Studies in Biomimetic Alkaloid Syntheses. 4. An Alternative Route to Secodine Intermediates Providing Syntheses of Minovine, Vincadifformine, Ervinceine, and *N*(a)-Methylervinceine

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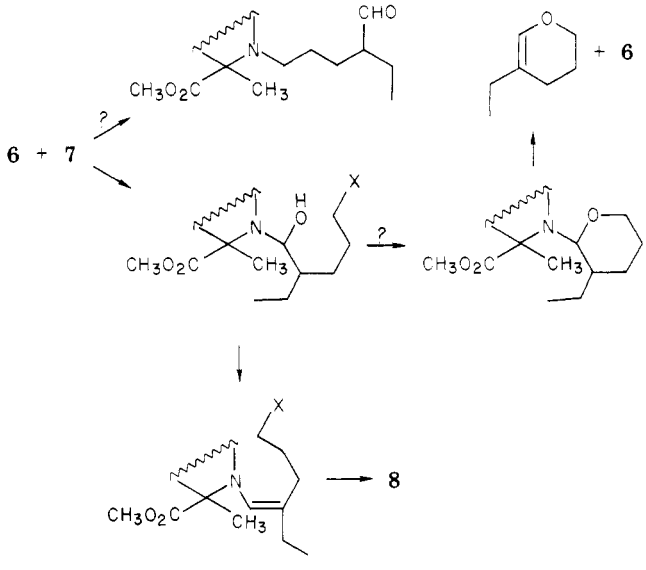
The condensation of tryptamine, *N*(a)-methyltryptamine and 6-methoxytryptamine with methyl pyruvate furnished the tetrahydro-β-carbolines **6a–c**. On reaction with 5-chloro-2-ethylpentanal (**7b**) these 1,1-disubstituted tetrahydrocarbolines gave vincadifformine (**4a**), minovine (**4b**), and ervinceine (**4c**). The latter was also obtained by alkylation of methyl 8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**1d**) with 2-ethyl-5-mesyloxypentanal (**7c**). Vincadifformine and ervinceine were converted to the corresponding *N*(a)-methyl derivatives (**4b,d**) with sodium hydride and methyl iodide in *N*,*N*-dimethylformamide.

Our earlier syntheses of vincadifformine (**4a**) were based on transformations of the indoloazepines **1a,b** to a biogenetically postulated secodine intermediate **3** and its cyclization.[1,2] It was possible to isolate the spiroenammonium precursor **2a** and to show that the decarbomethoxylation and fragmentation of this compound are concerted, thus implying a secodine intermediate **3**. However, since the secodine intermediate **3** was not observed directly, but was found to undergo cyclization to vincadifformine (**4a**), it became of interest to see if this intermediate **3** could be generated by an alternative synthesis. Thus the route in Scheme II, which also furnishes a practical synthesis of vincadifformine and derivatives, was developed.

We anticipated that formation of the indoleacrylic ester moiety of the secodine **3** by a Hofmann fragmentation should not only be possible through the previously utilized concerted β-elimination reactions of the quaternized indoloazepines **2a,b**, but that an indoleacrylic ester **3** should also arise from a 2-indolyl carbon bearing a quaternary nitrogen substituent. The required precursor for this synthesis was readily prepared by condensation of tryptamine (**5a**) with methyl pyruvate, which gave the α,α-disubstituted tetrahydro-β-carboline **6a** in 72% yield. Heating of this secondary amine with 5-bromo-2-ethylpentanal (**7a**)[1] gave vincadifformine (**4a**). The yield of this transformation was quite low, but it could be greatly improved to 84% by the alternative use of 5-chloro-2-ethylpentanal (**7b**).[2] (See Scheme II)

