monoxides of diethyl sulfide (*m/e* 106), ethyl allyl sulfide (*m/e* 118), and methyl allyl sulfide (*m/e* 164). More detailed analyses of the complex mixtures obtained were not attempted except with butyl disulfide, where butanethiol could easily be identified as a major product.

Flash Photolysis of Acetone–1. A 50% acetone–D_2O solution was placed in a 5-mm rectangular quartz cuvette which had been modified to accept a serum cap through which a hypodermic needle was inserted for in situ gas purging. After a 10-min purge with purified nitrogen, the solution was excited by the emission (337 nm) from a nitrogen gas laser (8-ns pulse) with a maximum energy of 5 mJ/pulse. Transient absorptions were monitored at right angles to the exciting beam. Transient lifetimes could be monitored; the photodetection equipment, digitization, and computer-controlled data acquisition and processing array have been described.[33] Under such conditions, a very short-lived transient could be observed upon monitoring at 360 nm. This transient, as might be expected if it were the acetone triplet,[34] disappeared when the solution was made 0.1 M in **1**. No new transient absorptions (of microsecond lifetime) could be detected in the 360–450 nm range in the quenched solution.

Acknowledgment. We gratefully acknowledge the financial support for this research by the Research Corporation and the Robert A. Welch Foundation. We are thankful to Dr. M. A. J. Rodgers of the University of Texas Center for Fast Kinetics Research for his assistance in the flash photolysis experiments and to Dr. James Hudson for help in the complex GC–MS analysis.

Registry No.—**1**, 544-40-1; **2**, 2168-93-6; **3**, 598-04-9; **4**, 5076-20-0; **5**, 431-03-8; **6**, 123-54-6; **7**, 626-53-9; **8**, 115-22-0; **9**, 75-07-0; **10**, 67-63-0; **11**, 76-09-5; **12**, 629-45-8; **13**, 6861-61-6; **14**, 109-79-5; **15**, 764-59-0; **16**, 1120-72-5; acetone, 67-64-1; cyclohexanone, 108-94-1; cyclohexene, 110-83-8.

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Simplified Analogues of Lysergic Acid. 6. Derivatives of 1-Methyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine

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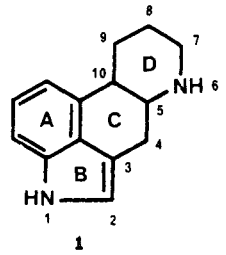
Received September 5, 1978

The synthesis of a series of simplified analogues **6–10** of the ergot alkaloids **11–15**, in which the ergoline A, B, and C rings have been replaced by the indan ring system, is described. The key intermediate, 1-methyl-3-oxo-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine (**20**), was prepared and then elaborated to the corresponding analogues of lysergol, setoclavine, isosetoclavine, lysergene, and decarboxylysergic acid. Both the primary alcohol 1-methyl-3-(hydroxymethyl)-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine (**6**) and the corresponding aldehyde (**26**), which was found to exist entirely in the enolic form, were extremely resistant to oxidation.

The naturally occurring ergot alkaloids exhibit marked central and peripheral pharmacological effects, including serotonin antagonism, vasoconstriction, oxytocic activity, and psychotropic activity.[1] These compounds have recently received considerable attention since they also inhibit the pituitary secretion of the hormone prolactin;[2,3] such activity may be useful in the treatment of human breast cancer.[4]

The ergot alkaloids may be classified into two structural groups,[1] the lysergamide alkaloids and the clavine alkaloids.



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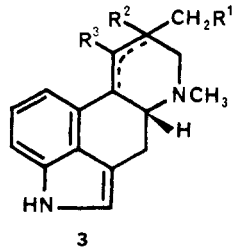

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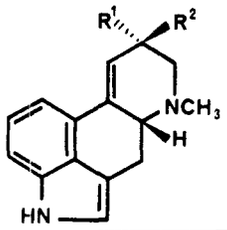
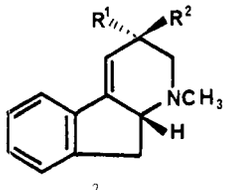
Table I. $\Delta^{9,10}$-Ergoline Derivatives



compd	R^1	R^2
lysergol (11)	H	CH_2OH
setoclavine (12)	OH	CH_3
isosetoclavine (13)	CH_3	OH
lysergene (14)		$=CH_2$
decarboxylysergic acid (15)	H	H
lysergic acid (2)	H	COOH
lysergic acid diethylamide (5)	H	$CONEt_2$

Both groups have the ergoline ring system (1) as the basis of their structure. The lysergamides are all amides of lysergic acid (2), whereas the clavine alkaloids (3) have various combinations of H and OH for R^1, R^2, and R^3 and either an 8,9 or 9,10 double bond.

