was used without purification for the preparation of phosphinate **7**.

3-Iodopropyl Methylphenylphosphinate (7). To 28.4 g (0.2 mol) of freshly distilled CH_3I was added dropwise 18.2 g (0.1 mol) of trimethylene phenylphosphonite (**6**) during stirring under N_2. The reaction was exothermic and the mixture started to reflux. After the addition of **6** was complete, the excess CH_3I was distilled in vacuo, leaving **7** as clear viscous liquid. During an attempted distillation at 150–160 °C (0.5 mm), it decomposed to give 12.3 g (83%) of 1,3-diiodopropane and 16.9 g (96%) of trimethylene bis(methylphenylphosphinate) (**9**). The structures of **7** and **9** were identified by NMR spectra. Their IR spectra showed P=O absorptions at 1295 cm^{-1} (m) and P–O–C absorptions at 1020 cm^{-1} (m).

Poly(propane phenylphosphinate) (8). A mixture of 18.2 g (0.1 mol) of **6** and 0.644 g (0.002 mol) of **7** was sealed in a heavy-wall glass tube under vacuum. The tube was heated at 160 °C for 6 h. The reaction mixture turned light brown and slightly viscous. It was cooled to room temperature, and the contents were isolated by breaking the tube. The polymer was dried at 100 °C (0.3 mm). Its thermolysis at 300 °C (0.5–1.0 mm) for 20 min gave essentially no volatile decomposition products.

Registry No.—**1**, 7526-31-0; **2** (charged form), 68900-51-6; **2** (uncharged form), 68900-56-1; **3**, 68900-52-7; **4**, 68900-57-2; **5**, 68900-53-8; **6**, 7526-32-1; **7**, 68900-54-9; **8**, 68900-58-3; **9**, 68900-55-0; 2,2-dimethyl-1,3-propanediol, 126-30-7; phenylphosphonous dichloride, 644-97-3.

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Studies in Biomimetic Alkaloid Syntheses. 3. Syntheses of Ervinceine and Vincadifformine Analogues from Tetrahydro-γ-carbolines through Secodine Intermediates

Martin E. Kuehne,* Thomas H. Matsko, John C. Bohnert, and Curtis L. Kirkemo

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

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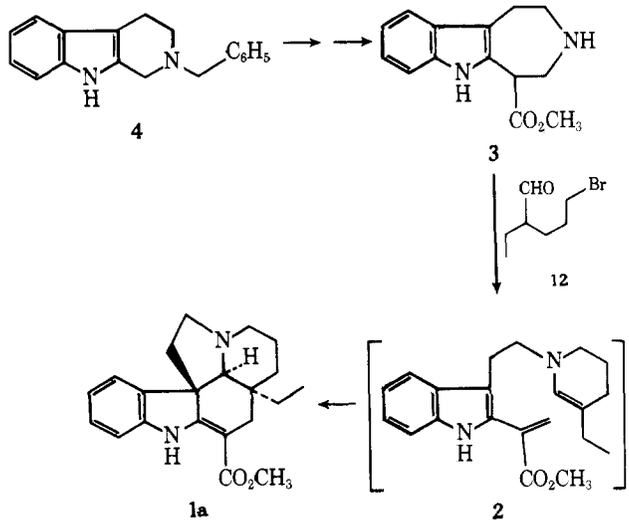
The chlorination of tetrahydro-γ-carbolines **10a–e** and reactions of the resultant chloroindolenines **11a–e** with thallium dimethyl malonate gave the indoloazepines **6b–f.** The 3-spiropyrrolidino-2-alkylideneindoline intermediate **7b** of this transformation could be isolated and characterized. Debenzylation of the indoloazepines **6b–f** to the secondary amines **14a–e** and reactions of the latter with halo aldehydes **12** or **15** yielded vincadifformine **1a** and its aryl-substituted analogues **1b–e.** The structure of ervinceine was established as 16-methoxyvincadifformine (**1e**). The spiroenammonium precursor **13b** of a secodine intermediate **2** was isolated and characterized.

A total synthesis of vincadifformine **1a,** recently reported from our laboratory,[1] proceeds by way of the biogenetically postulated[2,3] secodine intermediate **2** (Scheme I). This intermediate could be generated from an indoloazepine **3** through a spiroannelation and fragmentation sequence. The indoloazepine **3** was in turn obtained from a tetrahydro-β-carboline **4** by a biomimetic oxidative alkylation, followed by debenzylation and decarboxylation reactions. The present report describes an alternative approach to such indoloazepine precursors and their variations and reactions, which extend the scope of the synthesis to other alkaloids. These studies also substantiated mechanistic considerations in key steps of the vincadifformine synthesis.

Our earlier synthesis[1] of the indoloazepine **3** was based on chlorination of the tetrahydro-β-carboline **4** with *tert*-butyl hypochlorite, thus furnishing the chloroindolenine **5** (Scheme II). On reaction with thallium *tert*-butyl methyl malonate this chloride gave the indoloazepine **6a.** Formation of the seven-membered heterocycle was postulated to arise from rearrangement of an initial malonate to imine adduct, with generation of a 3-spiropyrrolidino-2-alkylideneindoline intermediate **7a.** It was proposed that such an intermediate would undergo fragmentation to a zwitterionic immonium malonate **8a,** with subsequent cyclization of the latter finally leading to formation of the indoloazepine ring system.

Since none of the reactive intermediates of the proposed

Scheme I



sequence were isolated during the transformation of the chloroindolenine **5** to the indoloazepine **6a,** it was of interest to see if intermediacy of the key 3-spiropyrrolidino-2-alkylideneindoline **7a** could be confirmed by an alternative synthesis such as by the chlorination and alkylation of the iso-

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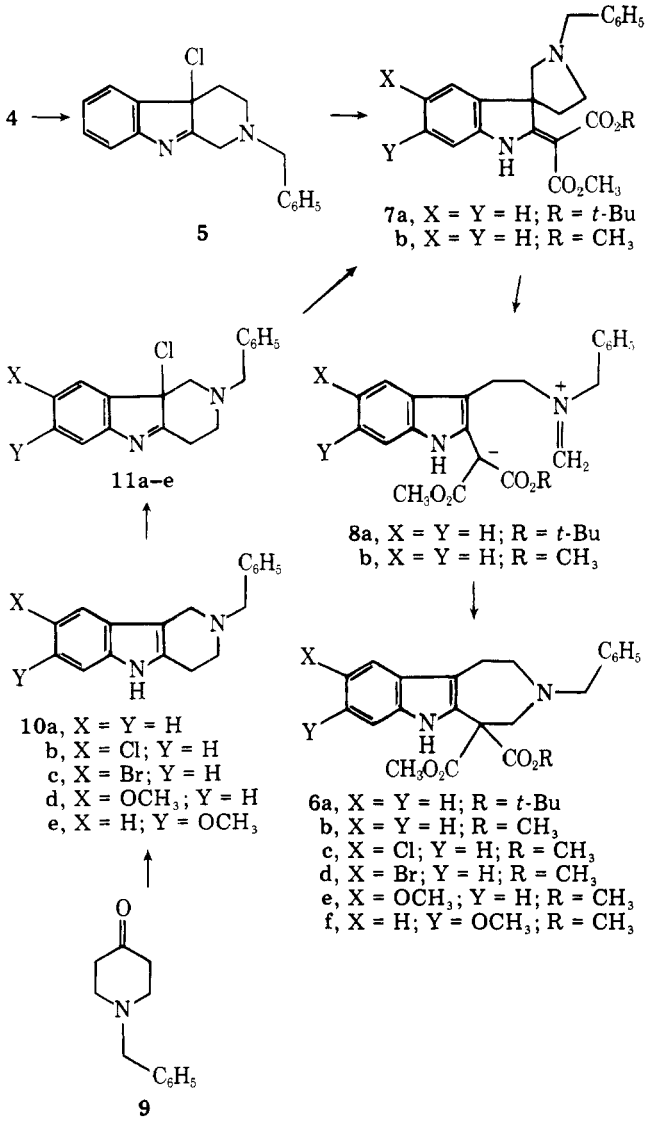
Scheme II