In the reactions of the indoloazepines with bromo- or chloroaldehydes (**7a,b**), high yields of vincadifformine (**4a**) had been obtained in either case.[2] However, in contrast to those reactions, higher temperatures are required for reactions of the tetrahydro-β-carboline **6a** at comparable reaction times (110 °C for **6a** vs. 22 °C for **1a**). These more strenuous reaction requirements may reflect the greater difficulty in forming an enamine from a secondary amine with nitrogen in a neopentyl-type position. Thus the difference in yield of vincadifformine (**4a**) derived from the chloro- vs. the bromoaldehyde (**7b** vs. **7a**) on reaction with the tetrahydro-β-carboline **6a** may be a consequence of relatively less amine alkylation by the alkyl halide **7b** vs. **7a**, in competition with the required prior enamine formation. However, a noted difference in haloaldehyde stability between **7a** and **7b**, or different extent of intramolecular carbinolamine O-alkylation and consequent haloaldehyde destruction, may also introduce alternative reactions in competition with enamine formation.



In order to see if fragmentation of the spiroenammonium intermediate **8a** required a concerted loss of the indolic *N*(a) proton, the corresponding *N*(a)-methyltetrahydro-β-carboline **6b** was subjected to the same reaction with the chloroaldehyde **7b** and found to produce minovine (**4b**) in 56% yield. The *N*(a)-methyltryptamine (**5b**) used for the synthesis of the tetrahydro-β-carboline **6b** was best prepared by *N*(a) methylation of the tryptamine phthalimide derivative and subsequent generation of the base **5b**.

Minovine (**4b**) was also obtained by methylation of vincadifformine (**4a**). Thus an alkylation of the latter with sodium hydride and methyl iodide in *N*,*N*-dimethylformamide gave a good yield of minovine, while small-scale alkylations of vincadifformine in liquid ammonia[3] resulted in product mixtures containing variable amounts of starting material, which then could not be easily removed by chromatography.

The new synthetic route to vincadifformine could be extended to a synthesis of ervinceine (**4c**) starting from 6-methoxytryptamine (**5c**). A comparison sample of ervinceine, previously synthesized from the indoloazepine diester **1c**,[2] was also obtained from a reaction of the monoester **1d** with the mesyl aldehyde **7c** in 73% yield. Alkylation of ervinceine then yielded the corresponding *N*(a)-methyl derivative (**4d**). One enantiomer of this

(1) M. E. Kuehne, D. M. Roland, and R. Hafter, *J. Org. Chem.*, **43**, 3705 (1978).

(2) M. E. Kuehne, T. H. Matsko, J. C. Bohnert, and Curtis Kirkemo, *J. Org. Chem.*, **44**, 1063 (1979).

(3) J. Mokry, I. Kompis, L. Dubavkova, and P. Sefcovic, *Experientia*, **19**, 311 (1963).

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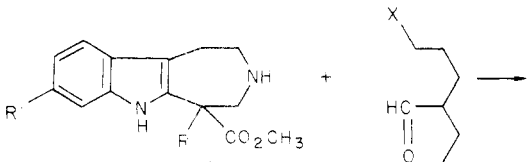
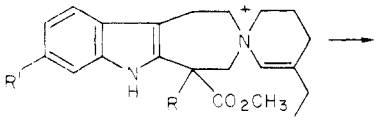
Scheme I

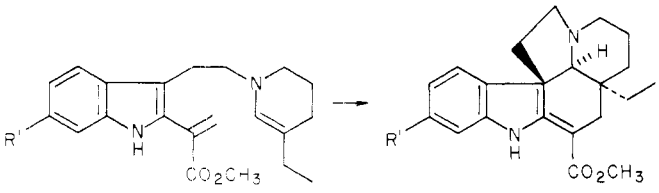


1a, R = CO_2CH_3; R′ = H
b, R = H; R′ = H
c, R = CO_2CH_3; R′ = OCH_3
d, R = H; R′ = OCH_3

7a, X = Br
b, X = Cl
c, X = OMes



2a, R = CO_2CH_3; R′ = H
b, R = H; R′ = H
c, R = H; R′ = OCH_3



3, R′ = H or OCH_3 4, R′ = H or OCH_3

compound, obtained by degradation[4] of vindoline (**9**), has recently been converted back[4] to vindoline (**9**), the indoline moiety of the "dimeric" oncolytic alkaloid vincaleucoblastine (VLB).

