, 53%), mp 180–182°, which was analytically pure after recrystallization from water: mp 182–183°; ir (KBr) 3475, 2930, 1600 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 4:1) δ 6.94 (m, Ar), 5.08 (d, J = 2.5 Hz, H_A), 2.85 (s, NCH_3), 2.53 (m, $H_{E,F}$), 1.99 (m, $H_{B\rightarrow D}$), 1.36 (s, CH_3), 1.34 (s, CH_3).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.10; H, 8.08; N, 5.25.

trans-**2-Methyl-5-dimethylcarbinol-2,6-*N*-methylimine-2,3,4,5-tetrahydrobenzoxocin (21).**—A solution of CH_3MgBr (10 ml of a 3 *M* solution, 30 mmol) was added to a suspension of **16** (1.16 g, 5 mmol) in xylene (50 ml) and the resulting mixture stirred under reflux for 6 hr. The reaction mixture was cooled to room temperature and decomposed by addition of saturated aqueous NH_4Cl (50 ml). The organic phase was separated and dried ($MgSO_4$), and the solvent evaporated. Glpc analysis (190° column temp, N_2 flow rate 46 ml/min) of the residue showed one major component (retention time 3.0 min) and one minor component (retention time 4.3 min) present in a 7:3 ratio, respectively. Elution from a basic alumina column (36 × 2 cm, 100 g) with CH_2Cl_2 gave first compound **21** which was identified as the major component by glpc. Evaporation of solvent left **21** as an oil (0.34 g, 26%). The analytical sample was prepared by evaporative distillation at 98°/5 μ yielding a light yellow-colored oil: nmr δ 6.93 (m, Ar), 5.80 (b, OH), 4.18 (b s, H_A), 2.34 (s, NCH_3), 2.25–1.10 (m, $H_{B\rightarrow F}$), 1.46 (s, $C(CH_3)_2$), 1.26 (C-CH_3); chemical ionization mass spectrum (CH_4 ionizing gas, 1.2 mm, 200° source temp) m/e (rel intensity) 262 (MH^+, 100), 246 (14), 244 (14).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.88; H, 8.89; N, 5.54.

trans-**1,2,2-Tridimethyl-5-dimethylcarbinol-6-(*o*-hydroxyphenyl)piperidine (22). A.**—Continued elution of the above alumina column with CH_2Cl_2 provided fractions containing the minor component amine **22**, which was obtained as an oil (0.04 g, 3%). Evaporative distillation at 120° (0.6 mm) gave the analytical sample: nmr δ 6.99 (m, Ar), 3.49 (d, J = 10.5 Hz, H_A), 2.05 (s, NCH_3), 2.40–1.30 (m, $H_{B\rightarrow F}$), 1.24 (s, CH_3), 1.15 (s, CH_3), 1.07 (s, CH_3), 1.05 (s, CH_3); chemical ionization mass spectrum (CH_4 ionizing gas, 1.2 mm, 200° source temp) m/e (rel intensity) 278 (MH^+, 100), 260 (48).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 74.10; H, 9.81; N, 4.85.

B.—A solution of CH_3MgBr (5 ml of a 3 *M* solution in Et_2O, 15 mmol) was added dropwise to a stirred, ice-cold solution of compound **16** (462.6 mg, 2 mmol) in xylene (10 ml) under nitrogen. The mixture was heated under reflux for 24 hr. The reaction mixture was then cooled on an ice bath before decomposition with saturated aqueous NH_4Cl (20 ml). The organic phase was separated and the aqueous phase washed with Et_2O (20 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left an amber oily residue (383.0 mg). Glpc analysis (190° column temp, N_2 flow rate 46 ml/min) of the residue showed the presence of compounds **21** (retention time 3.0 min) and **22** (retention time 4.3 min) in a 53:47 ratio, respectively. The oil was dissolved in xylene (10 ml) and was

treated again with CH_3MgBr (3 ml of a 3 *M* solution in Et_2O, 9 mmol). Following the same work-up procedure left an amber oily residue (354.2 mg) which on glpc was shown to consist of a 15:85 mixture of **21** and **22**. When repeated a third time, the methylation yielded an oily residue (262.5 mg) containing **21** and **22** as a 7:93 mixture. Compound **22** was separated from **21** on a basic alumina column (133 × 1 cm, 30 g), eluting with $CHCl_3$. Evaporative distillation of the residue obtained from fractions containing **22** at 120° (0.6 mm) yielded a light amber oil (132.1 mg, 24%) which was identical in all respects with the previously obtained pentamethyl compound.