meric starting tetrahydro-γ-carboline **10a**.[4] Chlorination of either *N*-benzyltetrahydro-β- or -γ-carboline (**4** or **10a**) and heating of the resultant chloroindolenines **5** or **11a** with thallium dimethyl malonate in benzene indeed gave the same indoloazepine **6b** in comparable high yields. While the intermediate chlorindolenines **5** and **11a** generally showed a divergent reaction chemistry,[5] their parallel transformation in this reaction with thallium dimethyl malonate to the same indoloazepine product **6b** supported the intermediacy of the spiroalkylidene intermediate **7b**.

When the alkylation of the chloroindolenine **11a** with thallium dimethyl malonate was carried out at room temperature in tetrahydrofuran, it was found that the spiroalkylidene intermediate **7b** could be isolated in about 80% yield and that it could be characterized as its hydrochloride salt. The base showed UV [λ_{max} (ϵ) 237 (17 229), 298 (8460), 340 (18 709) nm] and IR (ν_{max} 3300, 1710, 1660, 1570 cm^{-1}) absorptions characteristic of a β-aminoalkylidene malonate, with IR differentiation of the ester carbonyl functions as in the case of the 2-alkylideneindoline with a carbocylic 3-spiro substituent.[6] The same intermediate **7b** was also observed by TLC in the reaction of the chloroindolenine **5**, derived from tetrahydro-β-carboline with thallium dimethyl malonate in tetrahydrofuran. Subsequent heating of the isolated intermediate **7b** resulted in formation of the indoloazepine **6b**. This two-step transformation could also be followed by TLC in reaction mixtures of either tetrahydro-β- or -γ-carboline derived chloroindolenines (**5** or **11a**) with thallium dimethyl malonate stirred at room temperature in several solvents.

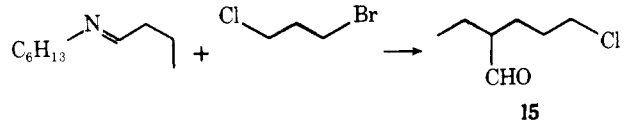
The conversion of a tetrahydro-γ-carboline **10a** to the indoloazepine **6b** proved to be of value for the eventual elaboration of aryl-substituted alkaloids of the vincadifformine class. The previously required tetrahydro-β-carboline precursors[1] are most directly synthesized from corresponding tryptamines. Thus the parent compounds such as **4** are readily accessible, but aryl-substituted examples require aryl-substituted tryptamines, which can only be obtained through relatively long synthetic sequences. On the other hand many aryl-substituted tetrahydro-γ-carbolines can be prepared from corresponding phenylhydrazones of 4-piperidones by Fischer indole reactions. Thus 8-chloro-, 8-bromo-, and 8-methoxytetrahydro-γ-carbolines, **10b,c,d**, were obtained in 83, 75, and 60% overall yields, respectively, through the corresponding para-substituted phenylhydrazones of *N*-benzyl-4-piperidone (**9**) and the *m*-methoxyphenylhydrazone gave the 7-methoxytetrahydro-γ-carboline **10e** as major product in 46% yield. Chlorination of these aryl-substituted tetrahydro-γ-carbolines **10b–e** and subsequent reactions with thallium dimethyl malonate resulted in formation of the corresponding indoloazepines **6c–f** (60, 60, 69, and 71% yields).

In our initial synthesis of vincadifformine **1a**[1] the indoloazepine *tert*-butyl methyl diester **6a** was monodecarboxylated and debenzylated to furnish the indoloazepine methyl ester **3**. Reaction of the latter with the bromo aldehyde **12** has given vincadifformine. While a bromo enamine intermediate could be demonstrated in this transformation, the subsequent spiroenamonium precursor **13a** of the secodine intermediate **2** was not established and was postulated only by analogy to a model compound prepared from azepine.[1] However, when the dicarbomethoxyindoloazepine **6b** was debenzylated and the resultant secondary amine **14a** was condensed with the bromo aldehyde **12**, a spiroenamonium product **13b** could be isolated and characterized as its tetraphenylborate salt **13c**. Reaction of the diester **13b** with triethylamine in methanol at 20 °C for 18 h resulted in complete conversion to vincadifformine.

The methylation of trimethylamine by methyl acetate requires more than 300 h at 100 °C,[7] and *N*-benzyl diester **6b** gave only a little of the corresponding monodecarbomethoxylated azepinoindole and was largely recovered after treatment with triethylamine in methanol at 60 °C for 10 h. Therefore the facile decarbomethoxylation of the diester **13b**, under much milder conditions, indicates a concerted decarboxylation and fragmentation process, that is, the generation of the secodine intermediate **2**, which undergoes cyclization to vincadifformine (Scheme III). Thus the full sequence of reactive intermediates previously proposed for the biomimetic vincadifformine synthesis was established.[8]

The direct use of dimethyl ester intermediates **14a–e** in the condensation with the bromo aldehyde and in situ decarboxylation with concerted fragmentation and generation of secodine intermediates also shortened the operational sequence of steps leading to vincadifformine and its derivatives.

For additional alkaloid syntheses the azepine esters **14b–e** were condensed with the bromo aldehyde **12**[1] or with the chloro aldehyde **15**. The latter was synthesized most directly by alkylation of the lithium salt of an imine derivative of butyraldehyde with 1-bromo-3-chloropropane.