The preceding paper in this series[5] described the synthesis of the simplified analogue 4 of lysergic acid diethylamide (LSD, 5) in which the ergoline A, B, and C rings have been replaced by the indan ring system. Compound 4 is highly effective in reversing guinea pig ileal contractions induced by the standard oxytocic agent ergonovine maleate.[5] In view of the pharmacological activity demonstrated by analogue 4, we now report the synthesis of the indan analogues 6–10 of the clavine alkaloids (see Table I) lysergol (11), setoclavine (12), isosetoclavine (13), lysergene (14), and of the synthetic derivative decarboxylysergic acid (15).



4: $R^1 = H$, $R^2 = CONEt_2$

6: $R^1 = H$, $R^2 = CH_2OH$

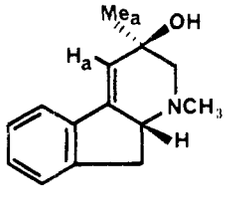
7: $R^1 = OH$, $R^2 = CH_3$

8: $R^1 = CH_3$, $R^2 = OH$

9: $R^1, R^2 = =CH_2$

10: $R^1 = R^2 = H$

30: $R^1 = H$, $R^2 = CH_2OAc$



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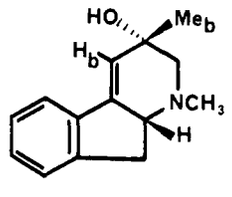

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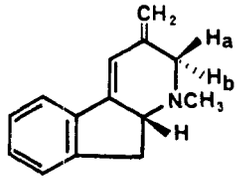

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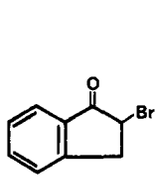
Treatment of 2-bromo-1-indanone (16) with 2 equiv of (methylamino)acetone ethylene ketal (17)[6] gave the ketal–ketone 18 in 79% yield. The hydrolysis of compound 18 to the diketone 19 was surprisingly slow,[7] requiring 24 h in 6 N HCl at 75 °C. Attempted cyclization of the diketone 19 to the tricyclic ketone 20 with sodium methoxide in methanol led only to the betaine 21, the dehydrogenation product of the desired 20.[8] The key intermediate 20 was, however, obtained in 76% yield by a modification of the method of Leemann and Fabbri,[9] allowing a solution of the hydrochloride of the ketal–ketone 18 in polyphosphoric acid to stand at room temperature for 48 h.



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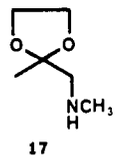

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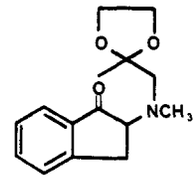

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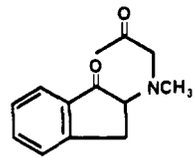

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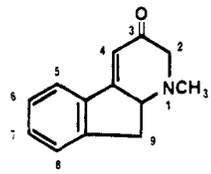

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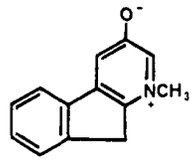

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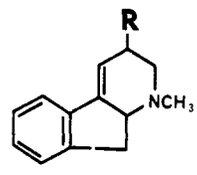


22: R = OH
23: R = Cl
24: R = OAc
26: R = CHO
29: R = COOH

Ketone 20 was reduced by sodium borohydride to the alcohol 22. Efforts to convert the hydroxyl group in 22 into a leaving group which could be displaced by cyanide ion were unsuccessful since all attempts to prepare the tosylate or mesylate of 22 or the chloride 23 failed. Although the alcohol 22 readily gave the acetate 24, the acetate could not be displaced by cyanide ion even in the presence[10] of 18-crown-6.

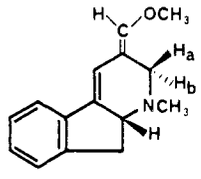
Treatment of ketone 20 with methyllithium at −78 °C afforded a 1:2 mixture (based on GLC separation and NMR integration data) of the tertiary alcohols 7 and 8, the indan analogues of setoclavine and isosetoclavine, respectively.

The structural assignments of 7 and 8 are based on the following evidence. The addition of organolithium reagents to cyclohexanones is known to occur from the least hindered direction.[11] Inspection of the Dreiding model of 20 shows that attack from the top side is hindered by the pseudoaxial C-2 and C-9a hydrogens. The opposite side of the ring has only the nitrogen lone pair in a pseudoaxial position, so that addition to the carbonyl may be expected to occur preferentially from that side. The NMR spectrum of a mixture of 7 and 8 is consistent with this conclusion. Two sets of signals are observed for the olefinic proton at 6.2 and 6.08 ppm. The signal at 6.2 ppm is assigned to proton H_a and the signal at 6.08 ppm to H_b. From Dreiding models, H_a should be farther downfield than H_b since the hydroxyl group in 8 (major product) is pseudoequatorial and therefore closer to proton H_a than the pseudoaxial hydroxyl group is to proton H_b. Separate signals also appear for the C-3 methyl groups at 1.74 and 1.60 ppm. The signal at 1.6 ppm is assigned to $(CH_3)_a$ and the signal at 1.74 ppm to $(CH_3)_b$ since $(CH_3)_a$ is pseudoaxial and thus far-

ther out of the deshielding plane of the neighboring double bond than the pseudoequatorial $(CH_3)_b$. The separation of **7** and **8** was not undertaken.