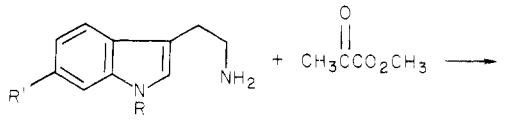
Experimental Section

α-Carbomethoxy-α-methyltetrahydro-β-carboline (6a). A solution of 4.0 g (20 mmol) of tryptamine hydrochloride and 2.0 mL (22 mmol) of methyl pyruvate in 80 mL of dry methanol was refluxed for 21 h, cooled, and concentrated under vacuum. The residual solid was dissolved in 40 mL of hot water and filtered, and 3 mL of concentrated ammonium hydroxide solution was added. The precipitated crystalline product was recrystallized from ethanol and water (3:5), giving 3.5 g (72% yield): mp 136–138 °C (lit.[5] mp 138 °C); NMR ($CDCl_3$) δ 8.6 (1 H, s), 7.3–7.9 (4 H, m), 3.9 (3 H, s), 3.3 (2 H, t), 2.8 (2 H, sp t).

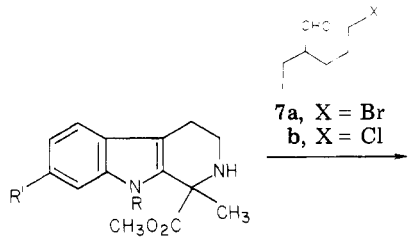
(±)-Vincadifformine (4a). A solution of 300 mg (1.23 mmol) of α-carbomethoxy-α-methyltetrahydro-β-carboline (**6a**), 0.22 mL (1.5 mmol) of 2-(3-chloropropyl)butyraldehyde, and 1 mg of *p*-toluenesulfonic acid in 25 mL of toluene was refluxed for 100 h under nitrogen with a Dean-Stark water separator. To the hot solution, 0.38 mL (3.0 mmol) of diazabicycloundecene (DBU) was then added and heating continued for 18 h. The reaction mixture was cooled and concentrated under vacuum, and the residue was dissolved in dichloromethane. Filtration through a column of Baker silica (25 g, 40-cm length) and elution with 3% methanol in dichloromethane gave 360 mg (84%) of crude vincadifformine (**4a**) after concentration under vacuum of the second 100 mL of eluate. The NMR spectrum of this product matched that of an authentic sample of *dl*-vincadifformine and TLC comparison indicated only minor impurities. Recrystallization from acetonitrile gave a sample, mp and mmp 124–125 °C (lit.[2,6] 124–125 °C): MS (80 eV), *m/e* (rel intensity) 124 (100), 214 (4), 338 (85) M^+.

1-Carbomethoxy-7-methoxy-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6c). A solution of 113 mg of 6-methoxytryptamine[7] and 80 μL of methyl pyruvate in 5 mL of methanol was refluxed under nitrogen for 18 h. The cooled reaction mixture was partitioned between 10 mL of saturated aqueous sodium carbonate and 15 mL of dichloromethane, and the aqueous phase was extracted with two 15-mL portions of dichloromethane. The combined organic extracts were washed with brine, filtered through phase separating paper, and concentrated. Trituration with 2 mL of ether gave 110 mg (80% yield) of product with mp 182–184 °C. An analytical sample was recrystallized from ethyl acetate to mp 184–185 °C: NMR ($CDCl_3$) δ 8.25 (br s, 1 H), 7.44 (d, 1 H), 6.85 (m, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.21 (t, 2 H), 2.72 (t, 2 H), 2.28 (br, s, 1 H), 1.70 (s, 3 H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.68; H, 6.76; N, 9.92.