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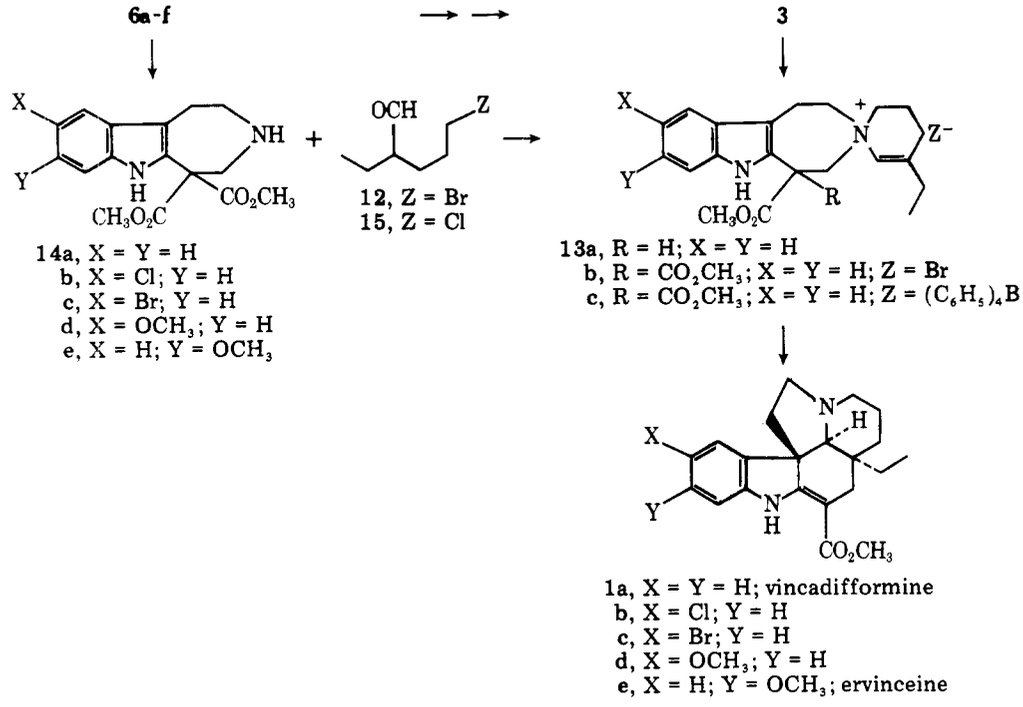
Scheme III



From the reactions of the aryl-substituted indoloazepine diesters **14b–e** with the halo aldehydes **12** or **15**, 15-chloro-, 15-bromo-, 15-methoxy- (**1b,c,d**), and 16-methoxyvincadifformine (**1e**)[9] were thus obtained directly in up to 82% yields. The last compound gave an NMR spectrum identical with that published for ervinceine[10] and differed substantially in its NMR spectrum from 15-methoxyvincadifformine. It was identical with a dihydro product obtained on hydrogenation of 16-methoxytabersonine by TLC, LC, solution IR, and mass spectra.[11]

Experimental Section

***N*-Benzyl-4-piperidone Phenylhydrazone.** To a solution of 600 mL of 1:1 H_2O/EtOH was added *N*-benzyl-4-piperidone (**9**) (38 g, 0.2 mol) and phenylhydrazine hydrochloride (32 g, 0.22 mol). The solution was stirred at 20 °C for 48 h and then made basic by the addition of saturated potassium carbonate (the addition should be at a rate which allows for control of the foaming). The product separated as an oil and was collected. The water layer was extracted with ethyl acetate, the combined organic fractions were dried ($MgSO_4$) and the solvent was removed under vacuum. Hexane (100 mL) was added and then removed under vacuum to help remove the remaining polar solvents. To the crystallizing product 200 mL of hexane was added and, after 20 min, vacuum filtration gave 50 g (87%) of the phenylhydrazone which was suitable for use in the next step. The product can be recrystallized from hexane: mp 80–81 ° C (lit.[12] 78–79 °C).

***N*-Benzyltetrahydro-γ-carboline (10a).** *N*-Benzyl-4-piperidone phenylhydrazone (49 g, 0.18 mol) was added with stirring to 250 mL of glacial acetic acid containing 6% by weight of anhydrous HCl. The solution immediately turned dark red and became quite hot. Stirring was continued until the solution had cooled to room temperature (~15–20 min). The solution was then made basic by careful addition of saturated aqueous potassium carbonate and extracted with dichloromethane. After drying ($MgSO_4$) and solvent removal the residue crystallized. The product was washed with ethanol and then recrystallized from ethanol to give 39.5 g (87%) of *N*-benzyltetrahydro-γ-carboline: mp 158–159 ° C (lit.[12] 161 °C); NMR ($CDCl_3$) δ 2.6–3.0 (m, 4 H), 3.75 (s, 2 H), 3.81 (s, 2 H), 7.0–7.5 (m, 9 H), 7.8–8.0 (br s, 1 H).

Dimethyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (6b). To a solution of 0.25 g (0.95 mmol) of *N*-benzyltetrahydro-γ-carboline and 110 μL of triethylamine in 7 mL of dry benzene, stirring at ~5 °C under nitrogen, was added dropwise 110 μL of *tert*-butyl hypochlorite (0.954 mmol). The mixture was stirred at 5 °C for 1.5 h then poured into ~3 mL of cold water in a separatory funnel. After gentle shaking the layers were allowed to separate and the H_2O layer was discarded. The benzene layer was dried by filtering through a cone of sodium sulfate in phase separation paper. The separatory funnel and filter cone were washed with dry benzene and the benzene filtrate was evaporated under vacuum to ~3 mL. Dry benzene was added to a volume of ~7 mL, then 0.335 g (1 mmol) of thallium dimethyl malonate was added and the vigorously stirring solution was refluxed under nitrogen for 23 h. The reaction was then cooled to room temperature and filtered through glass fiber paper and the benzene was evaporated under vacuum. The residue was taken up in dichloromethane and deposited on a column of SiO_2 (1.5 × 30 cm). Elution with dichloromethane yielded 0.195 g (52%) of a slightly colored product which had IR and NMR spectra identical with those of the product obtained in 46% yield from *N*-benzyltetrahydro-β-carboline by the same reaction sequence. Recrystallization from methanol afforded white crystals: mp and mmp 166–168 ° C; NMR ($CDCl_3$) δ 2.97 (s, 4 H), 3.8 (s, 2 H), 3.88 (s, 6 H), 3.93 (s, 2 H), 7.24–7.8 (m, 9 H), 8.64 (brs, 1 H); IR (KBr) ν_{max} 3510, 3010, 3000, 2950, 2940, 2920, 2880, 2825, **1750, 1705,** 1490, 1450, 1440, 1435, 1345, 1320, 1285, 1275, 1255, 1240, 1220 (br), 1185, 1165, 1145, 1135, 1125, 1110, 1090, 1075, 1055, 1035, 980, 960, 935, 700, 690, 670, 635 cm^{-1}; IR ($CHCl_3$) ν_{max} 3440, 3000, **1725,** 1455, 1425, 1210 (br), 1045, 1025, 975 cm^{-1}; MS (*m/e*) 392 (M^+). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.12; H, 6.25; N, 6.91.