The indan analogue **9** of lysergene (**14**) was obtained in 73% yield from ketone **20** via a Wittig reaction with the ylide generated from methyltriphenylphosphonium bromide. As is characteristic of the NMR spectra of the few clavine alkaloids which have been examined,[12,13] the C-2 protons are nonequivalent and appear as an AB quartet with a geminal coupling constant of J = 14 Hz. By analogy with the natural products, the downfield doublet at 3.5 ppm is assigned to the pseudoequatorial H_b proton and the upfield doublet at 3.25 ppm to the pseudoaxial H_a proton.

Similarly, ketone **20** reacted with the ylide from (methoxymethyl)triphenylphosphonium chloride to give the enol ether **25**. A comparison of the NMR spectrum of **25** with that of the



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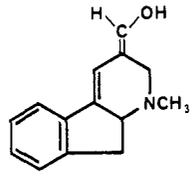

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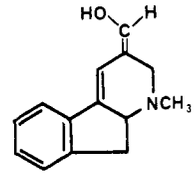


28

methylene compound **9** suggests that the methoxyl group is cis to the C-2 protons. Protons H_a and H_b again appear as an AB quartet. The pseudoequatorial H_b proton is displayed at 3.9 ppm and is deshielded by 0.4 ppm with respect to its position in the NMR spectrum of **9** due to the proximate methoxyl group. The IR spectrum shows the typical enol $-C{=}C-O-$ absorption at 1650 cm^{-1}.

As in the case of the ketal **18**, the enol ether **25** was hydrolyzed at an unexpectedly slow rate with 6 N HCl at room temperature for 24 h. Although the product was shown by high-resolution mass spectrometry to have the molecular formula $C_{14}H_{15}NO$ expected for the aldehyde **26**, spectral evidence suggests that the aldehyde exists as a mixture of the enols **27** and **28**. The IR spectrum shows no carbonyl absorbance; however, there is a 3300-cm^{-1} hydroxyl band and a strong absorbance at 1650 cm^{-1} (—C=C—O—) which is also prominent in the IR spectrum of the enol ether **25**. The UV spectrum [λ_{max} 233, 238 (log ϵ 4.00), 298 (4.18), and 317 (4.24)] closely resembled that of the enol ether **25** [λ_{max} 230, 235 (log 3.95), 295 (4.24), and 314 (4.34) nm], indicating the presence of the same chromophore. The compound showed no carbonyl reactions. No aldehyde proton was observed between 9 and 11 ppm in the NMR spectrum. Four signals appear between 6.9 and 7.3 ppm due to the two olefinic protons in the isomers **27** and **28**. Doublets at 6.8 and 7.3 ppm, showing allylic coupling (J = 2 Hz) to the C-9a proton, are assigned to the C-4 protons in **27** and **28**, respectively (the latter further downfield due to deshielding by the OH group). Singlets at 7.0 and 7.2 ppm are assigned to the C-9a protons in **28** and **27**, respectively (the latter at lower field since it is in the deshielding plane of the 4,4a double bond).

A variety of attempts were made to oxidize the mixture of enols **27** and **28** to the indan analogue **29** of lysergic acid. Treatment of the **27**–**28** mixture with silver(I) or silver(II) oxide in neutral medium or with Jones reagent gave no reaction. Silver(I) or silver(II) oxide in basic solution caused only decomposition.

In order to determine whether the enolic nature of the aldehyde was responsible for its resistance to oxidation, the indan analogue **6** of lysergol (**11**) was prepared to attempt its oxidation. The exocyclic double bond in compound **9** was selectively hydroborated with 9-BBN to give the analogue **6**, which appeared to be a single epimer at C-3 by NMR (one doublet at 3.6 ppm observed for the hydroxymethyl protons) and chromatography (TLC, GLC). We formulate this product

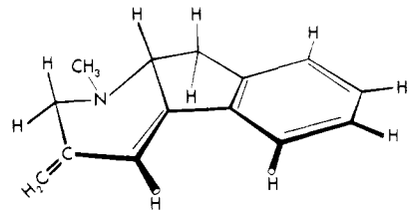
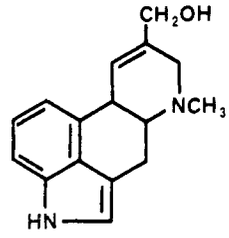


Figure 1. Dreiding model of compound **9**.

as the epimer with the hydroxymethyl group and the C-9a hydrogen syn. Studies on the hydroboration of methylenecyclohexanones[14] have shown that the borane adds to the double bond on the least hindered side. Since the methylene moiety in **9** (see Figure 1) occupies a steric environment identical with that of the carbonyl in **20**, in which addition from the top side is hindered by the C-2 and C-9a hydrogens, the hydroboration product must be epimer **6**. The 9-BBN has therefore added to **9** from the same direction as the methyl group in the major product of methyllithium addition to the ketone **20**. The alcohol **6** was converted to the acetate, **30**, NMR and GLC again indicating a single epimer.

