Synthesis of Insect Trail Pheromones: The Isomeric 3-Butyl-5-Methyloctahydroindolizines

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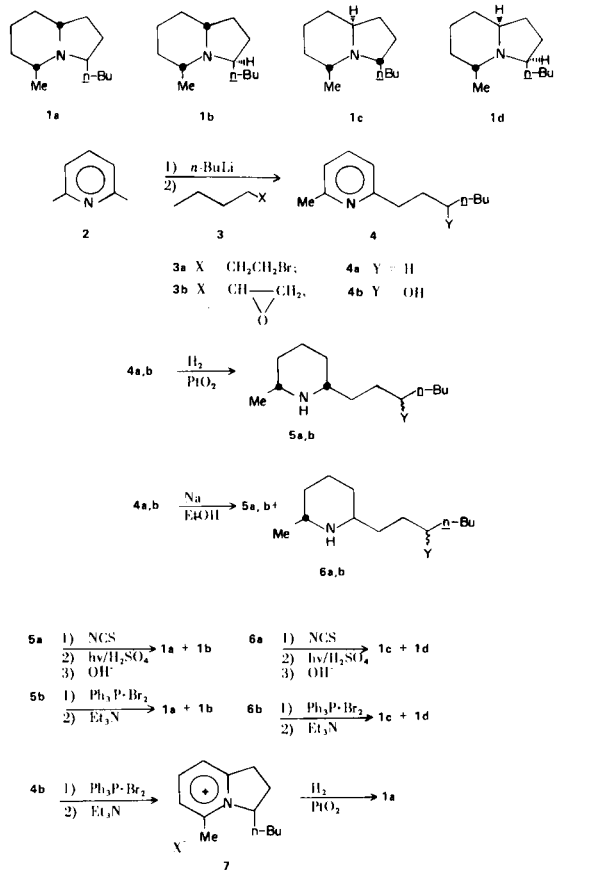
The syntheses of the geometrical isomers of 3-butyl-5-methyloctahydroindolizine are described. These compounds, reported as trail pheromones of Pharaoh ants, *Monomorium pharaonis* (L.), cannot be distinguished from each other by physical data alone and assignments must therefore be based on unambiguous synthesis. Routes to these compounds *via* suitably constituted dialkylpiperidines and a sequence involving a dialkylpyrrole are described. Infrared and nmr spectral data are presented. These data are examined for their potential in conformational analyses of these compounds.

Investigations of the chemical constitution of insect secretions that play a part in insect communication have uncovered some of the most biologically active substances known (1). To date, most of this interest has been focused on sex pheromones, but an equally fascinating (and chemically more intriguing) class of pheromones, namely trail markers, is rapidly becoming of interest. Only a few have been identified: a pyrrolic material from the Texas leafcutting ant *Atta texana* (Buckley) (2); a diterpene from a termite, *Nasutitermes exitiosus* (Hill) (3), a straight chain trienol from the eastern subterranean termites, *Reticulitermes flavipes* (Kollar) and *R. virginicus* (Kollar) (4), and a series of alkanoic acids from the ant, *Lasius fuliginosus* (Kollar) (5). Most recently, Ritter and coworkers isolated and identified a 3-butyl-5-methyloctahydroindolizine as a trail marker of the Pharaoh ant, *Monomorium pharaonis* (L.) (6). The pharaoh ant is a serious pest, particularly in hospitals, and established infestations are difficult to control with insecticides (6). The availibility of a trail pheromone could be very useful not only to monitor new infestations, but also to control existing ones by disrupting communications between worker ants and their nests which contain queens, larvae, and pupae. Unfortunately, only the gross structure of the pheromone was established; which of the four possible geometrical isomers (**1a-d**) is the natural product was not known. Furthermore, a convenient synthesis of **1a-d**, even as a mixture, had not been developed. We therefore undertook syntheses of **1a-d** that would permit isolation, characterization, and ultimately independent biological evaluation of each isomer. A successful approach to **1a-d** was outlined in a preliminary communication (7); this paper describes our total effort including experimental details, physical and ir spectral properties of the isomers, and a second (Hoffman-Loffler) synthetic approach.