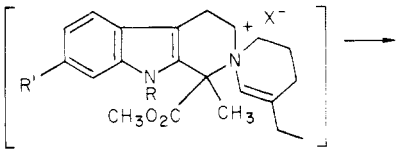
Scheme II



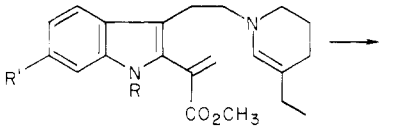
5a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = OCH_3



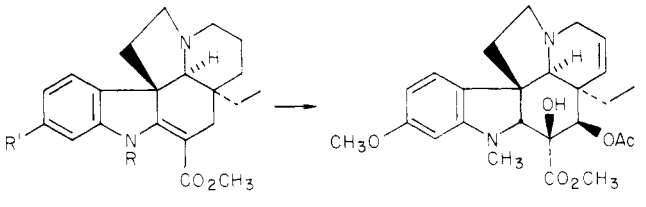
6a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = OCH_3



8a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = OCH_3



3a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = OCH_3



4a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = OCH_3
d, R = CH_3; R′ = OCH_3

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(±)-Ervinceine (16-Methoxyvincadifformine) (4c). Method A. To 130 mg (0.47 mM) of the methoxytetrahydrocarboline ester **6c** and a crystal of *p*-toluene sulfonic acid in 3 mL of toluene was added 100 μL (0.75 mM) of 5-chloro-2-ethylpentanal (**7b**) in

(4) J. P. Kutney, U. Bunzli-Trepp, K. K. Chan, J. P. de Souza, Y. Fujise, T. Honda, J. Katsube, F. K. Klein, A. Leutwiler, S. Morehead, M. Rohr, and B. R. Worth, *J. Am. Chem. Soc.*, **100**, 4220 (1978).
(5) G. Hahn, D. Scheles, L. Buerwald, and H. Werner, *Justus Liebigs Ann. Chem.*, **520**, 107 (1935).
(6) (a) C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, and M. M. Janot, *Tetrahedron Lett.*, 235 (1962); (b) J. Gosset, J. LeMen, and M. M. Janot, *Ann. Pharm. Fr.*, **20**, 448 (1962).
(7) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958). We thank Dr. A. J. Hannart of Omnium Chimique for an additional sample of 6-methoxytryptamine.

1 mL of toluene. With a Dean-Stark water trap containing 3 Å Davison molecular sieves and a nitrogen atmosphere, the mixture was refluxed for 72 h. Concentration and partitioning of the residue between 10 mL of 10% HCl and 5 mL of hexane, addition of excess KOH to the aqueous solution, followed by four extractions with 15 mL of dichloromethane and concentration gave a basic residue. This was purified by solution in 50 mL of ethyl acetate and rapid filtration of the solution through 3 g of Baker silica gel. The concentrated eluate gave 160 mg (92%) of ervinceine as an amber oil which was homogeneous by TLC (Merck silica gel, $R_f \sim 0.7$, ethyl acetate, detection with cerric ammonium nitrate showed a blue spot with yellow center). The product formed a picrate, mp and mmp 183–184 °C, and had spectroscopic data matching those of a sample prepared from the methoxyindoloazepine esters **1c**[2] and **1d**: NMR ($CDCl_3$) δ 8.90 (br s, 1 H), 7.00–7.28 (m, 1 H), 6.30–6.50 (m, 2 H), 3.76 (s, 6 H), 3.40–0.80 (m, 15 H), 0.58 (t, 3 H); MS (80 eV), *m/e* (rel intensity) 124 (100), 184 (12), 244 (12), 309 (12), 368 (90) M^+.