Several attempts were made to oxidize the alcohol **6** to the acid **29** or the aldehyde **26**. The reagents used included silver(I) or silver(II) oxide in alkaline or neutral medium, Jones reagent, pyridinium chlorochromate, and chromium trioxide in acetic acid. In all cases no reaction occurred. These results are in accord with the report by Floss et al.[15] that the hydroxymethyl group in elymoclavine (**31**) is extremely resistant



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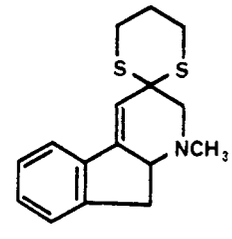

32

to the usual oxidizing agents.

Following the report by Kornfeld et al.[16] that decarboxylysergic acid (**15**) has interesting pharmacological properties, the propylene dithioketal **32** was prepared by treating ketone **20** with 1,3-propanedithiol and BF_3 etherate in nitromethane. Raney nickel desulfurization of compound **32** gave the indan analogue **10** of decarboxylysergic acid (**15**). Deactivation of the Raney nickel by refluxing it in acetone was necessary to prevent hydrogenation of the double bond to give the dihydro compound of **10**.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The 60-MHz NMR spectra were recorded on a Perkin-Elmer R12B instrument and the 100-MHz NMR spectra were taken on a Varian XL-100-15 instrument. Me_4Si was used as an internal standard in organic solvents, and sodium (trimethylsilyl)propanesulfonate (TMSP) was used in D_2O. IR spectra were recorded on a Perkin-Elmer 337 instrument. UV spectra were taken on a Cary 14 spectrometer. The electron impact mass spectra were obtained on an AEI MS-12 instrument at 70 eV, and the chemical ionization mass spectra were obtained on an AEI MS-902 instrument modified for chemical ionization using isobutane as the reagent gas. GLC analyses were performed on a Varian Aerograph Model 2100 gas chromatograph with a 6-ft U-shaped Pyrex column packed with 3% SE-30 on Chromosorb W. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley. Solutions were dried over $MgSO_4$.

2-[Methyl[(2-methyl-1,3-dioxolan-2-yl)methyl]amino]-indan-1-one Hydrochloride (18 HCl). A mixture of 21.0 g (0.10 mol)

of 2-bromo-1-indanone (**16**) and 33.0 g (0.25 mol) of (methylamino)-acetone ethylene ketal in 500 mL of dry benzene was refluxed for 17 h with a slow stream of nitrogen bubbling through the solution. The reaction mixture was cooled to 5 °C, and 17.6 g (83%) of (methylamino)acetone ethylene ketal hydrobromide was filtered off. The filtrate was washed with 500 mL of cold H_2O and extracted with 500 mL of cold 2 M HCl. The acid layer was basified to pH 9 with cold concentrated ammonium hydroxide, and the solution was extracted with benzene. The benzene was dried, filtered, and acidified with Et_2O–HCl. The solvents were removed in vacuo to yield a light grey solid. Recrystallization from EtOH–Et_2O afforded the hydrochloride of **18** (23 g, 79%): mp 172–174 °C dec; IR (KBr) 2500 (N^+H), 1725 (C=O) cm^{-1}; NMR (60 MHz, pyridine-d_5) δ 7.8–7.25 (m, 4, aromatic H), 4.05 (t, 1, J = 7 Hz, C-2 H), 3.9 (s, 4, OCH_2CH_2O), 3.35–3.1 (m, 2, C-3 H), 2.9 (s, 2, CH_2NCH_3), 2.6 (s, 3, NCH_3), 1.5 (s, 3, CH_3COO).

Anal. Calcd for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.77; N, 4.70. Found: C, 60.12; H, 6.64; N, 4.98.

2-(*N*-Methyl-*N*-acetonylamino)-1-indanone Hydrobromide (19 HBr). A solution of 2.0 g (7 mmol) of the hydrochloride of the ketal **18** in 20 mL of 48% HBr and 20 mL of H_2O was heated at 75 °C for 24 h under N_2. The mixture was filtered to remove a small amount of precipitate, and the filtrate was lyophilized. The resultant powder was crystallized from EtOH–Et_2O to yield the hydrobromide of **19** (1.6 g, 79%): mp 184–186 °C dec; IR (KBr) 2500 (N^+H), 1725 (aliphatic C=O), 1710 (indanone C=O) cm^{-1}; NMR (D_2O, 60 MHz) δ 7.9–7.1 (m, 4, aromatic H), 4.6 (m, 1, C-2 H), 3.8 (s, 2, NCH_2), 3.3–3.1 (m, 2, C-3 H), 2.5 (s, 3, NCH_3), 2.35 (s, 3, CH_3CO).

Anal. Calcd for $C_{13}H_{16}BrNO_2$: C, 52.37; H, 5.41; N, 4.69. Found: C, 51.94; H, 5.28; N, 4.92.