Scheme I



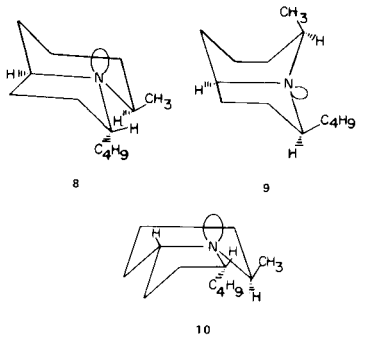
The Hofmann-Loffler reaction (8) is an historically important method of synthesizing both mono- and bicyclic pyrrolidines. Thus cyclization of a 2-heptyl-6-methylpiperidine (**5a** or **6a**) should give the gross structure **1**. This route seemed particularly attractive since the readily available 2,6-lutidine **2** would serve as a precursor of **5a** and **6a**. Indeed **5a** was easily synthesized by alkylating the lithium salt of **2** with 1-bromohexane and hydrogenating the resulting 2-heptyl-6-methylpyridine **4a** (Scheme 1).

The *trans*-dialkylpiperidine **6a** was more difficult to obtain. Sodium and ethanol reduction of **4a** gave a mixture of **5a** and **6a** with **5a** predominating by *ca.* 4:1; this predominance of the *cis* isomer is in agreement with the results of Hill *et al.*, (9) on the sodium/ethanol reduction of 2,6-lutidine. Reduction of **4a** with lithium in ethylenediamine gave **5a** plus some side products, but none of the desired *trans* isomer **6a**. A few attempts to effect epimerization of **5a** by heating it to 180-200° in the presence of platinum oxide were also unsuccessful. Fortunately, we were able to separate the sodium/ethanol mixtures of **5a** and **6a** by spinning band distillation.

The conditions we chose for the Hofmann-Loffler cyclizations were chlorination with *N*-chlorosuccinimide (NCS) in ether, photolysis of the resulting *N*-chloramines in concentrated sulfuric acid, and finally neutralization of the sulfuric acid with sodium hydroxide. This method did provide *ca.* 1:1 mixtures of **1a** and **1b** from **5a**, and **1c** and **1d** from **6a**; however, the yield of distilled material in each case was *ca.* 25%. Furthermore, the products were contaminated with what may have been alkenyl piperidines or possible quinolizidines though this point was not investigated in detail. In principal, elimination products, being secondary amines, should be separable from **1a-d** *via* the Hinsburg procedure. Treatment of our reaction products with benzenesulfonyl chloride as described by Corey (8) was completely without effect; however, the nitrogens of the 2,6-dialkylpiperidines are very hindered, and the Hinsburg separation is probably of little value in these cases. Thus, although all four isomers were obtainable by this route, the separation problems coupled with the low proportion of *trans*-2-heptyl-6-methylpiperidine available from reduction of the pyridine **4a** prompted us to investigate functionalization of the heptyl side chain at an earlier stage in the synthesis.

Accordingly, 2,6-lutidine anion (Scheme 1) was treated with 1,2-epoxyhexane to give the alcohol **4b**. This compound could be cyclized by first heating it with hydrogen bromide, isolating the bromoalkylpyridine (probably contaminated with alkenylpyridines), and then heating the base in acetone with sodium iodide to produce the dihydroindolizinium iodide **7** (X = I) in 25% overall yield. We also obtained **7** by generating the alkoxide ion of alcohol **4b** and allowing it to react with *p*-toluenesulfonyl chloride and sodium iodide in THF-HEMPA. The yield was somewhat higher in this case, but again elimination appeared to compete with the desired displacement. We then found that treatment of the hydrobromide salt of alcohol **4b** with triphenylphosphine and bromine in acetonitrile, followed by refluxing the free base of the resulting bromide in acetone provided **7** in 55% yield (isolated as the iodide). This process should prove superior to the HBr method generally employed for such cyclizations (9), particularly with secondary alcohols.

Scheme 2



8 9 10

Hydrogenation of the salt **7** gave the all *cis* (7) 3-butyl-5-methyloctahydroindolizine, **1a**.

The *cis*-piperidyl alcohols **5b** were then prepared by hydrogenation of the pyridyl alcohol **4b**. Treatment of **5b** with triphenylphosphine dibromide gave a 1:1 mixture of octahydroindolizines **1a** and **1b**. These were separated by spinning band distillation.