Alternative Procedures. 1. Reaction of the tetrahydro-γ-carboline **10a** with 1 equiv of *tert*-butyl hypochlorite in dichloromethane at −78 °C for 15 min, followed by warming to 18 °C, was followed by concentration under vacuum. A solution of the residual chlorination product in benzene was allowed to react with thallium dimethyl malonate at 20 °C for 3 h and at reflux for 2 h. The cooled reaction mixture was then stirred with an equal volume of saturated aqueous sodium chloride solution for 15 min to precipitate TlCl. Filtration, concentration, and crystallization from methanol gave the indoleazepine **6b** in 70% yield.

2. A reaction of 1.68 g (6.41 mmol) of the tetrahydro-γ-carboline **10a** in 30 mL of dry tetrahydrofuran (THF) with 0.82 mL (7.2 mmol) of *tert*-butyl hypochlorite, added over 30 s at −78 °C followed by warming to 20 °C over 10 min, gave complete conversion to the chloroindolenine **11a** (TLC R_f 0.52, 3:2 ether–hexane, silica gel, compared to R_f 0.14 for **10a**). Addition of 3.0 g (9.0 mmol) of thallium dimethyl malonate to the THF solution and stirring at 20 °C for 1.4 h showed complete reaction of the chloroindolenine **11a** and formation of the 3-spiro-2-alkylideneindoline **7b** (R_f 0.76, same system, blue stain with cerric ammonium sulfate). The solution was filtered through glass fiber paper and concentrated under vacuum. Trituration with 50 mL of ether, filtration and addition of ether saturated with HCl gas to the filtrate gave 2.2 g of the hydrochloride of **7b** (80%). A sample was recrystallized from methanol: mp 170 °C dec. Anal. Calcd for $C_{23}H_{25}N_2O_4Cl$: C, 64.41; H, 5.87; N, 6.53; Cl, 8.26. Found: C, 64.41; H,

5.83; N, 6.45; Cl, 8.55. The free base was generated by shaking 250 mg of the hydrochloride in 5 mL of dichloromethane and 25 mL of saturated aqueous $NaHCO_3$, yielding 225 mg of **7b:** NMR ($CDCl_3$) δ 2.12 (br d, 1 H), 2.40–3.10 (m, 5 H), 3.70–3.77 (3 s, 8 H), 6.70–7.61 (m, 10 H); hydrochloride UV (MeOH, HCl) λ_{max} (ϵ) 206 (17 636), 237 (17 229), 298 (8460), 340 (18 709) nm; the 340 λ_{max} was found to shift to 325 nm in basic solution; IR (KBr) ν_{max} 3300, 1710, 1660, 1570 cm^{-1}.

3. An analogous reaction of 10.0 g of the tetrahydro-γ-carboline **10a** in THF was allowed to stir for 20 h at 22 °C after addition of the thallium malonate. Filtration, concentration, and trituration with 100 mL of ether gave 2.44 g (16%) of the crystalline azepino diester **6b.** Concentration of the filtrate (containing nearly pure spiroalkylidene intermediate **7b** by TLC) and 11 h of reflux of the residue dissolved in 50 mL of THF gave an additional 9.33 g of **6b** (78% total).

Dimethyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (14a). To 1.6 g (4.08 mmol) of the diester benzylamine **6b** dissolved in 50 mL of acetic acid was added 0.2 g of 5% palladium on charcoal catalyst. Hydrogenation at atmospheric pressure with vigorous stirring showed termination of hydrogen uptake after 3 h. The solution was filtered through glass fiber paper and the flask and filter were washed with dichloromethane. The dichloromethane was removed under water aspirator vacuum and the acetic acid was distilled on a vacuum pump with a dry ice/acetone trap. (The product picks up color if the acetic acid is removed at lower vacuum at elevated temperature.) The residue was taken up in dichloromethane, washed with 10% aqueous sodium carbonate, dried over potassium carbonate, filtered, and concentrated under vacuum to a white powder: 1.23 g (100%); NMR ($CDCl_3$) δ 2.4 (br s, 1 H), 2.9 (t, 2 H), 3.1 (t, 2 H), 3.66 (s, 2 H), 3.72 (s, 6 H), 6.9–7.5 (m, 4 H), 8.66 (brs, 1 H); MS *m/e* 302 (M^+).

Dimethyl 3,3-[1′,5′-(2′-Ethyl-1′-pentenyl)]-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indolinium-5,5-dicarboxylate Bromide and Tetraphenylborate (13b,c). To a solution of 200 mg (0.664 mmol) of amino diester **14a** in 8 mL of dry methanol, stirring under N_2, was added 194 μL (1.32 mmol) of 5-bromo-2-ethylpentanal. The mixture was stirred for 8 h at 40 °C and concentrated and the residue taken up in dichloromethane. Evaporation of the dichloromethane yielded a yellowish foam. Ethyl acetate was added and the foam was broken up into an off-white solid. The solid was filtered and washed with ethyl acetate under N_2 and then dried under vacuum to yield 0.225 g (71%) of an off-white powder: IR (KBr) ν_{max} 3400, 2950, 1735 (br), 1455, 1435, 1255 (br), 750 cm^{-1}; UV (EtOH) λ_{max} 222, 284, 292 (sh) nm. Since the solid is hygroscopic and decomposes in $CDCl_3$ the tetraphenylborate salt was prepared for analysis.

Solutions of 100 mg (0.209 mmol) of the spiro bromide in 2 mL of dry methanol and of 72 mg (0.210 mmol) of sodium tetraphenylborate in 2 mL of dry methanol were prepared. These solutions were each filtered through glass wool plugs and the filters were rinsed with ~1 mL of dry methanol. To the vigorously stirring spiro bromide solution was added at once the sodium tetraphenylborate solution. Upon addition the solution was clear yellow. After ~10 s it became cloudy and a solid precipitated. The suspension was stirred 0.5 h and filtered and the solid was washed with dry methanol and dried under vacuum to yield 120 mg (80%) of a white powder. The material resisted all attempts at crystallization, depositing an amorphous white solid from all solvent systems employed. From acetone–methanol the material had mp 244–247 °C; IR (KBr) ν_{max} 3420 (br), 3050, 3000, 2980, 1755 (sh), 1735, 1580, 1475, 1465, 1455 (sh), 1430, 1275, 1220, 775, 760, 740, 735, 710, 610 cm^{-1}. Anal. Calcd for $C_{47}H_{49}N_2O_4B$: C, 78.76; H, 6.87; N, 3.91. Found: C, 78.93; H, 6.59; N, 3.69.