Method B. A solution of the amino ester **1d** (100 mg, 0.369 mmol), the mesyloxy aldehyde **7c** (0.0835 g, 0.401 mmol), and triethylamine (0.122 g, 1.20 mmol) in 5 mL of anhydrous methanol was stirred at 65 °C under nitrogen for 17 h. The solvent was evaporated under vacuum, and the residual oil was chromatographed by PTLC (1.5 mm silica, 3% methanol in dichloromethane). The band of ervinceine was located by spraying the edge of the plate with ceric ammonium sulfate, producing a characteristic blue color. Elution of ervinceine from the separated band with 1:10 methanol in ether and concentration yielded 0.0981 g (73%) of ervinceine (**4c**) identical with the above preparation and the previously characterized sample.[2]

2-Ethyl-5-mesyloxypentanal (7c). To a solution of 2.55 g (0.01 mol) of 4-dimethoxymethyl-1-methanesulfonyloxyhexane[1] in 40 mL of diethyl ether, 20 mL of 1.2 N HCl was added, and the mixture was stirred at reflux for 12 h. Solid potassium carbonate (3 g) was slowly added, the organic layer was separated, and the aqueous layer was extracted with 25 mL of ether. The combined ether solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated to 1.66 g of the aldehyde **7c**: NMR ($CDCl_3$) δ 9.57 (d, 1 H) 4.20 (m, 2 H), 3.00 (s, 3 H), 2.23 (m, 1 H), 1.88–1.09 (m, 6 H), 0.92 (t, 3 H); IR_{max} (film) 2955, 2930, 2870, 2700, 1715, 1450, 1340, 1170, 970–910, 820 cm^{-1}.

Methyl 8-Methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (1d). A solution of dimethyl 3-benzyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate[2] (1.00 g, 2.37 mmol), lithium chloride (0.111 g, 2.61 mmol), and 128 μL of water in 10 mL of *N,N*-dimethylformamide was stirred under nitrogen at 140 °C for 2 h. The mixture, which became heterogeneous in this time, was cooled to 20 °C, poured into 200 mL of water, and extracted with two 75-mL portions of benzene. The benzene solutions were washed with brine, dried over K_2CO_3, filtered, and concentrated under vacuum to 0.747 g (86%) of the mono ester, which was purified by chromatography on silica, eluting with 2.5% methanol in dichloromethane, and crystallized from methanol to mp 118–119 °C: NMR ($CDCl_3$) δ 8.12 (s, 1 H), 7.2 (m, 6H), 6.6 (m, 2 H), 3.66 (s, 5 H), 3.54 (s, 3 H) 3.5–3.2 (m, 3 H), 3.1–2.6 (m, 4 H).

The above *N*-(benzylamino) monoester product (0.375 g, 1.03 mmol) and 38 mg of 10% Pd/C catalyst were stirred in acetic acid at 20 °C under 1 atm of hydrogen for 17 h. After filtering and washing the catalyst with methanol, the solvents were evaporated under vacuum, and the residue was dissolved in dichloromethane. Extraction with saturated aqueous K_2CO_3 solution and brine, drying over K_2CO_3, filtration, and concentration gave 0.276 g (97%) of the amino ester **1d**, which was crystallized from methanol to mp 166–167 °C: NMR ($CDCl_3$) δ 8.6 (s, 1 H), 7.25 (d, 1 H, J = 8 Hz), 6.68 (m, 2 H), 3.74 (s, 3 H), 3.64 (s, 3 H), 3.58–2.70 (m, 7 H), 2.30 (br s, 1 H). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67, H, 6.61; N, 10.21. Found: C, 65.45; H, 6.62; N, 10.02.

***N*(a)-Methyltryptamine (5b).** A solution of 3.20 g (20.0 mmol) of tryptamine and 3.10 g (20.0 mmol) of phthalic anhydride in 40 mL of toluene was refluxed under a Dean-Stark water separator for 12 h. Cooling and filtering the solution and concentrating the filtrate gave a crude phthalimide, which was recrystallized from ethanol to produce 4.85 g (84%) of phthalimide, mp 164–165 °C (lit.[8] mp 164–165 °C).