Reduction of **4b** with sodium/ethanol produced a mixture of **5b** and the *trans*-piperidyl alcohol **6b** in which **5b** predominated by 4:1. Fractional crystallization of an acetonitrile solution of the mixture provided two crops of pure **5b** and enriched the mother liquor in the *trans*-piperidyl alcohol **6b** to *ca.* 1:1. Spinning band distillation achieved final purification of **6b**. Alcohol **6b** was then cyclized with triphenylphosphine dibromide to a mixture of octahydroindolizines **1c** and **1d**, which, in turn, were also separated by spinning band distillation. Attempts to separate pairs of octahydroindolizines by fractional crystallization of their hydroiodides or picrates were only partially successful.

During an investigation of orchidaceae alkaloids, Luning and Lundin (10) synthesized and separated the racemates of 5,7-dimethyloctahydroindolizine. The infrared spectra of these compounds exhibited marked differences in Bohlman band intensities which, in concert with nmr data, aided materially in the structural assignments. Bohlman bands occur at 2700-2800 cm^{-1} and were originally discovered in quinolizidines that have one or more α-hydrogens oriented *trans*-biaxially to the nitrogen lone

pair (11). That Bohlman's criteria for *trans*-quinolizidines were applicable to octahydroindolizines was demonstrated by Theobald and Lingard (12) who compared the spectrum of octahydroindolizine (containing Bohlman bands) to that of dihydro-β-erythroidine (no Bohlman bands).

We attempted to employ the ratio of the intensity of the Bohlman band at 2790 cm^{-1} to that of the CH band at 2869 as an internal standard to estimate the relative amounts of *trans*-biaxially oriented α-CH. The strongest absorption at 2790 cm^{-1} was observed in the spectrum of **1b**. The nmr spectrum of **1b** in trifluoroacetic acid (See Table 1) showed a ratio of α-axial H (H_A) to α-equatorial H (H_E) of ~2:1 (13). In addition, the CH_3 doublet appeared at 1.43 δ, which is expected for an equatorial CH_3 at that position (9). These data suggest the *trans* juncture and the conformation **8** for **1b** (see Scheme 2).

Compound **1a** had lower intensity Bohlman absorption, which was unexpected since the *trans* juncture of the all *cis* **1a** would have 3 axial hydrogens on carbon adjacent to nitrogen. The methyl doublet appeared at 0.10 Hz lower field than for **1b** and the α-H's were observed as a single broad envelope. Possibly the *trans* conformation in which the 3 and 5 substituents are eclipsed is extremely crowded, and the molecule acts to relieve this by producing a boat form of the six-membered ring in which the methyl group is axially oriented, *e.g.*, **9**.

Compound **1d**, the geometry of which was determined by an alternate synthesis described subsequently, showed further diminished Bohlmann bands, a methyl doublet at δ = 1.37, and a ratio of 2:1 for H_A: H_E. The *trans* conformation (6-ring chair) would place the methyl axially, however an axial orientation of a 5-methyl produces a doublet at δ = ~ 1.5 (10). A *cis* ring juncture, on the other hand would have had a 1:2 ratio of H_A: H_E. We therefore tentatively assign the *trans* conformation (6-ring boat) in which the methyl is equatorial and the ratio H_A: H_E is 2:1, **10**. Compound **1c** had the least intense Bohlmann bands, H_A: H_E was ≈ 1:1.3, and the methyl absorption more complicated.

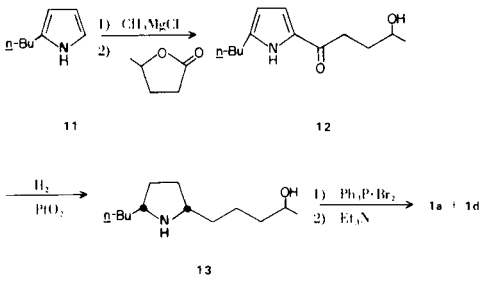
It is evident from these considerations that the spectral data may be of some value in assigning conformational preferences, but they could not, as we had hoped, serve as the basis for unambiguous assignments. At this point we were confident of the structures of **1a** and **1b**, **1a** because of the *cis* addition of hydrogen to **7**, and **1b** because the 2- and 6-substituents on the piperidine ring were also known to be *cis*. We also knew that **1c** and **1d** were those isomers in which the 2- and 6-substituents on the piperidine ring were *trans*, but the configurations of the butyl groups had not yet been determined.