trans-**1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (23).** **A.**—The piperidone **18** (7.90 g, 30 mmol) in CF_3COOH (75 ml) was heated at reflux for 45 min. The ratio of peak areas in the nmr spectrum of the resulting reaction mixture at δ 3.74 (NCH_3 of **30**) and at δ 3.52 (NCH_3 of **23**) was 6:94, respectively. The residue obtained after removing solvent was dissolved in Et_2O (150 ml) and the resulting solution washed with 5% aqueous NaOH (150 ml). The aqueous layer was back-extracted with Et_2O (150 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated to give a solid residue (5.45 g). Glpc analysis (190° column temp, N_2 flow rate 35 ml/min) of the residue showed one major peak (retention time 4.8 min). The crude product was chromatographed with $CHCl_3$ on a column of silica gel (5.4 × 37 cm, Bio-Sil A, 200–325 mesh, 380 g). Evaporation of solvent from fractions containing the major component by glpc left a glass which crystallized from 50% aqueous MeOH (10 ml) as a colorless solid (2.94 g, 40%), mp 99–104°. Sublimation at 100° (10 μ) followed by recrystallization from Me_2CO provided the analytical sample: mp 102–104°; ir (KBr) 2955, 1670, and 1650 (lactam $\nu_{C=O}$); nmr δ 7.06 (m, Ar), 4.21 (d, J = 9.5 Hz, H_A), 3.15 (s, NCH_3), 2.46 (m, $H_{E,F}$), 1.74 (m, $H_{B\rightarrow D}$), 1.36 (s, $C(CH_3)_2$); electron impact mass spectrum *m/e* (rel intensity) 245 (86), 230 (39), 228 (14), 202 (18), 152 (29), 145 (11), 136 (68), 135 (100), 134 (61), 120 (14), 118 (14); high-resolution mass spectrum, calcd (for $C_{15}H_{19}NO_2$) *m/e* 245.1416, found 245.1427; calcd [for C_8H_9NO (**29**)] 135.0684, found 135.0684.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.57; H, 7.79; N, 5.82.

B.—A solution of the 19:1 mixture of *trans*-1-methyl-5-isopropenyl-6-(*o*-hydroxyphenyl)-2-piperidone (**26**) and 1-methyl-5-isopropylidene-6-(*o*-hydroxyphenyl)-2-piperidone (**27**) (15.45 g, 0.063 mol) in CF_3COOH (150 ml) was heated at reflux for 35 min. The ratio of peak areas in the nmr spectrum of the reaction mixture at δ 3.74 ppm (NCH_3 of **30**) and at δ 3.52 (NCH_3 of **23**) was 14:86, respectively. The residue obtained after removing CF_3COOH was dissolved in Et_2O (300 ml), and the Et_2O solution was washed with 5% aqueous NaOH (2 × 150 ml) and dried ($MgSO_4$). Glpc analysis (190° column temp, N_2 flow rate 35 ml/min) showed two peaks with retention times 4.8 (corresponding to **23** and **30**) and 5.8 min (corresponding to **31**) with the ratio of peak areas 92:8, respectively. Acidification of the aqueous layer with concentrated HCl to pH 4 caused precipitation of starting material (3.17 g, 20%), identified by mp 205–209° and by nmr. Evaporation of solvent from the Et_2O layer left a glass (10.85 g, 70%), which was chromatographed with $CHCl_3$ on a column of silica gel (5.4 × 86 cm, Bio-Sil A, 200–325 mesh, 880 g). Evaporation of solvent from fractions producing the major glpc peak with retention time 4.8 min left a solid residue (7.88 g) which when crystallized from 50% aqueous MeOH (16 ml) yielded pure **23** (5.41 g, 35%), mp 99–104°. Continued elution of the column (eluent vol 3.9–6.1 l.) yielded **2,2-dimethyl-3-(*N*-methyl-β-propionamido)chromene (31)** (0.48 g, 3%), mp 134–137°. The analytical sample was obtained by crystallization from 2-butanone: mp 144–144.5°; ir (KBr) 3260 (ν_{N-H}, shifts to 2400 cm^{-1} after deuterium exchange with D_2O), 2910, 1645 (amide $\nu_{C=O}$), 1575 (amide II band), ($CDCl_3$) 3450 (ν_{N-H}, shifts to 2565 after deuterium exchange with D_2O), 2960, 1660 (amide $\nu_{C=O}$), 1515 (amide II band); nmr δ 6.97 (m, Ar), 6.05 (b, NH, exchangeable with D_2O, $t_{1/2}$ for exchange about 10 min), 6.04 (s, vinyl proton), 2.82 (d, J = 5 Hz, collapsed to a singlet after D_2O addition), 2.44 (s, CH_2–CH_2), 1.42 (s, $C(CH_3)_2$).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.51; H, 7.76; H, 5.93.