A portion of the hydrobromide was dissolved in H_2O and double decomposed with aqueous lithium picrate to yield the picrate of **19**. Recrystallization from EtOH afforded an analytical sample, mp 148 °C dec.

Anal. Calcd for $C_{19}H_{18}N_4O_9$: C, 51.12; H, 4.06; N, 12.55. Found: C, 51.03; H, 4.22; N, 12.61.

1-Methyl-3-hydroxy-9*H*-indeno[2,1-*b*]pyridinium Picrate (21 Picrate). A solution of 0.54 g (0.01 mol) of sodium ethoxide in 10 mL of dry EtOH was added dropwise with stirring to a suspension of 0.6 g (2 mmol) of the hydrobromide of the diketone **19** in 20 mL of dry EtOH under N_2 while maintaining the temperature at −30 to −25 °C with a dry ice–acetone bath. The reaction mixture was warmed to −10 °C for 15 min and recooled to −25 °C, and 5 mL of H_2O was added to decompose the excess NaOEt. The solution was poured into 50 mL of H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with H_2O, dried, and evaporated to give a dark oil. The oil was dissolved in EtOH, and a saturated solution of picric acid in EtOH was added. The picrate was collected (0.55 g, 63%) and recrystallized from EtOH–Et_2O: mp 225 °C dec; NMR (60 MHz, Me_2SO-d_6) δ 8.6 (s, 2, picric acid H), 7.7–7.4 (m, 6, aromatic H), 4.35 (s, 5, NCH_3 and C-9 H); chemical ionization mass spectrum, M_r 197 (free base) (calcd for $C_{13}H_{11}NO$, 197).

Anal. Calcd for $C_{19}H_{14}N_4O_8$: C, 53.53; H, 3.31; N, 13.14. Found: C, 53.46; H, 3.53; N, 12.84.

1-Methyl-3-oxo-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine Hydrochloride (20 HCl). A solution of 8.0 g (28 mmol) of the hydrochloride of the ketal **18** in 70 mL of nitromethane was added to 125 g of 85% polyphosphoric acid. The mixture was allowed to stand at room temperature for 48 h with a slow stream of N_2 bubbling through. Ice was added to decompose the PPA, and the pH was adjusted to 9 with concentrated ammonium hydroxide while keeping the temperature of the solution below 10 °C. The mixture was extracted with $CHCl_3$. The $CHCl_3$ was dried and evaporated to yield the ketone **20** as a red oil (crude yield 5.0 g, 90%): IR (liquid film) 1660 (C=O), 1640 (C=C) cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 7.5 (m, 4, aromatic H), 6.3 (d, 1, J = 1.5 Hz, C-4 H), 3.7–2.6 (m, 5, methylene and methine H), 2.5 (s, 3, NCH_3).

The oil was taken up in dry Et_2O and acidified with Et_2O–HCl solution. The solvent was removed in vacuo, and recrystallization of the resultant solid afforded the hydrochloride of **20** (5.0 g, 76%): mp 265 °C dec; IR (KBr) 2500 (N^+H), 1660 (C=O), 1640 (C=C) cm^{-1}; NMR (60 MHz, Me_2SO-d_6) δ 8.0–7.5 (m, 4, aromatic H), 6.75 (s, 1, olefinic H), 4.9 (t, 1, J = 6 Hz, C-9a H), 4.1 (s, 1, C-2 H), 3.5 (d of d, 2, J = 10, 6 Hz, C-9 H), 3.0 (s, 3, HCH_3); chemical ionization mass spectrum, M_r 199 (free base) (calcd for $C_{13}H_{13}NO$, 199).

Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; Cl, 15.04. Found: C, 65.88; H, 6.23; Cl, 14.78.

1-Methyl-3-hydroxy-1,2,3,9a-tetrahydro-9*H*-indeno-[2,1-*b*]pyridine Hydrochloride (22 HCl). To a stirred suspension of 1.88 g (8 mmol) of the hydrochloride of the ketone **20** in 50 mL of absolute EtOH at 5 °C was added dropwise a solution of 0.76 g (20 mmol) of $NaBH_4$ in 40 mL of absolute EtOH. The mixture was stirred at room temperature for 4 h and then poured into 300 mL of H_2O. The pH was adjusted to 9 with concentrated ammonium hydroxide and the solution extracted with Et_2O. The Et_2O was dried, filtered, and acidified with Et_2O–HCl solution. After the solvent was removed, recrystallization of the resultant solid gave the hydrochloride of the alcohol **22** (1.5 g, 79%): mp 198 °C dec; IR (KBr) 3300 (OH), 2600 (N^+H) cm^{-1}; NMR (60 MHz, Me_2SO-d_6) δ 7.6–7.2 (m, 4, aromatic H), 6.25 (s, 1, olefinic H), 5.0 (broad s, 1, exchangeable H), 4.5 (m, 1, CHOH), 3.8–2.9 (m, 5, methylene and methine H), 2.9 (s, 3, NCH_3).

Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; Cl, 14.91. Found: C, 65.42; H, 6.61; Cl, 14.96.