The fact that catalytic hydrogenation resulted in virtually exclusive *cis* addition of hydrogen to dialkylpyridines had thus defined the relationships of the hydrogens at positions 5 and 9 of all four isomers. It followed that the stereochemistry at positions 3 and 9 would similarly be defined if a synthesis of the octohydroindolizines could be achieved from an appropriately functionalized pyrrole. The Grignard reagent from 2-butylpyrrole, **11**, was allowed to react with γ-valerolactone to give **12**. Hydrogenation of **12** was presumed to give the *cis*-dialkylpyrrolidine, **13** (14). Cyclization of **13** with triphenylphosphine/bromine, as before, produced a mixture of octahydroindolizines consisting mainly of **1a** and **d**, thereby establishing **1d** as the isomer with hydrogens at positions 3 and 9 situated *cis* to one another.

Minor amounts of **1b** and **1c** were also found in the product mixture, indicating that the 2,5-dialkylpyrrole tended to give some *trans*-2,5-dialkypyrrolidines on hydrogenation (~ 15%). However, the fact that **1a** (all *cis*) was one of the major products from this reaction requires that **1d** likewise be *cis*.

Several experiments were conducted to assess the possibility of synthesizing the octahydroindolizines, other than **1a**, with some selectivity. The *cis*-piperidyl alcohol, **5b**, was oxidized to the ketone **14** (See Scheme 4) with chromic oxide; and the perchlorate salt of **14** was refluxed in toluene to give the ternary iminium salt **15**. Lithium

Scheme 3



Scheme 4

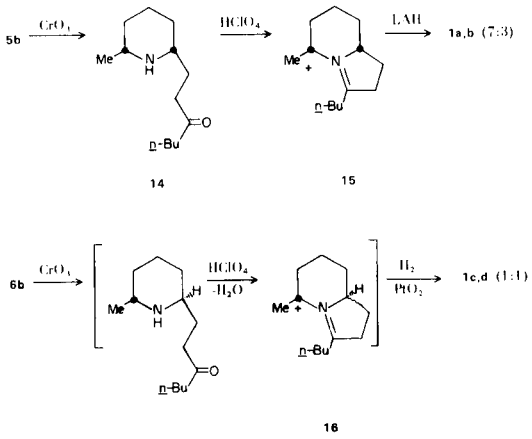


Table I

Nmr Spectral Data for the 3-Butyl-5-Methyloctahydroindolizines in Trifluoroacetic Acid

Compound	δ CH_3	δ H_A: H_E	H_A: H_E
1a	1.53	2.9-3.9	--
1b	1.43	3.0-3.7; 3.7-4.2	2.0
1c	1.43 ?, 1.48	3.1-3.6; 3.6-4.2	1.3
1d	1.37	3.0-3.8; 3.8-4.3	2.1

aluminum hydride reduction of **15** gave **1a** and **1b** in a ratio of 7:3. That **1a** predominated was not unexpected since delivery of hydride is known to occur from the least hindered side of a molecule. The *trans* piperidyl alcohol **6b** was similarly oxidized and cyclized to the salt **16**. Hydrogenation of **16** produced **1c** and **d** in equal amounts, which implied that the two sides of this molecule are sterically equivalent. Although the ternary iminium salts of the 2,6-dialkylpiperidine, **15** and **16**, were readily prepared, no ternary iminium salt was obtained from benzaldehyde and *cis*-2-heptyl-6-methylpiperidinium perchlorate even in refluxing *p*-cymene. Steric hindrance of the nitrogen of **5a** presumably accounts for the failure of the condensation, and the carbonyl must apparently be part of the side chain for reaction to occur.

EXPERIMENTAL

Temperatures are uncorrected. Ir spectra were obtained with either a Perkin Elmer 457A spectrophotometer as 3% carbon tetrachloride solutions or as films or nujol mulls with a Perkin Elmer 137 spectrophotometer. Nmr spectra were obtained with a Varian Associates T60 spectrometer; resonance frequencies were determined relative to internal TMS. Spinning band distillations were performed with a Perkin Elmer NFT-51 Annular Still. Gas chromatograms were obtained with either a Varian Aerograph 1520B Chromatograph or a Hewlett-Packard 5700A instrument. A variety of columns were employed for gas chromatography. Those referred to below are: IGEPAL, 5% on Anakrom ABS, 1.83 m x 6 mm; DEGS, 10% on Chromosorb W(AW), 1.83 m x 6 mm, and Carbowax 20M, 10% on Chromosorb W (AW), 1.83 m x 6 mm. Elemental analyses were carried out by Galbraith Laboratories Inc., Knoxville, Tennessee.