C.—Water (20 ml) was added to a suspension of the hydrobromide **28** (1.24 g, 3.80 mmol) in $CHCl_3$ (40 ml). The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (20 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left a solid residue (0.70 g) which was recrystallized from 50% aqueous MeOH (2 ml) to yield **23** (0.51 g, 55%), mp 102–104°.

cis-**1,5,5-Trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (30).** **A.**—A solution of a 19:1 mixture of *trans*-1-methyl-5-isopropenyl-6-(*o*-hydroxyphenyl)-2-piperidone (**26**) and 1-methyl-5-isopropylidene-6-(*o*-hydroxyphenyl)-2-piperidone (**27**) (490.6 mg, 2 mmol) in CF_3COOH (5 ml) was heated at reflux for 24 hr, under which conditions conversion into this cis cyclic product is complete. The solvent was evaporated and the purple, oily residue dissolved in Et_2O (20 ml). The solution was washed with 5% aqueous NaOH (20 ml) and dried ($MgSO_4$) and the solvent evaporated, leaving a solid residue (372.8 mg, 76%) mp 106–113°. The analytical sample was recrystallized three times from acetone: mp 115–116°; ir (KBr) 2925, 1650 (lactam $\nu_{C=O}$); nmr 6.97 (m, Ar), 4.63 (d, J = 5 Hz, H_A), 3.35 (s, NCH_3), 2.45–1.60 (m, $H_{B\rightarrow F}$), 1.41 (s, CH_3), 1.39 (s, CH_3).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.99; N, 5.65.

B.—A solution of the chromene **31** (31.3 mg) in CF_3COOH (0.6 ml) was heated (bath 82°) for 4 hr. The nmr spectrum of the reaction mixture was identical with that of pure **30** in CF_3COOH: nmr (CF_3COOH) δ 7.16 (m, Ar), 5.12 (d, J = 5 Hz, H_A), 3.74 (s, NCH_3), 3.14–1.77 (m, $H_{B\rightarrow F}$), 1.54 (s, CH_3), 1.51 (s, CH_3).

trans-**1-Methyl-5-dimethylcarbinol-6-(*o*-methoxyphenyl)-2-piperidone (24).**—A solution of CH_3MgBr (1 mol of a 3 *M* solution in Et_2O) was added dropwise to a stirred solution of compound **13** (69.33 g, 0.25 mol) in THF (1300 ml) at 0°. The mixture was stirred at room temperature for 2 hr and then cooled to 0° before dropwise addition of saturated aqueous NH_4Cl (1 l.). The organic phase was separated and the aqueous phase extracted with Et_2O (600 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic phases left a residue which was crystallized from acetone (100 ml) to give 40.35 g of product, mp 107–109°. Concentration of the mother liquors to 30 ml yielded additional product (6.70 g, total crude yield 68%), mp 107–109°. The analytical sample was obtained by crystallization from C_6H_6–pentane and from aqueous EtOH: mp 108–109°; ir (KBr) 3370, 2920, 1615 (lactam $\nu_{C=O}$); nmr δ 7.08 (m, Ar), 5.02 (d, J = 3 Hz, H_A), 3.86 (s, OCH_3), 2.78 (s, NCH_3), 2.49 (m, $H_{E,F}$), 2.17 (s, OH), 1.89 (m, $H_{B\rightarrow D}$), 1.36 (s, CH_3), 1.30 (s, CH_3).