1-Methyl-3-acetoxy-1,2,3,9a-tetrahydro-9*H*-indeno-[2,1-*b*]pyridine Hydrochloride (24 HCl). A solution of 0.8 g (4 mmol) of the alcohol **22** (free base) in 25 mL of acetic anhydride was stirred at room temperature for 24 h. The reaction mixture was poured into 50 mL of H_2O, and the solution was basified to pH 9 with concentrated ammonium hydroxide. The solution was extracted with $CHCl_3$. The $CHCl_3$ was dried, filtered, and acidified with Et_2O–HCl. After the Et_2O was removed in vacuo, the resultant solid was washed with cold acetone to remove the light purple color. Recrystallization from absolute EtOH gave 0.8 g (73%) of the hydrochloride of **24**: mp 177 °C dec; IR (KBr) 2500 (N^+H), 1745 (C=O) cm^{-1}; NMR (100 MHz, D_2O) δ 7.2 (s, 4, aromatic H), 5.8 (broad s, 1, olefinic H), 5.8 (m, 1, CHOAc), 3.5–2.5 (m, 5, methylene and methine H), 2.5 (s, 3, NCH_3), 2.05 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.49; Cl, 12.67. Found: C, 64.13; H, 6.56; Cl, 12.58.

1,3-Dimethyl-3-hydroxy-1,2,3,9a-tetrahydro-9*H*-indeno-[2,1-*b*]pyridine Hydrochloride (7 HCl and 8 HCl Mixture). To a solution of 1.0 g (5 mmol) of the ketone **20** (free base) in 50 mL of dry Et_2O at −70 °C under N_2 was added dropwise 6.5 mL of 1.56 M methyllithium in ether with stirring. The reaction mixture was allowed to warm to room temperature and stirred for an additional 20 min. After the solution was recooled to −50 °C, 2 mL of H_2O was added. The Et_2O was dried, filtered, and acidified with Et_2O–HCl. The solvent was evaporated, and the residue was recrystallized from absolute EtOH to give a mixture of the hydrochlorides of **7** and **8** (0.9 g, 65%): mp 255 °C dec; IR (KBr) 3350 (OH), 2600 (N^+H) cm^{-1}; NMR (100 MHz, D_2O) δ 7.3 (m, 4, aromatic H), 6.2 (s, 2/3, olefinic H in **8**), 6.08 (d, 1/3, J = 2 Hz, olefinic H in **7**), 4.0–2.6 (m, 5, methylene and methine H), 3.2 (s, 3, NCH_3), 1.75 (s, 1, tertiary CH_3 in **7**), 1.6 (s, 2, tertiary CH_3 in **8**).

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.80; H, 7.21; Cl, 14.08. Found: C, 66.61; H, 7.22; Cl, 14.02.

1-Methyl-3-methylene-1,2,3,9a-tetrahydro-9*H*-indeno-[2,1-*b*]pyridine Hydrochloride (9 HCl). To a suspension of 3.6 g (10 mmol) of methyltriphenylphosphonium bromide in 80 mL of dry THF was added dropwise with stirring 5 mL (10 mmol) of 2 M *n*-butyllithium in hexane under N_2. After 10 min at room temperature, the solid dissolved and ylide formation was evident by the orange color of the solution. A solution of 1.4 g (7 mmol) of the ketone **20** (free base) in 40 mL of dry THF was added dropwise, and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into 200 mL of H_2O and extracted with Et_2O. The Et_2O was dried, filtered, and acidified with Et_2O–HCl. After the solvent was removed in vacuo, the resultant solid was crystallized from nitromethane to yield the hydrochloride of **9** (1.2 g, 73%): mp 260 °C dec; IR (KBr) 2500 cm^{-1} (N^+H); NMR (60 MHz, D_2O) δ 7.6 (s, 4, aromatic H), 6.8 (s, 1, olefinic H), 5.6 (s, 2, $C=CH_2$), 4.4–3.5 (m, 5, methylene and methine H), 3.3 (s, 3, NCH_3).

Anal. Calcd for $C_{14}H_{16}ClN$: C, 71.94; H, 6.90; Cl, 15.17. Found: C, 71.68; H, 6.82; Cl, 14.94.

The free base was liberated to give the following NMR spectrum (100 MHz, $CDCl_3$): δ 7.5–7.2 (m, 4, aromatic H), 6.5 (s, 1, C-4 H), 4.9 (m, 2, $C=CH_2$), 3.5 (d, 1, J = 14 Hz, equatorial C-2 H), 3.25 (d, 2, J = 14 Hz, axial C-2 H), 3.1–2.8 (m, 3, methylene and methine H), 2.45 (s, 3, NCH_3).