2-Heptyl-6-methylpyridine (**4a**).

One mole of *n*-butyllithium (15% in hexane) was cooled to -5° and then treated dropwise with stirring (nitrogen) with one mole of 2,6-lutidine (**2**). After addition was complete, the mixture was allowed to warm to room temperature, and then was treated dropwise with one mole of 1-bromohexane (**3a**). A cooling bath was applied as necessary to maintain the temperature at *ca.* 25°. Stirring was continued 45 minutes after the addition was complete; then water (200 ml.) was slowly added. The layers were separated, and the aqueous layer was extracted with ether. The combined organic portions were washed with water and with brine and then dried, concentrated, and distilled to give 126 g. (66%) of **4a**, b.p. 81° / 0.4 mm; n_D^{20} 1.5052.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.62; H, 11.00; N, 7.33.

1-(6-Methyl-2-pyridyl)-3-heptanol (**4b**).

The procedure for the synthesis of **4a** was followed except that 1,2-epoxyhexane (**3b**) was used instead of 1-bromohexane. Distillation of the crude product gave 60% of **4b**, b.p. 115° / 0.3 mm; n_D^{27} 1.5022.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.57; H, 100 ; N, 6.57.

cis-2-Heptyl-6-methylpiperidine (**5a**).

Platinum oxide (1 g.) was added to a solution of **4a** (20 g.) in glacial acetic acid (175 ml.), and the mixture was hydrogenated overnight in a Parr apparatus at 50 psi. The catalyst was removed by filtration, the solvent was stripped *in vacuo*, and the residue was partitioned between aqueous sodium carbonate and ether. The ether was evaporated, and the residue was distilled to give 16.7 g. (81%) of **3a**, b.p. 67° / 0.3 mm; n_D^{20} 1.5052. The gas chromatogram (Carbowax 20M, 190°) consisted of a major peak (*ca.* 99%) and a later minor peak (**6a**) with relative retention of 1.18.

Anal. Calcd. for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 79.07; H, 13.75; N, 6.96.

cis-2-(3-Hydroxyheptyl)-6-methylpiperidine (**5b**).

Hydrogenation of **4b** under the conditions described for the synthesis of **5a** gave **5b** (63%), m.p. 51-55°. Recrystallization from acetonitrile raised the m.p. to 56-60°.

Anal. Calcd. for $C_{13}H_{27}NO$: C, 73.18; H, 12.76; N, 6.57. Found: C, 73.26; H, 12.63; N, 6.39.

trans-2-Heptyl-6-methylpiperidine (**6a**).

A solution of **4a** (43.7 g.) in boiling absolute ethanol (400 ml.) was treated with excess sodium over a period of several hours, and the thick mixture was finally refluxed overnight. Excess sodium was decomposed by adding more thanol; then the mixture was partitioned between ether and brine. The combined ether extracts were concentrated to near dryness, and the residue was partitioned between ether and water. Evaporation of the ether gave 41.4 g. (92%) of a clear oil shown by glc (Carbowax 20M, 190°) to consist of **5a** (78%) and **6a** (22%). A sample of **6a** was obtained (9.5 g. from 60 g. of the *cis, trans* mixture) by spinning band fractional distillation monitored by glc, b.p. 141-143° / 27 mm; n_D^{24} 1.4538. Picrate.

Anal. Calcd. for $C_{19}H_{30}N_4O_7$: C, 81.16; H, 11.55; N, 7.28. Found: C, 80.95; H, 11.94; N, 7.04.

trans-2(3-Hydroxyheptyl)-6-methylpiperidine (**6b**).