(±)-Vincadifformine (1a). Method 1. To a solution of 0.150 g (0.497 mmol) of the diester amine **13b** in 12 mL dry methanol, stirring under nitrogen, was added 0.145 mL (0.993 mmol, 0.192 g) of 5-bromo-2-ethylpentanal. The solution was stirred 18 h at 20 ° C and it was then heated to 40 °C and 0.2 mL of triethylamine was added. After 20 h of continued stirring at 40 °C the solution was cooled and the solvent was evaporated, leaving a viscous orange oil. Column chromatography on silica and eluting first with methylene chloride to remove excess bromo aldehyde and then with ether yielded a yellow product. Crystallization from aqueous acetonitrile gave 0.0923 g (55%) of **1a:** mp 124–125 °C;[1] IR (KBr) ν_{max} 3350, 2950, 2930, 2760, 1665, 1600, 1460, 1425, 1325, 1305, 1290, 1275, 1250, 1235, 1225, 1215, 1205, 1185, 1160, 1155, 1045, 755 cm^{-1}; NMR ($CDCl_3$) δ 0.6 (t, 3 H), 0.9–3.3 (m, 15 H), 3.8 (s, 3 H), 6.8–7.36 (m, 4 H), 9.02 (br s, 1 H); MS *m/e* 338 (M^+), 124 (100%).

Method 2. A sample of the spiroenamonium bromide **13b** was dissolved in methanol in a UV cell and the spectrum was followed at 20 °C after addition of a drop of triethylamine. A gradual change of the typical indolic chromophore of **13b** to the characteristic chromophore of vincadifformine (λ_{max} 327 nm) was nearly complete after 8 h and showed no change after 18 h. TLC (R_f 0.6, 5% MeOH in CH_2Cl_2, silica, blue stain with cerric ammonium nitrate) showed conversion of **13b** to vincadifformine.

2-Benzyl-7-methoxy-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indole (10e). A solution of 3.25 g (17.2 mmol) of *N*-benzyl-4-piperidone (**9**) and 3.00 g (17.2 mmol) of *m*-methoxyphenylhydrazine hydrochloride in 50 mL of glacial acetic acid was stirred under N_2 for 2 h and then 120 mL of an 8% solution of dry HCl in acetic acid was added. After stirring for 2 h at 75 °C the solution was concentrated under vacuum to 50 mL and cooled to 22 °C, and 100 mL of dichloromethane was added. The stirred mixture was made basic by addition of aqueous K_2CO_3. After separation of the dichloromethane, the aqueous portion was extracted with additional dichloromethane. The combined extracts were dried over K_2CO_3 and concentrated to a brown oil which was chromatographed on silica with 3% methanol in dichloromethane as eluting solvent. Crystallization from 95% ethanol gave 2.28 g (46%) of the methoxytetrahydro-γ-carboline **10e:** mp 172–173 °C; NMR ($CDCl_3$) δ 10.30 (br s 1 H), 7.30 (m, 5 H), 7.07 (d, J = 8 Hz, 1 H), 6.75 (d, J = 2 Hz, 1 H), 6.53 (d of d, J = 8 and 2 Hz, 1 H), 3.71 (s, 3 H), 3.70 (s, 2 H), 3.53 (s, 2 H), 2.75 (s, 4 H); IR (KBr) ν_{max} 3410, 1640, 1610, 1580 cm^{-1}; MS (80 eV) *m/e* 292 (M^+), 173 (base); UV (ethanol) λ_{max} 238, 295 nm. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.05; H, 7.04; N, 9.58.

2-Benzyl-8-methoxy-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indole (10d). Following the procedure for the 7-methoxytetrahydro-γ-carboline **10e,** but using *p*-methoxyphenylhydrazine hydrochloride, the 8-methoxy isomer **10d,** mp 119–120 °C, was prepared in 53% yield: NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.27 (m, 5 H), 6.93 (d, J = 8 Hz, 1 H), 6.72 (d, J = 2 Hz, 1 H), 6.65 (d of d, J = 8 and 2 Hz, 1 H), 3.74 (s, 5 H), 3.62 (s, 2 H), 2.67 (m, 4 H); IR (KBr) ν_{max} 3390, 2930, 2820, 2760, 1595, 1485, 1455, 1220, 1150, 1030, 985, 835, 825, 805, 760, 735, 705, 700 cm^{-1}; UV (ethanol) λ_{max} 238, 290 nm. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.05; H, 6.86; N, 9.47.

2-Benzyl-8-chloro-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indole (10b). A heavy precipitate formed on stirring 2.00 g (11.2 mmol) of 4-chlorophenylhydrazine and 2.11 g (11.2 mmol) of *N*-benzyl-4-piperidone for 2 h under nitrogen in 40 mL of acetic acid at 22 °C. On addition of 60 mL of 8% HCl in acetic acid a clear red solution formed. This was heated for 2 h at 75 °C, generating a precipitate. After concentration under vacuum at 70 °C to 40 mL and cooling to 22 °C the precipitate was filtered and rinsed with dichloromethane. After suspension of the residual solid in 100 mL of dichloromethane and 100 mL of water and addition of potassium carbonate until all initial solid had dissolved the phases were separated and the strongly basic aqueous phase was extracted with 50 mL of dichloromethane. After drying (K_2CO_3), concentration, and crystallization from 95% ethanol 2.77 g (84%) of the tetrahydro-γ-carboline **10b,** mp 117–118 °C, was obtained: NMR ($CDCl_3$) δ 8.12 (s, 1 H), 7.29 (m, 6 H), 6.96 (s, 2 H), 3.74 (s, 2 H), 3.60 (s, 2 H), 2.70 (m, 4 H); the compound showed solvent of crystallization at δ 1.96, which could be removed on drying at 60 °C (0.05 mm); IR (KBr) ν_{max} 3300, 2940, 2840, 2790, 2765, 1590, 1450, 1055, 975, 900, 855, 805, 750, 700 cm^{-1}; UV (ethanol) λ_{max} 240, 290 nm. Anal. Calcd for $C_{18}H_{17}N_2Cl$: C, 72.84; H, 5.77; N, 9.44; Cl, 11.95. Found: C, 72.70; H, 5.87; N, 9.38; Cl, 12.11.

2-Benzyl-8-bromo-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indole (10c). Following the procedure for the 8-chlorotetrahydro-γ-carboline **10b,** but using 4-bromophenylhydrazine hydrochloride, the 8-bromo isomer **10c,** mp 122–123 °C, was formed in 86% yield: NMR ($CDCl_3$) δ 8.18 (s, 1 H), 7.42 (d, J = 2 Hz, 1 H), 7.32 (s, 5 H), 7.07 (d of d, J_{H7-H9} = 2 Hz, J_{H7-H6} = 8 Hz, 1 H), 6.86 (d, J = 8 Hz, 1 H), 3.72 (s, 2 H), 3.58 (s, 2 H), 2.66 (m, 4 H); IR (KBr) ν_{max} 3400, 2905, 2890, 2800, 2780, 1570, 1440, 1050, 980, 790, 740, 695 cm^{-1}; UV (ethanol) λ_{max} 240, 290 nm. Anal. Calcd for $C_{18}H_{17}N_2Br$: C, 63.35; H, 5.02; N, 8.21; Br, 23.42. Found: C, 63.25; H, 5.18; N, 8.18; Br, 23.69.