1-Methyl-3-(methoxymethylene)-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine Hydrochloride (25 HCl). To a suspension of 4.1 g (12 mmol) of (methoxymethyl)triphenylphosphonium chloride in 50 mL of dry THF at room temperature under N_2 was added dropwise 6 mL (12 mmol) of 2.0 M *n*-butyllithium in hexane with stirring. After 1 h, the mixture was cooled to −30 °C and 1.5 g (7.5 mmol) of the ketone **20** (free base) in 50 mL of dry THF was added dropwise. The solution was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was poured into 200 mL of H_2O and extracted with $CHCl_3$. The $CHCl_3$ was dried, filtered, and acid-

ified with Et_2O–HCl. After the solvents were removed in vacuo, the residue was triturated with 250 mL of dry THF. The solid which did not dissolve was collected and crystallized from absolute EtOH to give the hydrochloride of **25** (1.9 g, 90%): mp 295 °C dec; IR (KBr) 2500 (N^+H), 1650 (C=C) cm^{-1}; NMR (60 MHz, D_2O) δ 7.3–7.7 (m, 5, aromatic H and C=CHOCH$_3$), 6.5 (s, 1, C-4 H), 4.5–3.0 (m, 5, methylene and methine H), 3.7 (s, 3, OCH_3), 3.0 (s, 3, NCH_3); UV (95% EtOH) λ_{max} (log ϵ) 230, 235 (3.95), 295 (4.24), 314 (4.34) nm.

Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; Cl, 13.44; Found: C, 68.12; H, 6.95; Cl, 13.41.

The free base was liberated and gave the following NMR spectrum (100 MHz, $CDCl_3$): δ 7.2–7.0 (m, 4, aromatic H), 6.3 (d, 1, J = 2 Hz, C-4 H), 6.05 (s, 1, C=CHOCH$_3$), 3.9 (d, 1, J = 15 Hz, equatorial C-2 H), 3.6 (s, 3, OCH_3), 3.2 (d, 1, J = 15 Hz, axial C-2 H), 3.3–2.6 (m, 3, methylene and methine H), 2.4 (s, 3, NCH_3).

1-Methyl-3-(hydroxymethylene)-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine Hydrochloride (27 HCl and 28 HCl Mixture). The enol ether hydrochloride **25** HCl (250 mg, 1 mmol) was dissolved in 25 mL of H_2O, and 25 mL of concentrated HCl was added slowly with stirring. The mixture was heated at 75 °C for 5 min to redissolve a small amount of precipitate and then cooled to room temperature and stirred under N_2 for 24 h. The reaction mixture was lyophilized to give a mixture of the enols **27** and **28** as their hydrochloride salts (250 mg, 98%). The product was obtained as a colorless amorphous solid which decomposed upon heating: IR (KBr) 3300 (OH), 2500 (N^+H), 1650 (C=C) cm^{-1}; NMR (100 MHz, D_2O) δ 7.6 (m, 4, aromatic H), 7.3–6.9 (m, 2, C-4 H and C=CHOH), 5.0–2.4 (m, 5, methylene and methine H), 2.4 (s, 3, NCH_3); UV (95% EtOH) λ_{max} (log ϵ) 233, 238 (4.0), 298 (4.18), 317 (4.24) nm; mass spectrum, exact mass 213.1152 (calcd for $C_{14}H_{15}NO$, 213.1150).

1-Methyl-3-(hydroxymethyl)-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine Hydrochloride (6 HCl). A solution of 1.5 g (7.5 mmol) of the methylene compound **9** (free base) in 40 mL of dry THF was added dropwise to a stirred solution of 50 mL (25 mmol) of 0.5 M 9-BBN in THF under N_2. The mixture was stirred for 6 h at room temperature. The excess 9-BBN was decomposed by adding 5 mL of H_2O dropwise. The organoborane intermediate was oxidized by adding 8.5 mL of 3 N NaOH, followed by the slow dropwise addition of 6 mL of 30% hydrogen peroxide at a rate such that the temperature did not rise above 50 °C. The mixture was heated at 40 °C for 1 h and then poured into 50 mL of H_2O. The solution was extracted with $CHCl_3$. The $CHCl_3$ was dried, filtered, and acidified with Et_2O–HCl. The solvents were removed in vacuo, and the residue was crystallized from nitromethane to yield the hydrochloride salt of the alcohol **6** (1.5 g, 80%): mp 185 °C dec; IR (KBr) 3300 (OH), 2500 (N^+H) cm^{-1}; NMR (free base) (60 MHz, $CDCl_3$) δ 7.3 (m, 4, aromatic H), 5.95 (s, 1, olefinic H), 3.65 (d, 2, J = 6 Hz, CH_2OH), 3.5–2.8 (m, 7, methylene and methine H and OH), 2.5 (s, 3, NCH_3).

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.80; H, 7.21; Cl, 14.08. Found: C, 66.59; H, 7.03; Cl, 14.28.