A solution of 0.58 g (2.0 mmol) of the phthalimide in 1.5 mL of dimethylformamide (DMF) was added over 2 min to 0.22 mmol of 50% sodium hydride in mineral oil suspended in 1 mL of DMF. After the solution was stirred at 20 °C under N_2 for 30 min, 0.25 mL (4.0 mmol) of methyl iodide was added. The dark-brown solution turned pale yellow. After 15 min, the mixture was poured into 40 mL of half saturated brine, and the resultant precipitate was filtered after 20 min and washed with water. Recrystallization of the *N*-methyl derivative from ethanol gave 0.40 g (65%), mp 174–175 °C (lit.[9] 175–176 °C or lit.[10] mp 177–178 °C).

A mixture of 824 mg (2.7 mmol) of the *N*-methyltryptaminephthalimide and 0.7 mL (14 mmol) of hydrazine hydrate (85% solution, Fisher) in 80 mL of ethanol was refluxed for 24 h, then 20 mL of 10% aqueous HCl was added, and the solution was refluxed an additional 30 min. After cooling, concentrating, and partitioning the residue between 60 mL of saturated aqueous sodium carbonate and 60 mL of dichloromethane, the aqueous portion was extracted with 60 mL of dichlormethane, and the combined organic extracts were washed with brine. Concentration and Kugelrohr distillation gave 0.45 g (96%), bp 95–105 °C (0.06 mm). The oil was dissolved in ethyl acetate, and HCl gas was bubbled into the solution. The resultant amine hydrochloride was filtered and washed with ethyl acetate containing HCl and then with ether. The *N*(a)-methyltryptamine hydrochloride had mp 201–202 °C (lit.[11,12] mp 198–199 °C).

1-Carbomethoxy-1-methyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indole (6b). A mixture of 160 mg of *N*(a)-methyltryptamine hydrochloride and 0.1 mL (ca. 50% excess) of methyl pyruvate in 5 mL of methanol was refluxed under nitrogen for 30 h. The cooled solution was concentrated under vacuum, and the residue was partitioned between 20 mL of 10% aqueous HCl and 10 mL of hexane. The aqueous layer was made basic with KOH and extracted with three 20-mL portions of dichloromethane. The extracts were washed with brine and concentrated to dryness, and the residue was dissolved in ethyl acetate and passed through 4 g of Baker silica gel. Concentration and Kueglrohr distillation (bp 150–160 °C, 0.03 mm) gave 158 mg (80%) of the tetrahydro-β-carboline **6b**: NMR ($CDCl_3$) δ 7.3 (m, 4 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.18 (t, 2 H), 2.78 (t, 2 H), 2.22 (br s, 1 H), 1.75 (s, 3 H). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.50; H, 6.94; N, 10.63. A picrate recrystallized from ethanol had mp 190–191 °C.

Minovine (4b). A. The preparation followed the procedure given for ervinceine. Starting with 129 mg of the β-carboline **6b** and using 50 mL of ether in place of ethyl acetate in the filtration through 2 g of silica gel gave 140 mg of crude product which showed two components by TLC [$R_f \sim 0.2$ and 0.7, major (minovine), ethyl acetate, silica gel, detection with cerric ammonium nitrate, blue spot with orange center for minovine]. Preparative TLC gave 65 mg (37%) of minovine as an oil with an NMR spectrum identical with that of a sample obtained by methylation of (±)-vincadifformine. The synthetic sample crystallized slowly from 10:1 hexane–ether and had mp and mmp 119–121 °C. A picrate was recrystallized from methanol–ether, mp and mmp 194–197 °C. The contaminant at R_f 0.2 was found to arise from minovine on storage. In subsequent reactions, minovine was obtained in 56% yield without preparative TLC.