Dimethyl 3-Benzyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (6f). To a solution of 2.5 g (8.56 mmol) of the methoxytetrahydro-γ-carboline **10e** and 1.07 mL of triethylamine in 60 mL of dichloromethane, stirring under N_2 at −78 °C, was added under the liquid surface, via syringe, 5 mL of a solution of 1.2 mL of *tert*-butyl hypochlorite in 4.4 mL of dichloromethane. The mixture was stirred for 15 min and allowed to warm to 20 °C. The solvent was removed under vacuum, leaving a viscous brown oil. TLC (Al_2O_3, CH_2Cl_2) showed clean conversion to the chloroindolenine.

The crude product was taken up in 50 mL of dry benzene, 3.45 g (0.0103 mol, 1.2 equiv) of thallium dimethyl malonate was added, and the slurry was stirred vigorously under nitrogen for 2 h at 20 °C and an additional 3.5 h at reflux. The mixture was allowed to cool to 20 °C and saturated NaCl solution was added to precipitate TlCl. The

mixture was filtered through glass fiber paper (GF/A) and the flask and filter cake were rinsed with benzene. The organic layer was separated and the aqueous layer was extracted with benzene. The combined benzene layers were washed with saturated brine, dried ($MgSO_4$), and filtered and the solvent was removed under vacuum to give a brownish solid. Crystallization from methanol yielded 2.19 g of white crystals. Chromatography (SiO_2, 5% MeOH in CH_2Cl_2) of the mother liquor yielded fractions containing the desired product which upon combination, solvent removal, and crystallization from MeOH with seeding yielded an additional 0.36 g of off-white crystals: total yield, 2.56 g (71%); NMR ($CDCl_3$) δ 8.29 (br s, 1 H), 7.28 (m, 6 H), 6.70 (d of d, 2 H), 3.78 (s, 2 H), 3.76 (s, 3 H), 3.72 (s, 6 H), 3.66 (s, 2 H), 2.84 (s, 4 H); IR (KBr) ν_{max} 3462, 1905, 1790, 1635, 1575, 1515, 1255, 1220, 1210 cm^{-1}; MS (80 eV) *m/e* 422 (M^+). An analytical sample recrystallized from MeOH had mp 132–134 °C. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 67.90; H, 6.40; N, 6.45.

Dimethyl 3-Benzyl-9-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (6e). Following the procedure for preparation of the 8-methoxyindoloazepine **6f,** the 9-methoxy isomer **6e,** mp 128–130 °C, was prepared in 69% yield: NMR ($CDCl_3$) δ 8.34 (br s, 1 H), 7.29 (m, 6 H), 6.90 (m, 2 H), 3.81 (s, 5 H), 3.76 (s, 6 H), 3.67 (s, 2 H), 2.87 (s, 4 H); IR (KBr) ν_{max} 3400, 2960, 2840, 1749, 1722, 1480, 1465, 1450, 1430, 1250, 1220, 1140, 1030, 835, 740, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.26; H, 6.24; N, 6.47.

Dimethyl 3-Benzyl-9-chloro-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (6c). Following the procedure for preparation of the 9-methoxyindoloazepine **6f,** the 9-chloro product **6c,** mp 111–113 °C, was prepared in 60% yield: NMR ($CDCl_3$) δ 8.49 (s, 1 H), 7.22 (m, 8 H), 3.78 (s, 2 H), 3.74 (s, 6 H), 3.65 (s, 2 H), 2.84 (s, 4 H); IR (KBr) ν_{max} 3404, 2960, 2920, 2890, 2840, 1725, 1455, 1430, 1320, 1260, 1250, 1230, 1130, 1050, 880, 803, 802, 740, 735, 695 cm^{-1}; UV (ethanol) λ_{max} 239, 295 nm. Anal. Calcd for $C_{23}H_{23}N_2O_4Cl$: C, 64.71; H, 5.43; N, 6.56; Cl, 8.31. Found: C, 64.67; H, 5.55; N, 6.52; Cl, 8.59.

Dimethyl 3-Benzyl-9-bromo-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (6d). Following the procedure for preparation of the 9-methoxyindoloazepine **6f,** the 9-bromo product **6d,** mp 116–118 °C, was prepared in 60% yield: NMR ($CDCl_3$) δ 8.48 (br s, 1 H), 7.54 (s, 1 H), 7.25 (s, 5 H), 7.14 (s, 2 H), 3.77 (s, 2 H), 3.72 (s, 6 H), 3.62 (s, 2 H), 2.81 (s, 4 H); IR (KBr) ν_{max} 3440, 2950, 2905, 2815, 1745, 1732, 1465, 1435, 1245, 1220, 1140, 1045, 1025, 790, 740, 695 cm^{-1}; UV (ethanol) λ_{max} 238, 293 nm. Anal. Calcd for $C_{23}H_{23}N_2O_4Br$: C, 58.60; H, 4.92; N, 5.94; Br, 16.95. Found: C, 58.52; H, 4.86; N, 5.72; Br, 17.11.

Dimethyl 8-Methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (14e). The 8-methoxyazepinoindole **6f** (2.16 g, 5.12 mmol) was debenzylated according to the procedure given for the parent compound **6b,** giving 1.72 g (100%) of a white foam, which crystallized from methanol: NMR ($CDCl_3$) δ 8.76 (br s, 1 H), 7.4 (d, 1 H), 6.8 (m, 2 H), 3.8 (s, 3 H), 3.78 (s, 6 H), 3.7 (s, 2 H), 3.14 (m, 2 H), 2.90 (m, 2 H), 2.34 (s, 1 H); IR (KBr) ν_{max} 3405, 3395, 1755, 1730, 1640, 1600, 1275, 1255, 1235, 1210 cm^{-1}; MS *m/e* 332. An analytical sample recrystallized from MeOH had mp 158–159 °C. Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 60.85; H, 6.15; N, 8.17.

Dimethyl 9-Methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (14d). Debenzylation of the 9-methoxyazepinoindole **6e** according to the procedure given for the parent compound **6b** and crystallization from methanol gave the secondary amine **14d** as a methanolate in quantitative yield: mp 95–105 °C; NMR ($CDCl_3$) δ 8.75 (br s, 1 H), 7.10 (d, J = 8 Hz, 1 H), 6.99 (d, J = 2 Hz, 1 H), 6.77 (d of d, J = 8 and 2 Hz, 2 H), 3.82 (s, 3 H), 3.74 (s, 8 H), 3.03 (m, 4 H), 2.38 (br s, 1 H); IR (KBr) ν_{max} 3400, 3300, 2950, 2840, 1740, 1720, 1250, 1215, 1050 cm^{-1}. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.33; H, 6.68; N, 7.66.