1-Methyl-3-(acetoxymethyl)-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine Hydrochloride (30 HCl). A solution of 220 mg (1 mmol) of the alcohol **6** (free base) in 25 mL of acetic anhydride was stirred at room temperature for 18 h under N_2. The excess anhydride was decomposed with ice, and the pH was adjusted to 9 with concentrated ammonium hydroxide. The solution was extracted with $CHCl_3$. The $CHCl_3$ was washed with saturated aqueous $NaHCO_3$, dried, and filtered. The filtrate was acidified with Et_2O–HCl and the solvents were evaporated. The resultant solid was crystallized from acetone to give the hydrochloride salt of the acetate **30** (200 mg, 78%): mp 210 °C dec; IR (KBr) 2400 (N^+H), 1740 (C=O) cm^{-1}; NMR (free base) (60 MHz, $CDCl_3$) δ 7.4 (m, 4, aromatic H), 6.0 (s, 1, olefinic H), 4.25 (d, 2, J = 6 Hz, CH_2OAc), 3.5–2.8 (m, 6, methylene and methine H), 2.5 (s, 3, NCH_3), 2.2 (s, 3, O_2CCH_3).

Anal. Calcd for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86; Cl, 12.07. Found: C, 65.52; H, 6.98; Cl, 11.79.

1-Methyl-3-oxo-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine 1,3-Propylene Dithioketal (32 HCl). A solution of 2.0 g (10 mmol) of the ketone **20** (free base), 2.2 g (20 mmol) of 1,3-propanedithiol, and 2 mL of freshly distilled BF_3·Et_2O in 20 mL of nitromethane was stirred for 4 days at room temperature under N_2 (reaction progress monitored by GLC). The reaction mixture was poured into 100 mL of H_2O, and the solution was basified to pH 9 with concentrated ammonium hydroxide. The solution was extracted with $CHCl_3$, and the $CHCl_3$ was dried and evaporated to give the dithioketal **32** as a red oil (0.5 g, 80%): NMR (free base) (100 MHz, $CDCl_3$) δ 7.5–7.2 (m, 4, aromatic H), 6.05 (s, 1, olefinic H), 3.6 (d, 1, J = 14 Hz, equatorial C-2 H), 2.8 (d, 1, J = 14 Hz, axial C-2 H), 3.3–2.0 (m, 9, methylene and methine H), 2.6 (s, 3, NCH_3).

The oil was dissolved in Et_2O and the Et_2O acidified with Et_2O–HCl. After the solvent was removed in vacuo, the resultant solid was crystallized from absolute EtOH to give the hydrochloride salt of the dithioketal **32**, mp 235 °C dec.

Anal. Calcd for $C_{16}H_{20}ClNS_2$: C, 58.61; H, 6.15; S, 19.56. Found: C, 58.41; H, 6.25; S, 19.34.

1-Methyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]pyridine Picrate (10 Picrate). To a solution of the dithioketal **32** (free base) (1.0 g, 3.5 mmol) in 50 mL of acetone at 5 °C was added 10 g of W-2 Raney nickel which had been heated in refluxing acetone for 2 h prior to use. The mixture was stirred at 5 °C for 3 h under N_2. The catalyst was filtered off and washed with acetone. The combined acetone filtrate and washings were treated with Norit, and the solvent was evaporated. The desulfurized product **10** was obtained as a red oil (0.5 g, 80%): NMR (free base) (100 MHz, $CDCl_3$) δ 7.7–7.2 (m, 4, aromatic H), 6.0 (m, 1, olefinic H), 3.2–1.5 (m, 7, methylene and methine H), 2.4 (s, 3, NCH_3).

The oil was dissolved in EtOH, and a saturated solution of picric acid in EtOH was added. The picrate of **10** was collected and recrystallized from EtOH, mp 222–225 °C dec.

Anal. Calcd for $C_{19}H_{18}N_4O_7$: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.34; H, 4.73; N, 15.43.

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Registry No.—**6**, 68950-37-8; **6** HCl, 68950-38-9; **7** HCl, 68950-39-0; **8** HCl, 68950-40-3; **9**, 68950-41-4; **9** HCl, 68950-42-5; **10**, 68950-43-6; **10** picrate, 68950-44-7; **16**, 68950-45-8; **17**, 4388-98-1; **18** HCl, 68950-46-9; **19** HBr, 68950-47-0; **19** picrate, 68950-49-2; **20**, 68950-50-5; **20** HCl, 68950-51-6; **21**; 68950-52-7; **21** picrate, 68950-53-8; **22**, 68950-54-9; **22** HCl, 68950-55-0; **24** HCl, 68950-56-1; **25**, 68950-57-2; **25** HCl, 68950-58-3; **27** HCl, 68950-59-4; **28** HCl, 68950-60-7; **30** HCl, 68950-61-8; **32**, 68950-62-9; **32** HCl, 68950-63-0; 1,3-propanedithiol, 109-80-8.

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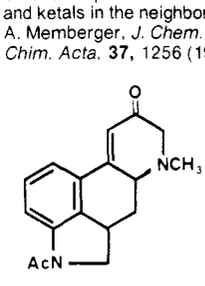

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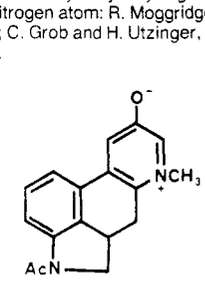

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