B. A solution of 34 mg (0.10 mmol) of (±)-vincadifformine in 1 mL of DMF was added at 20 °C to a mixture of 10 mg (0.2 mmol) of 50% NaH–mineral oil in 1 mL of DMF. After 20 min, 20 μL (0.3 mmol) of methyl iodide was added to the brown solution. Then after 10 min, 5 mL of water was added, resulting in deposition of a gummy product. Decantation of the solvent, addition of ether, filtration of the ether solution through phase separating paper, and concentration of the residue under vacuum gave 30 mg (85%) of minovine, which showed no indolic NH singlet at δ 8.9 and the presence of the N–CH_3 singlet at δ 3.24, integrating for three protons. A picrate was prepared with mp 194–197 °C;

(8) R. H. F. Manske, *J. Am. Chem. Soc.*, **51**, 1202 (1929).
(9) S. Sugasawa and M. Murayama, *Chem. Pharm. Bull.*, **6**, 194 (1958).
(10) T. Hino, *Chem. Pharm. Bull.*, **9**, 988 (1961).
(11) H. Wieland, W. Kung, and H. Mittasch, *Justus* Liebigs *Ann. Chem.*, **613**, 1 (1939).
(12) A. W. Jackson and A. E. Smith, *J. Chem. Soc., Suppl.*, 5510 (1964).

regeneration of the free base gave minovine, mp 119–121 °C (lit.[3] mp 120–122 °C): MS (80 eV), *m/e* (rel intensity) 124 (100), 168 (7), 228 (4), 267 (7), 352 (55) M^+.

(±)-*N*(a)-Methylervinceine (4d). A solution of 35 mg (0.095 mmol) of (±)-ervinceine in 1 mL of dimethylformamide (DMF) was added to 10 mg (0.21 mmol) of 50% sodium hydride oil dispersion and 1 mL of DMF. After the solution was stirred under nitrogen for 0.5 h, 20 μL (~3 equiv) of methyl iodide was added, and stirring was continued for 15 min. The precipitate which formed on pouring the reaction mixture into 5 mL of water was filtered, washed with water, and dissolved in dichloromethane, and the solution was dried over sodium sulfate, filtered, and concentrated to 32 mg (88% yield) of an amorphous product, which showed only one product on TLC (R_f ~ 0.7, ethyl acetate, silica, detection with cerric ammonium nitrate, blue spot with orange center). Preparative TLC of the sample (Merck silica, ethyl acetate) gave 26 mg of recovered product which failed to crystallize: NMR ($CDCl_3$) δ 7.00–7.26 (m, same line shape as in ervinceine, 1 H), 6.30–6.50 (m, 2 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.22 (s, 3 H), 3.20–0.80 (m, 15 H), 0.64 (t, 3 H); MS (80 eV), *m/e* (rel intensity) 124 (100), 191 (10), 258 (10), 323 (15), 382 (90) M^+. A picrate had mp 115–118 °C.

Comparative TLC of Vincadifformine (4a), Minovine (4b), Ervinceine (4c), and *N*(a)-Methylervinceine (4d). With Merck silica on aluminum sheets (No. 5755), unactivated, ethyl acetate as solvent, and detection by spray with 10% cerric ammonium nitrate in phosphoric acid, the title compounds gave the following results: **4a**, R_f 0.86, blue with yellow center fades to yellow; **4b**, R_f 0.82, blue with orange center fades to purple with yellow center; **4c**, R_f 0.78, blue with yellow center fades to yellow; **4d**, R_f 0.72, blue with orange center fades to rose.

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Registry No. (±)-**1d**, 70369-12-9; (±)-**4a**, 18374-17-9; (±)-**4b**, 19621-72-8; (±)-**4b** picrate, 70469-81-7; (±)-**4c**, 69126-63-2; (±)-**4c** picrate, 70369-13-0; (±)-**4d**, 67497-53-4; (±)-**4d** picrate, 70369-14-1; **5a**, 61-54-1; **5a** HCl, 343-94-2; **5b**, 7518-21-0; **5b** HCl, 2826-96-2; **5c**, 3610-36-4; (±)-**6a**, 70369-15-2; (±)-**6b**, 70369-16-3; (±)-**6b** picrate, 70369-17-4; (±)-**6**, 70369-18-5; (±)-**7b**, 70369-19-6; (±)-**7c**, 66859-10-7; tryptamine phthalimide, 15741-71-6; *N*-methyltryptamine phthalimide, 70369-20-9; (±)-4-dimethoxymethylmethanesulfonyloxyhexane, 66859-28-7; dimethyl (±)-3-benzyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate, 70369-21-0; methyl (±)-3-benzyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate, 70369-22-1; methyl pyruvate, 600-22-6.