Dimethyl 9-Chloro-(and 9-bromo-)1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (14b and 14c). In order to avoid extensive dehalogenation found on reductive debenzylation according to the procedure given for the parent compound **6b,** the chloro and bromo derivatives **6c** and **6d** were hydrogenated in methanol containing 3% anhydrous HCl. The hydrogenation was stopped after 1.05 equiv of hydrogen had been taken up. While the chloroamine **14b** was obtained cleanly, some dehalogenation of the bromo compound could not be avoided. The chloroazepinoindole **14b,** mp 137–138 °C, was thus obtained in quantitative yield on crystallization from methyl acetate–hexane: NMR ($CDCl_3$) δ 8.86 (br s, 1 H), 7.44 (br s, 1 H), 7.14 (m, 2 H), 3.77 (s, 6 H), 3.68 (s, 2 H), 2.99 (m, 4 H), 2.28 (br s, 1 H); IR (KBr) ν_{max} 3370, 3350, 2930, 2830, 1735, 1715, 1463, 1435, 1260, 1240, 1215, 800 cm^{-1}; MS (80 eV) *m/e* 336 (M^+). Anal. Calcd for $C_{16}H_{17}N_2O_4Cl$: C, 57.06; H, 5.09; N, 8.32; Cl, 10.53. Found: C, 56.96; H, 5.34; N, 8.09; Cl, 10.43.

The bromoazepinoindole **14c** was obtained in about 80% purity. The compound was contaminated by the dehalogenated product **14a** as seen by TLC and NMR spectra, which showed respective NH signals at δ 8.98 and 8.86 (concentration dependent in $CDCl_3$) for **14c** and **14a.** A difficult separation and purification of **14c** promoted direct use of the crude product in the subsequent synthetic step: NMR ($CDCl_3$) δ 8.98 (br s, 1 H), 7.59 (s, 1 H), 7.18 (br s, 2 H), 3.76 (s, 6 H), 3.66 (s, 2 H), 2.99 (m, 4 H), 2.26 (br s , 1 H); MS (80 eV) *m/e* 380 (M^+).

(±)-16-Methoxyvincadifformine (1e). To a solution of 0.45 g (1.4 mmol) of diester amine **14e** and one crystal of *p*-toluenesulfonic acid in 30 mL of dry MeOH, stirring under N_2, was added 0.22 mL (0.29 g, 1.5 mmol) of bromo aldehyde **12.** Stirring was continued for 0.5 h at 20 °C and 10 h at 40 °C. At this time TLC (SiO_2, 5% methanol in dichloromethane) showed no starting material. To the solution 0.5 mL of triethylamine was added and the solution was heated to 60 °C and stirred for 4 h. The solution was cooled to 20 °C and the solvent was removed to yield an orange gummy solid. Chromatography (SiO_2 column with 5% methanol in dichloromethane) gave no separation, so the material was subjected to preparative TLC on 2-mm SiO_2 plates, developing with ether. Collection of the bands at $R_f \approx 0.7$, washing the silica with 10% methanol in ether, filtration, and solvent removal yielded a white foam: 0.293 g, 59%; NMR ($CDCl_3$) δ 8.88 (br s, 1 H), 7.04 (d, 1 H), 6.36 (m, 2 H), 3.74 (s, 6 H), 3.27–0.69 (m, 15 H), 0.55 (t, 3 H); an NMR spectrum in CCl_4 matched that published for ervinceine;[10] IR (KBr) ν_{max} 3390, 1685, 1620, 1500, 1270 cm^{-1}; MS (80 eV) *m/e* 368 (M^+), 124 (base); UV (ethanol) λ_{max} (log ϵ) 249 (4.00), 330 (4.12) nm. TLC of this material (SiO_2, 5% MeOH in CH_2Cl_2) showed one spot of $R_f \approx 0.4$ which stained blue with ceric ammonium sulfate–phosphoric acid spray reagent. The product was crystallized from methanol, mp 90–92 °C.

A crystalline picrate was formed by addition of 53.8 mg of picric acid in the minimum amount of ethanol to 72 mg of the amine also in the minimum amount of ethanol. Recrystallization from 95% ethanol gave an analytical sample with mp 183–184 °C dec. Anal. Calcd for $C_{28}H_{31}N_5O_{10}$: C, 56.27; H, 5.23; N, 11.72. Found: C, 56.34; H, 5.47; N, 11.90.

Reduction of 16-Methoxytabersonine to 16-Methoxyvincadifformine (1e). A suspension of 10 mg of 16-methoxytabersonine hydrochloride in 1.5 mL of water and 5 mg of PtO_2 was stirred under hydrogen at atmospheric pressure. After 2.5 h the hydrogen uptake stopped. The solution was filtered, made basic with ammonium hydroxide, and extracted with dichloromethane. Concentration gave 9 mg of 16-methoxyvincadifformine showing identity with the synthetic sample in chloroform solution IR, MS, and TLC (see comparative TLC section).

(±)-15-Chloro-, (±)-15-Bromo-, and (±)-15-Methoxyvincadifformine (1b,c,d). These compounds were prepared by the procedure given for vincadifformine (**1a**). The chloro and bromo products were purified by preparative TLC on Merck silica, developed with 2% methanol in dichloromethane. The bromovincadifformine (**1c**), R_f 0.60, was readily separated from the minor vincadifformine (**1a**) component, R_f 0.48, formed from the contaminating indoloazepine **14a.** The chloro compound, **1b** (yield 70%), crystallized from methanol: mp 131–132 °C; NMR (CCl_4) 8.98 (br s, 1 H), 7.02 (m, 2 H), 6.71 (d, J = 8 Hz, 1 H), 3.72 (s, 3 H), 3.20–0.80 (br m, 15 H), 0.64 (t, 3 H); IR ($CHCl_3$) ν_{max} 3370, 2930, 2770, 1665, 1600, 1465, 1290, 1260, 1150 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 225 (s, 4.11), 311 (4.20), 338 (4.17) nm; MS (80 eV) *m/e* (rel %) 372 (45), 125 (15), 124 (100). Anal. Calcd for $C_{21}H_{25}N_2O_2Cl$: C, 67.64; H, 6.76; N, 7.51; Cl, 9.51. Found: C, 67.67; H, 6.75; N, 7.41; Cl, 9.77.

The bromo compound **1c** (yield 51%) resisted crystallization: NMR (CCl_4) δ 8.94 (br s, 1 H), 7.10 (m, 2 H), 6.58 (d, J = 10 Hz, 1 H), 3.64 (s, 3 H), 3.20–0.76 (br m, 15 H), 0.60 (t, 3 H); IR ($CHCl_3$) 3360, 2930, 2775, 1665, 1600, 1460, 1290, 1260, 1150 cm^{-1}; UV (MeOH) λ (log ϵ) 225 (sh, 4.11), 310 (4.19), 331 (4.17) nm; MS (80 eV) *m/e* (rel %) 418 (12), 416 (12), 125 (39), 124 (100). The compound formed a picrate which crystallized from 95% ethanol, mp 203–204 °C. Anal. Calcd for $C_{27}H_{28}N_5O_9Br$: C, 50.16; H, 4.37; N, 10.83. Found: C, 49.92; H, 4.43; N, 10.64.