A solution of **4b** (170 g.) in refluxing absolute ethanol (700 ml.) was treated with sodium (*ca.* 90 g.) over several hours (small portions of ethanol were added occasionally when the mixture became too thick). After the mixture was refluxed overnight, more ethanol was added to decompose excess sodium; then water was added, and much of the ethanol was stripped *in vacuo*. The residue was extracted with ether; the ether solution was washed with water, dried, and stripped to give 169.5 g. of an oil. Gas chromatography (DEGS, 200°) indicated **5b** and **6b** in the approximate ratio of 4:1 plus an unidentified component whose retention time was slightly longer than that of **6b** (presumably a tetrahydropyridine derivative).

The crude product was dissolved in acetonitrile (250 ml.), and

the solution was seeded with crystalline **5b**. After the mixture had been chilled at -20° for 2 hours, 68.2 g. of **5b** was collected by filtration, m.p. 54-58°. The acetonitrile was stripped from the filtrate, and the residue was again subjected to the sodium-ethanol reduction conditions (overnight with excess sodium). The third component was now absent. An acetonitrile solution of the product was again seeded with **5b**; chilling gave an additional 41.3 g. of **5b**, m.p. 52-57°. Material recovered from the mother liquors, 59.3 g. of a mixture containing 60% *trans* isomer (**6b**), was spearated by spinning band distillation to give 21.9 g. of **6b**, b.p. 77° / 0.005 mm; n_D^{25} 1.4732. An additional 1.5 g. was obtained from the pot residue by performing a short path distillation.

Anal. Calcd. for $C_{13}H_{27}NO$: C, 73.18; H, 12.76; N, 6.57. Found: C, 73.35; H, 12.75; N, 6.60.

Hofmann-Loffler Cyclizations of **5a** and **6a**.

N-Chlorosuccinimide (7.5 g.) was stirred at room temperature for 1 hour with a solution of **5a** (10 g.) in ether (100 ml.). The mixture was cooled and filtered, and the filtrate was washed successively with cold water, cold 1.5*M* sulfuric acid, and cold water. Evaporation of the dried solution gave 10.8 g. (92%) of the *N*-chloramine which was added directly to concentrated sulfuric acid that had previously been cooled to *ca.* -70°. The mixture was then warmed with an ice bath, and when it became fluid enough to permit magnetic stirring, irradiation was begun with a Hanovia 450-W mercury lamp in a quartz vessel. After 15 minutes the ice bath was replaced with a water bath (25°). After 45 minutes at 25°, ice was added followed by aqueous sodium hydroxide (< 40°) until the mixture was alkaline. Extraction with ether and distillation of the extract gave 2.45 g. (*ca.* 25%) of a clear oil, b.p. 60-65° / 0.3 mm that consisted (Carbowax, 180°) of isomers **1a** and **1b** plus a third, perhaps olefinic, component in the approximate ratio of 2:2:1 with relative retentions of 1.00:1.25:1.33.

The same procedure applied to **6a** (7.95 g.) gave 1.67 g. (21%) of a *ca.* 1:1 mixture of **1c** and **1d**, b.p. 65-67° / 0.35 mm. No unexpected products were observed in the gas chromatogram of this material.

Triphenylphosphine Dibromide Cyclization of **4b**.

Alcohol **4b** (5.2 g., 0.025 mole) was dissolved in benzene (35 ml.), and 48% hydrobromic acid (4.25 g.) was added. The mixture was stripped of solvent *in vacuo*, and the residue was dissolved in dichloromethane (35 ml.) and dried (magnesium sulfate). The crude hydrobromide obtained by filtration and removal of solvent was dissolved in acetonitrile (25 ml.). Triphenylphosphine (7.3 g.) was added; then the mixture was cooled in an ice bath and treated dropwise with bromine (4.5 g.). The resulting solution was heated overnight under reflux, stripped of solvent, diluted with water (25 ml.), and extracted with ether (2 x 25 ml.). The aqueous phase was made alkaline with 1 *N* potassium hydroxide (50 ml.) and extracted with dichloromethane (3 x 20 ml.). The organic extract containing the bromoalkylpyridine was dried (magnesium sulfate) and concentrated. The residue was dissolved in acetone (25 ml.), and this solution was heated 3 hours under reflux. The solution was concentrated *in vacuo*, and the residue was dissolved in water (10 ml.) and extracted with ether (2 x 15 ml.). A solution of sodium iodide (7.5 g.) in water (10 ml.) caused the iodide **7** to precipitate. Recrystallization from ethylene dichloride-ether gave 4.35 g. (55%), m.p. 126-127°.