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.12; H, 8.29; N, 5.04.

trans-**1-Methyl-5-(2-bromoisopropyl)-6-(*o*-hydroxyphenyl)-2-piperidone (25).**—A solution of BBr_3 (97 g, 0.39 mol) in CH_2Cl_2 (388 ml) was added dropwise to a solution of the piperidone **24** (35.78 g, 0.129 mol) in CH_2Cl_2 (900 ml) at room temperature. The susepension was stirred at room temperature for 48 hr before dropwise addition of H_2O (600 ml). The resulting mixture was extracted twice with Et_2O (1800 and 600 ml). Evaporation of solvent from the combined, dried ($MgSO_4$) organic layers left **25** as a colorless solid (35.12 g, 84%), mp 129–132°. Recrystallization from aqueous EtOH and from 2-butanone provided the analytical sample: mp 134–135°; ir (KBr) 3400, 2950, 1600 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 1:1) δ 6.95 (m, Ar), 5.06 (d, J = 4 Hz, H_A), 4.42 (b, OH), 2.81 (s, NCH_3), 2.58 (m, $H_{E,F}$), 2.28 (m, H_B), 2.07 (m, $H_{C,D}$); 1.84 (s, $C(CH_3)_2$). The Beilstein test for halogen was positive.

Anal. Calcd for $C_{15}H_{20}NO_2Br$: C, 55.22; H, 6.18; N, 4.29. Found: C, 55.32; H, 6.14; N, 4.51.

trans-**1-Methyl-5-isopropenyl-6-(*o*-hydroxyphenyl)-2-piperidone (26).**—Water (400 ml) was added to a hot solution of **25** (33.00 g, 0.101 mol) in EtOH (200 ml) and the mixture heated on a steam bath for 30 min. The suspension was stored at 1° to yield solid **26** (16.44 g, 66%), mp 205–210°. The analytically pure product was prepared by recrystallization from 2-butanone: mp 218–219°; ir (KBr) 3060, 2925, 1600 (lactam $\nu_{C=O}$); nmr ($CDCl_3$–Py-d_5, 3:1) δ 6.96 (m, Ar), 5.04 (d, J = 4.5 Hz, H_A), 4.88 (s, 1 olefinic proton) 4.78 (s, 1 olefinic proton), 4.15 (b, OH), 2.84 (s, NCH_3), 2.63 (m, $H_{B,E,F}$), 1.83 (m, $H_{C,D}$), 1.76 (s, CCH_3).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.17; H, 7.67; N, 5.84.

trans-**1-5,5-Trimethyl-2-oxo-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine Hydrobromide (28).**—Evaporation of solvent from the filtrate after crystallization of **26** left a glass which crystallized on trituration with 2-butanone to give a colorless solid (4.15 g, 13%), mp 157–160°. The analytical sample of the amide hydrobromide **28** was prepared by dissolution in a minimum of $CHCl_3$ followed by precipitation with 2-buta-

none: mp 177–178° dec; ir (KBr) 2950, 2315 (broad band) 1650, 1580, 1480, 1455, 1380, 1345, 1300, 1255, 1110, 1028, 965, 870, 822, 750, 650, 590, 505; nmr δ 12.17 (s, OH), 7.08 (m, Ar), 4.73 (d, J = 9.5 Hz, H_A), 3.52 (m, $H_{E,F}$), 3.38 (s, NCH_3), 2.01 (m, $H_{B\rightarrow D}$), 1.39 (s, CCH_3), 1.36 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 0.5 mm, 200° source temp) m/e (rel intensity) 246 (100) 245 (6), 135 (4); electron impact mass spectrum m/e (rel intensity) 245 (61), 230 (28), 152 (22), 145 (14), 136 (58), 135 (100), 134 (47), 120 (17); 118 (14); 82 (28), 80 (28).

Anal. Calcd for $C_{15}H_{20}NO_2Br$: C, 55.22; H, 6.18; N, 4.29. Found: C, 55.18; H, 5.98; N, 4.09.