The methoxy compound, **1d** (yield 82%), was amorphous: NMR ($CDCl_3$) δ 8.75 (br s, 1 H), 6.77 (br s, 1 H), 6.62 (m, 2 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.38–0.80 (m, 15 H), 0.58 (t, 3 H); IR ($CHCl_3$) ν_{max} 3380, 2925, 2760, 1660, 1600, 1210, 1140 cm^{-1}; UV λ_{max} (MeOH) (log ϵ) 228 (sh, 4.10), 313 (4.23), 331 (4.14) nm; MS (80 eV) *m/e* 368 (M^+), 124 (base). A picrate was recrystallized from 95% ethanol, mp 152–153 °C. Anal. Calcd for $C_{28}H_{31}N_5O_{10}$: C, 56.27; H, 5.23; N, 11.72. Found: C,

56.30; H, 5.25; N, 11.66.

Comparative TLC Analyses of Aryl-Substituted Vincadifformines. TLC analyses on Merck 60 F254 silica, developing with 2.5% methanol in dichloromethane and visualizing with ceric sulfate in phosphoric acid, gave the following results: vincadifformine (**1a**), R_f 0.37, staining blue fading to smoky gray then yellow; 15-chlorovincadifformine (**1b**), R_f 0.55, staining light pale blue and fading rapidly to yellow; 15-bromovincadifformine (**1c**), R_f 0.54, staining smoky blue and fading rapidly to a smoky purple and eventually to brown; 15-methoxyvincadifformine (**1d**), R_f 0.28, staining was dependent upon concentration (A heavy spot would show a flash of blue before changing over the course of ~10 min from green through yellow and brown to light reddish purple. A lighter spot showed no flash of blue, becoming green immediately and then proceeding through the above changes.); 16-methoxyvincadifformine (**1e**), R_f 0.31, staining blue, and in the case of a heavy spot a yellow center was present. (The spot faded to smoky blue, to olive green and eventually to yellow.)

5-Chloro-2-ethylpentanal (15). A solution of lithium diisopropylamide (65 mmol) was prepared by addition of 28.8 mL of 2.3 N *n*-butyllithium to 9.9 mL of diisopropylamine stirred in 60 mL of dry tetrahydrofuran and cooled to −78 °C. A solution of 10.0 g (65 mmol) of *N*-butylidenecyclohexylamine in 10 mL of tetrahydrofuran was then added dropwise, followed after 15 min by 11.3 g (71 mmol) of 1-bromo-3-chloropropane, which was added over 5 min. The solution was allowed to warm to 20 °C over 4 h, stirred at 20 °C for 2 h, and then poured into 100 mL of 3% HCl and stirred for 12 h. The organic material was extracted with ether and the extracts were washed with 3% HCl and brine. After drying ($MgSO_4$), the extracts were concentrated under vacuum and residual product was distilled to give 5.2 g (54% yield) of the chloro aldehyde **15**: bp 55 °C (0.3 mm); IR (neat) ν_{max} 2700, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (t, 3 H), 1.4–2.0 (m, 6 H), 2.2 (m, 1 H), 3.6 (t, 2 H), 9.8 (d, 1 H). A 2,4-dinitrophenylhydrazone derivative had mp 110–111 °C. Anal. Calcd for $C_{13}H_{17}N_4O_4Cl$: C, 47.49; H, 5.21; N, 17.04. Found: C, 47.63; H, 5.50; N, 16.76.

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Registry No.—(±)-**1a,** 18374-17-9; (±)-**1b,** 69069-54-1; (±)-**1c,** 69069-55-2; (±)-**1c** picrate, 69069-56-3; (±)-**1d,** 69069-57-4; (±)-**1d** picrate, 69089-21-0; **1e,** 25858-80-4; (±)-**1e,** 69126-63-2; (±)-**1e** picrate, 69126-64-3; **6b,** 69069-58-5; **6c,** 69069-59-6; **6d,** 69069-60-9; **6e,** 69069-61-0; **6f,** 69069-62-1; **7b,** 69069-63-2; **7b** hydrochloride, 69069-78-9; **9,** 3612-20-2; **10a,** 6208-43-1; **10b,** 19685-91-7; **10c,** 69069-64-3; **10d,** 69069-65-4; **10e,** 69069-66-5; **11a,** 69069-67-6; **11e,** 25858-80-4; **12,** 51048-46-5; **13b,** 69069-68-7; **13c,** 69069-70-1; **14a,** 69069-71-2; **14b,** 69069-72-3; **14c,** 69069-73-4; **14d,** 69069-74-5; **14e,** 69069-75-6; **15,** 62498-23-1; **15** 2,4-dinitrophenylhydrazone, 69069-76-7; *N*-benzyl-4-piperidone phenylhydrazone, 69069-77-8; thallium dimethyl malonate, 69120-36-1; *m*-methoxyphenylhydrazine hydrochloride, 39232-91-2; *p*-methoxyphenylhydrazine hydrochloride, 19501-58-7; 4-chlorophenylhydrazine, 1073-69-4; 4-bromophenylhydrazine hydrochloride, 622-88-8; 16-methoxytabersonine hydrochloride, 11021-77-5; *N*-butylidenecyclohexylamine, 1197-52-0; 1-bromo-3-chloropropane, 109-70-6.

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Mass Spectrometric Location of Triple Bonds in Fatty Acids and Fragmentation Mechanisms of *N*-Acylpyrrolidines[1]

Anthony J. Valicenti, Wayne H. Heimermann, and Ralph T. Holman*

The Hormel Institute, University of Minnesota, Austin, Minnesota 55912

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Mass spectra of the pyrrolidide derivatives of isomeric octadecynoic acids are characterized by simple fragmentation patterns. Examination of the spectra indicates that if the triple bond in acetylenic fatty acids occurs between Δ5 and ω2, the unsaturation may be located by observing the most intense peak in each 14-amu cluster of fragments. *An interval of 10 amu (rather than the usual 14) between fragments corresponding to C_{n-2} and C_{n-1} of the acyl moiety indicates a triple bond at C_n. Confirmation of triple bond location is provided by intense peaks at C_{n-2} and C_{n+2}.* The rule has been found valid for all isomers within this series including Δ15, which produces a spectrum similar to but distinguishable from Δ17. Derivatization is accomplished by heating the fatty acyl moiety (methyl ester, triglyceride, phospholipid, etc.) with pyrrolidine. Because derivatization is performed on the carboxyl group, quantitation is assured regardless of the number and type of substituent groups present in the molecule. Electron impact of *N*-acylpyrrolidines produces fragments which arise from both amide-directed fragmentation (ADF) and substituent-directed fragmentation (SDF). ADF predominates in the acetylenic isomers which conform to the general rule for location of triple bonds. Simple spectra are obtained in which the position of the substituent group may be deduced directly without necessitating a library search.

Mass spectrometry (MS), although an extremely powerful aid in determination of structure, has been, until recently, unable to clearly distinguish isomeric unsaturated fatty acids. For example, the mass spectrum of methyl 9,12-octadecadienoate (linoleate) is quite similar to that of the isomeric methyl 9-octadecynoate (sterolate).[2a] The reason for this is twofold: (a) most of the carbon–carbon bonds in the molecules are equivalent in energy, thus yielding many ions of similar

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