Anal. Calcd. for $C_{13}H_{20}IN$: C, 49.22; H, 6.36; I, 40.00; N, 4.42. Found: C, 49.11; H, 6.32; I, 39.77; N, 4.25.

Hydrogenation of **7** to **1a**.

The salt **7** (3.5 g., 0.011 mole) was dissolved in aboslute ethanol (70 ml.). Platinum oxide (0.3 g.) was added, and the mixture was shaken under an initial pressure of 45 psi hydrogen for 5 hours. The solution was filtered and concentrated to produce a quantitative yield of **1a** as its hydriodide salt. Recrystallization from ethylene dichloride-ether gave m.p. 281-220°.

Anal. Calcd. for $C_{13}H_{26}IN$: C, 48.30; H, 8.11; I, 39.26; N, 4.33. Found: C. 48.15; H, 8.16; I, 39.37; N, 4.31.

Treatment of the crude salt with aqueous base and extraction with ether gave, after drying and removal of ether, **1a**, contaminated only by traces of its isomer (5% IGEPAL, 135°, n_D^{25} 1.4669).

Anal. Calcd. for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.91; H, 12.78; N, 7.34.

Triphenylphosphine Dibromide Cyclizations of **5b** and **6b**.

The following prodecure is typical. A solution of **6b** (8.32 g., 0.039 mole) in absolute ethanol (70 ml.) was cooled and treated dropwise with 48% hydrobromic acid (4.5 ml.). The solvent was stripped *in vacuo*, and two portions of benzene were added and stripped to remove traces of alcohol and water. The residue was dissolved in acetonitrile (150 ml.), and triphenylphosphine (10.3 g.) was added. The mixture was stirred and cooled under nitrogen while bromine (2.2 ml.) was added dropwise. The resulting solution was stirred at room temperature 1 hour, refluxed 30 minutes, and then cooled and treated dropwise with triethyl amine (25 ml.). The mixture was stirred 30 minutes at 0°, heated briefly to reflux, cooled, and diluted with aqueous sodium carbonate. Most of the acetonitrile and triethyl amine were stripped *in vacuo*, and the residue was filtered through Celite. The Celite was washed well with petroleum ether, and both liquid phases were transferred to a separatory funnel. The aqueous phase was thoroughly extracted with petroleum ether, and the combined extracts were washed with water, dried, and concentrated. The residue was taken up in a small volume of hexane and filtered to remove a little residual triphenylphosphine oxide; removal of the solvent left 5.81 g. (76%) of a 1:1 mixture of **1c** and **1d** as a slightly red oil. This material was combined with the product from a similar preparation and with the Hofmann-Loffler product from **6a**. Spinning band distillation provided samples of **1d** (~ 99% purity, IGEPAL, 135°, n_D^{25} 1.4695) and **1c** (~ 96% purity, IGEPAL, 135°, n_D^{25} 1.4699); b.p. of each ~125° / 30 mm. Variable water pressure prevented more exact b.p. measurement despite use of a manostat. Relative retentions are 1.00:1.09 (**1d**:**1c**).

Anal. Calcd. for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: for **1c**: C, 79.81; H, 12.82, N, 7.15. Found: for **1d**: C, 79.71; H, 12.80; N, 7.12.

The perhydroindolizines **1a** and **1b** were similarly prepared from the *cis*-piperidylheptanols **5b** and were also separated by spinning band distillation. **1a** (99% purity, glc identity with product from **4b**) and **1b** (99% purity, IGEPAL, 135°, n_D^{25} 1.4704 b.p. of **1a** 119-121° / 27 mm and **1b** ~ 125° / 27 mm.

Anal. Calcd. for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found for **1b**: C, 79.80; H, 12.77; N, 7.33.

cis-2-(6-Methylpiperidyl)-3-heptanone (**14**).

A cold solution of **5b** (15.7 g.) in glacial acetic acid was treated with chromic oxide (8.5 g.) in portions over 10 minutes. The mixture was stirred in the cold 30 minutes and then at room temperature 30 minutes. Glc analysis revealed the presence of

some unreacted **5b**; therefore, another 4 g. of chromic oxide was added, and the mixture was stirred an additional 45 minutes at room temperature. Most of the acetic acid was removed *in vacuo*, and the residue was partitioned between ethyl ether and aqueous sodium hydroxide. Distillation of the ether solution gave 10.0 g. (64%) of **14**, b.p. 83°, 0.2 mm as a clear oil that yellowed upon exposure to air.