***trans*-1,5,5-Trimethyl-2-hydroxy-1,2,3,4,4*a*,5,10*b*-heptahydro[1]benzopyrano[4,3-*b*]pyridine (33).**—A solution of compound **23** (2.45 g, 10 mmol) in THF (50 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (50 ml) at 0°. The suspension was stirred at room temperature for 24 hr and the reaction mixture decomposed by addition of H_2O (0.8 ml), 15% aqueous NaOH (0.8 ml), and finally H_2O (2.4 ml). After stirring an additional 2 hr, the white solid was filtered and Et_2O (100 ml) added to the filtrate. Glpc analysis (150° column temperature, N_2 flow rate 35 ml/min) of the filtrate indicated one major product with retention time 5.9 min along with trace amounts (<1%) of a material with retention time 7.1 min corresponding to the retention time of pure **37** (see below). The organic solution was extracted with 5% HCl (50 ml) and, after cooling on an ice bath the extract was adjusted to pH 11 by addition of 15% aqueous NaOH to precipitate a colorless solid (1.55 g, 63%), mp 109–110° dec. The solid was washed with water (15 ml) and air-dried. A sample obtained by removing the solvent from an Et_2O solution of this product was analytically pure: mp 110–110.5° dec; ir (KBr) 3040, 2930, 1385, 1365 [δ $C(CH_3)_2$]; nmr (recorded immediately after dissolution of **33** in $CDCl_3$) δ 8.92 (b, 1 H, observed at −65° but not at 25°), 7.30 (m, Ar), 4.72 (b, 1 H), 4.03 (b, 1 H), 2.18 (s, NCH_3), 1.98 (b, 5 H), 1.42 (s, CCH_3), 1.17 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 1.0 mm, 220° source temperature) m/e (rel intensity) 230 ($MH^+ - H_2O$, 100), 229 (47), 228 (11), 173 (11), 161 (11); electron impact mass spectrum m/e (rel intensity) 230 (15), 229 (82), 228 (14), 214 (38), 173 (11), 161 (11), 186 (10), 183 (36), 120 (13), 159 (12), 157 (27), 146 (13), 145 (100), 136 (21), 115 (13).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.18; H, 8.44; N, 5.80.

***trans*-1,2,5,5-Tetramethyl-2-hydroxy-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (38).**—A solution of CH_3-MgBr (10 ml of a 3 M solution in Et_2O, 30 mmol) was added to a stirred solution of compound **23** (2.45 g, 10 mmol) in THF (25 ml). The mixture was heated at reflux for 73 hr. After cooling, saturated aqueous NH_4Cl (25 ml) was added. The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 25 ml). Glpc analysis (190° column temp, N_2 flow rate 35 ml/min) of the combined organic phases showed only one peak with retention time 2.2 min. The combined organic phases were extracted with 5% aqueous HCl (50 ml), and the aqueous extract was cooled on an ice bath before the pH was adjusted to 12 by addition of 15% aqueous NaOH to yield a light yellow solid (2.25 g, 86%), mp 87–89° dec, which was washed with water (2 × 5 ml) and with Et_2O (5 ml) and dried over P_2O_5 at 25° (5 μ) for 2 hr: mp 87–89°; ir λ_{max}^{KBr} 3120 (broad), 2915, 1385, 1365 [δ $C(CH_3)_2$]; nmr (recorded 1 hr after dissolution of **38** during which time conversion of carbinolamine into enamine **39** was complete) δ 7.08 (m, Ar), 4.87 (m, H_E), 4.48 (b, H_2O), 3.90 (m, H_A), 2.14 (s, NCH_3), 1.92 (m, $H_{B\rightarrow D}$), 1.83 (d, J = 1 Hz, vinylic CCH_3), 1.41 (s, CCH_3), 1.12 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 2.0 mm, 220° source temp) m/e (rel intensity) 244 ($MH^+ - H_2O$, 100) 243 (59); electron impact mass spectrum m/e (rel intensity) 243 (92), 229 (19), 228 (100), 214 (25), 145 (87).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.68; H, 8.69; N, 5.43.

***trans*-1,2,5,5-Tetramethyl-1,4,4a,5,10b-pentahydro[1]benzopyrano[4,3-*b*]pyridine (39).**—The carbinolamine **38** (261.4 mg, 1 mmol) was heated in an evaporative distillation apparatus at 80° (0.2 mm) in the dark. The enamine **39** (189.1 mg, 78%) condensed on the cold finger as an oil and was stored over $CaSO_4$ at 1° in the dark: ir ($CDCl_3$) 2970, 1650 (enamine C=C), 1390, 1375 [δ $C(CH_3)_2$]; nmr δ 7.08 (m, 4 Ar), 4.87 (m, H_E, exchangeable with D_2O), 3.90 (m, H_A), 2.14 (s, NCH_3), 1.92 (m, $H_{B\rightarrow D}$), 1.83 (d, J = 1 Hz, vinylic CCH_3, exchangeable with D_2O), 1.41 (s, CCH_3), 1.12 (s, CCH_3); chemical ionization mass spectrum (methane ionizing gas, 0.5 mm, 200° source temp) m/e (rel intensity) 244 (MH^+, 18), 243 (64), 228 (100); high-resolution mass spectrum, calcd 244.1701 (MH^+), found 244.1700.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.76; H, 8.53; N, 5.74.