Michael Additions in Anhydrous Media. Novel Synthesis of Oxygenated Coumarins

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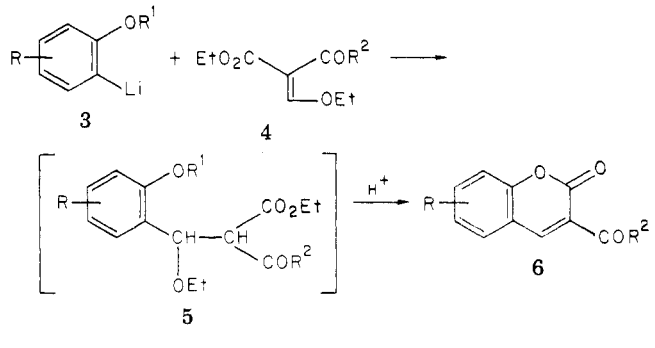
A general procedure is described where an aryllithium, generated by metalation of a protected phenol with *n*-butyllithium, adds in a conjugate manner to diethyl ethoxymethylenemalonate to give after acid hydrolysis an oxygenated 3-carbethoxycoumarin. By this procedure the ethyl vinyl ethers **9**, **11**, **13**, and **15** are converted into the corresponding coumarins **10**, **12**, **14**, and **16** in a single reaction vessel in good yield.

The coumarin moiety is widely distributed in nature. Many natural products which contain this subunit exhibit such useful and diverse biological activity as antifungal,[1] anticoagulant,[2] antispasmotic,[3] anticholerostatic,[4] and molluscacide[5] activity. In addition, other coumarins are of much interest as a result of their toxicity,[6] carcinogenicity,[7] and photodynamic effect.[8,9] In this paper a direct, efficient, and operationally convenient approach to the synthesis of oxygenated coumarins based on the Michael addition of aryllithiums to ethoxymethylenemalonates or ethoxymethyleneacetoacetates will be presented.

Scheme I



Results and Discussion

The approach described herein originated from our observation that methyl- and *n*-butyllithium add cleanly in a conjugate manner to ethyl ethoxymethyleneacetoacetate (eq 1). Since many aromatic compounds can be regioselectively metalated, we reasoned that a synthetic approach to the coumarin skeleton via Michael addition of aryllithium reagents followed by lactonization and elimination should be possible. This idea has been realized and is outlined in Scheme I.

(1) D. P. Chakraborty, A. Das Gupta, and P. K. Bose, *Ann. Biochem. Exp. Med.*, **17**, 57 (1957).
(2) R. B. Arora and C. N. Mathur, *Br. J. Pharmacol.*, **20**, 29 (1963); K. P. Link, *Harv. Lect.*, **39**, 162 (1943).
(3) R. E. Willette and T. O. Soine, *J. Pharm. Sci.*, **51**, 2, 149 (1962).
(4) D. Molho, E. Boschetti, and L. Fontaine, U.S. Patent 3175943 (1965); *Chem. Abstr.*, **64**, 14040a (1966).
(5) A. Schonberg and N. Latif, *J. Am. Chem. Soc.*, **76**, 6208 (1954).
(6) S. Kadis, A. Ciegler, and S. Ajl, *Microb. Toxins*, **7**, Chapter 1 (1972).
(7) G. P. Ellis and G. B. West, *Prog. Med. Chem.*, **10**, 109–115 (1974).
(8) R. Hoffmann, P. Wells, and H. Morrison, *J. Org. Chem.*, **36**, 102 (1971).
(9) P. Wells and H. Morrison, *J. Am. Chem. Soc.*, **97**, 154 (1975).

0022-3263/79/1944-2480$01.00/0