Preparation of 1-(5-Butylpyrrol-2-yl)-4-hydroxy-1-pentanone.

A solution of commercial methylmagnesium chloride (3.1*M*, 30 ml.) was cooled, stirred, and treated dropwise with a solution of 2-butylpyrrole (11 g.) in ether (30 ml.). The resulting solution was cooled to -78°, treated dropwise with a solution of γ-valerolactone (9.3 g.) in ether (20 ml.), allowed to warm to room temperature, and finally refluxed 1 hour. Water and then aqueous ammonium chloride were added to the cooled mixture; the layers were separated; and the organic phase was washed with aqueous sodium carbonate, water, dilute hydrochloric acid, water and brine in that order. Evaporation of the dried filtrate gave 14.2 g. (71%) of a light yellow oil. When a solution of this oil in hexane was chilled, a white solid precipitated that was collected and again recrystallized from hexane to give 5.3 g. of pure **12**, m.p. 61.5-63°.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 71.00; H, 9.65; N, 6.01.

Hydrogenation and Cyclization of 2-(5-Butyl)pyrryl 2-hydroxy butyl Ketone (**12**).

A solution of **12** (1.00 g.) in acetic acid (10 ml.) was hydrogenated (50 psi) over platinum oxide (0.2 g.) for 16 hours at room temperature. The solution was filtered and concentrated *in vacuo*, and the residue was partitioned between aqueous sodium carbonate and dichloromethane. The organic phase was washed with water and with brine, dried, and stripped to give 0.77 g. of a clear oil (**13**). The absence of a carbonyl absorption in the ir spectrum and of any aromatic hydrogen absorptions in the nmr spectrum confirmed that reduction was complete (gas chromatographic analysis was uninformative because of excessive tailing on all columns investigated).

The crude product was converted to its hydrobromide salt and and treated with triphinylphosphine and bromine as described for **5b** and **6b**. The product was 0.37 g. of a light brown oil that that consisted of approximately equal parts of **1a** and **1d** (*ca.* 85%) and also contained small amounts of **1b** and **1c** (*ca.* 15%).

Cyclization of Ketone **14** to 3-Butyl-5-methyl-1,2,6,7,8,8a-hexahydro-5*H*-indolizinium Perchlorate (**15**).

The ketone (2.1 g., 0.010 mole) was dissolved in 25 ml. of benzene to which was then added 70% perchloric acid (1.4 g.) in 1 ml. of ethyl acetate. The solvent was removed on a flash evaporator. Toluene (25 ml.) and triethylamine (3 drops) were added to the crude perchlorate salt of **14**, and water was azeotroped from the resulting mixture (3 hours). The product crystallized on chilling and was collected and washed with ether giving **15** (2.8 g., 96%), m.p. 103-105.5° (THF-ethyl ether); ir (mull), no NH, 1655 cm^{-1} ($C{=}N^+$).

Anal. Calcd. for $C_{13}H_{24}ClNO$: C, 53.17; H, 8.23; Cl; 12.07; N, 4.77. Found: C, 53.06; H, 7.98; Cl, 12.15; N, 4.97.

Reduction of **15** with Lithium Aluminum Hydride.

The perchlorate **15** (0.3 g., 0.001 mole) was warmed in THF (15 ml.) containing excess LAH for 1 hour. The product was worked up in the usual manner giving *ca.* 0.2 g. of bicyclic amines **1a** and **1b** in a ratio of 7:3.

Oxidation of **6b** and Sebsequent Conversion to Bicyclic Amines.

The oxidation of **6b** to a ketone was carried out as described for **14**. This material was heated with perchloric acid and toluene to remove water and to produce the corresponding salt **16** also as described. This salt was an oil and was employed directly for the reduction step: ir (film), no NH, 1650 cm^{-1}. Hydrogenation was performed with platinum oxide at 45 psi hydrogen for 4 hours. After the usual work up, the product was analyzed by glc and was identified as a 1:1 mixture of **1c** and **1d**.

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(15) Mention of a proprietary product or company does not imply endorsement by the Department of Agriculture.