***trans*-1,2,5,5-Tetramethyl-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (41).**—A solution of the carbinolamine **38** (2.09 g, 8 mmol) in acetic acid (100 ml) was hydrogenated in the presence of 10% Pd/C (0.40 g) in a Parr hydrogenator (35 psi, 24 hr). The catalyst was filtered and solvent evaporated from the filtrate at 16° (0.2 mm). Aqueous NaOH (5%, 80 ml) and Et_2O (80 ml) were added to the oily residue. The organic layer was separated and the aqueous layer extracted with Et_2O (80 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated, leaving a light brown, solid residue (1.89 g, 96%), mp 87–90°. Glpc analysis (150° column temp, N_2 flow rate 37 ml/min) showed only one peak with retention time 4.4 min. The analytical sample was obtained by sublimation at 60° (0.2 mm), yielding a colorless solid: mp 91–92°; ir ($CDCl_3$) 2920, 1385, 1370 [δ $C(CH_3)_2$]; nmr δ 7.10 (4 Ar), 3.79 (d, J = 11 Hz, H_A), 3.12 (b, H_G), 1.97 (s, NCH_3), 1.90–1.25 (b, $H_{B\rightarrow F}$), 1.37 (s, C-5 CH_3), 1.18 (d, J = 7 Hz, C-2 CH_3), 1.13 (s, C-5 CH_3); chemical ionization mass spectrum (methane ionizing gas, 0.5 mm, 200° source temp) m/e (rel intensity) 246 (MH^+, 61), 245 (100), 230 (39); electron impact mass spectrum m/e (rel intensity) 245 (59), 231 (35), 230 (59), 173 (45), 162 (32), 148 (27), 145 (100), 134 (26); high-resolution mass spectrum, calcd 245.1779 (M^+), found 245.1774.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.09; H, 9.28; N, 5.63.

***trans*-1,5,5-Trimethyl-1,2,3,4,4a,5,10b-heptahydro[1]benzopyrano[4,3-*b*]pyridine (42).**—A solution of compound **23** (735.9 mg, 3 mmol) in THF (6 ml) was added dropwise to an ice-cold solution of diborane in THF (6 ml of a 1 M solution, 6 mmol). The solution was heated at reflux for 2 hr and cooled and the reaction decomposed by the dropwise addition of 6 N aqueous HCl (6 ml). After stirring for 1 hr with evolution of H_2, NaOH (2 g, pellets) was added followed by H_2O (4 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 10 ml). Glpc analysis (150° column temp, N_2 flow rate 35 ml/min) of the combined organic phases produced only one peak with retention time 7.1 min. Evaporation of solvent from the combined, dried ($MgSO_4$) organic phases left a clear, colorless, oily residue (459.8 mg, 66%). The analytical sample was prepared by evaporative distillation at 65° (10 μ): ir ($CDCl_3$) 2930, 1385, 1365, [δ $C(CH_3)_2$]; nmr δ 7.10 (m, Ar), 3.81 (d, J = 11 Hz, H_A), 3.08 (m, $H_{G,H}$), 2.18 (s, NCH_3) 1.80 (m, 3 H), 1.37 (s, CCH_3), 1.30 (m, 2 H), 1.13 (s, CCH_3); chemical ionization mass spectrum (isobutane ionizing gas, 0.5 mm, 220° source temp) m/e (rel intensity) 232 (MH^+, 100), 231 (23) 230 (9); electron impact mass spectrum 231 (100), 230 (31), 188 (19), 162 (62), 150 (21), 149 (62), 148 (87), 147 (19), 145 (44), 134 (32), 107 (21).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.95; H, 9.08; N, 5.97.

Registry No.—**10,** 1125-90-2; **11,** 37406-49-8; **12,** 37406-50-1; **13,** 37406-51-2; **14,** 37406-52-3; **15,** 37406-53-4; **16,** 37406-54-5; **17,** 37447-24-8; **18,** 37406-55-6; **21,** 37406-56-7; **22,** 37406-57-8; **23,** 37406-58-9; **24,** 37406-59-0; **25,** 37406-60-3; **26,** 37406-61-4; **28,** 37406-62-5; **30,** 37406-63-6; **31,** 37447-25-9; **33,** 37406-68-1; **38,** 37406-64-7; **39,** 37406-65-8; **41,** 37406-66-9; **42,** 37406-67-0.

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