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SYNTHESIS OF ISOQUINOLINE ALKALOIDS. TOTAL SYNTHESIS OF (±)-STYLOPINE

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ABSTRACT.—A total synthesis of (±)-stylopine [**1**], an alkaloid of the protoberberine type, was carried out using a 3,4-dihydroisoquinoline [**2**]-boron trifluoride complex and the propylenedithioacetal of methoxycarbonylpiperonal [**3**] as the main building blocks. The condensation product **4** was the key intermediate in the synthesis and was transformed either into stylopine [**1**] or 8-oxostylopine [**5**], as well as dihydrocoptisine [**9**].

Stylopine (tetrahydrocoptisine) [**1**], an alkaloid of the protoberberine type, was isolated for the first time in 1902 by Schlotterbeck and Watkins from *Stylophorum diphyllum* (1). Its structure was determined by Spath and Julian, who isolated it from *Corydalis tuberosa* (2). Since that time stylopine [**1**] in both the racemic and the optically active *S*-(−) form, has been found in many different plants of the families Fumariaceae and Papaveraceae (3).

The protoberberine alkaloids play an important role as precursors in the biosynthesis of a variety of related isoquinoline alkaloids, such as protopines, phthalideisoquinolines, spirobenzylisoquinolines, rhoeadines, indenobenzoazepines, secoberbines, and benzo[c]-phenanthridines. The transformations between these alkaloids have been reviewed by Hanaoka (4).

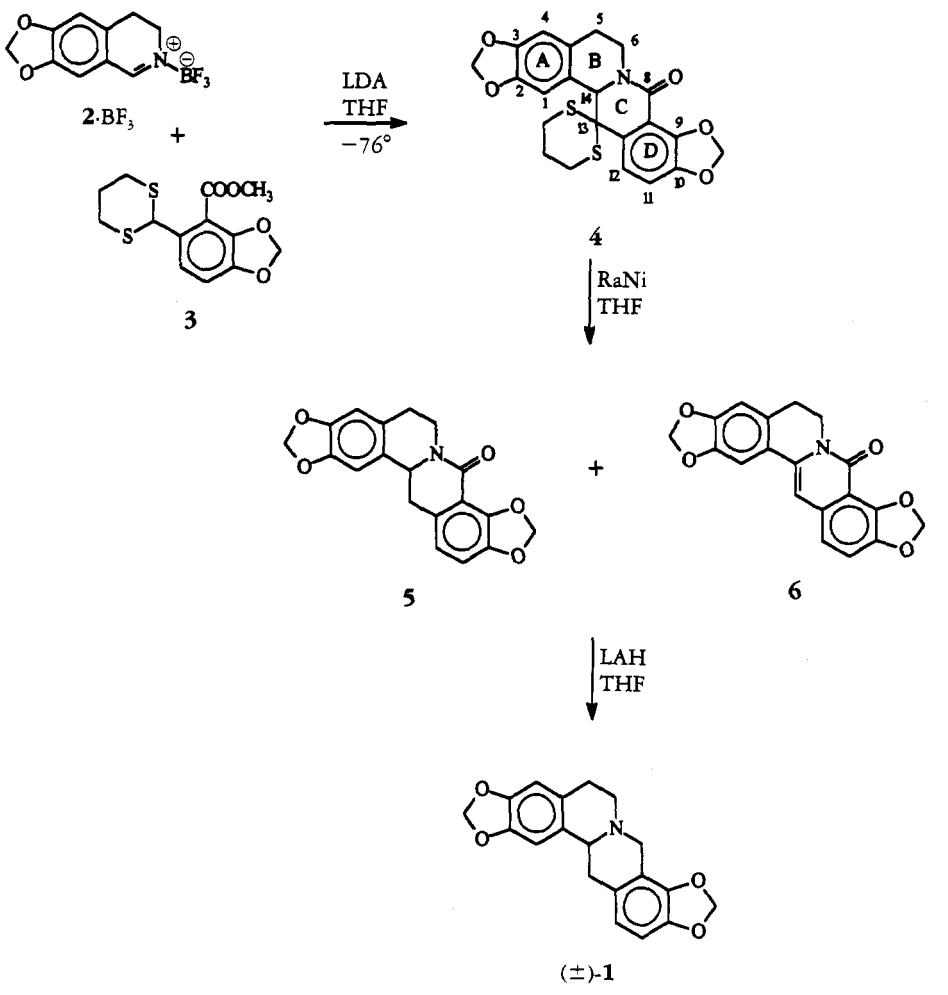
The protoberberine system has been synthesized in many different ways and there are several reviews that outline various approaches to the synthesis of this class of alkaloids (5,6), including syntheses of stylopine [**1**] itself (7–11).

In this paper we report a new and convergent synthesis of the protoberberine ring system from 3,4-dihydroisoquinoline [**2**] (12) and 1,3-dithiane [**3**] (13), according to a published synthetic strategy (13–18). This method has already been successful in the syntheses of 1,2-secobenzylisoquinolines (14,15), secoberbines (13,16), secophthalideisoquinolines (17), and benzylisoquinolines (18).

RESULTS AND DISCUSSION

Reaction of the 6,7-methylenedioxy-3,4-dihydroisoquinoline [**2**]-boron trifluoride complex (19), with the lithium salt of (2-methoxycarbonyl-3,4-methylenedioxyphenyl)-1,3-dithiane [**3**], resulted in formation of lactam **4** with the protoberberine carbon skeleton (Scheme 1).

The ir spectrum of lactam **4**, mp 267–268°, revealed a strong absorption band at 1650 cm^{-1}, characteristic of a δ-lactam. The ^{1}H-nmr spectrum indicated the presence of four methylene protons from the nitrogen-containing ring B manifested as four ddd at δ 2.67 (J_{gem}=15.1 Hz,J_{vic}=J_{vic}=2.5 Hz), 2.90 (J_{gem}=12.6 Hz,J_{vic}=12.6 Hz,J_{vic}=2.8 Hz), 3.49 (J_{gem}=15.1 Hz,J_{vic}=12.6 Hz,J_{vic}=4.5 Hz), and 4.92 (J_{gem}=12.6 Hz,J_{vic}=4.5 Hz,J_{vic}=2.1 Hz). The H-14 methine proton gave a singlet at δ 4.97. Methylene protons of the dithiane ring produced multiplets within the ranges δ 1.75–2.01 and 2.30–2.52. The protons of both methylenedioxy substituents appeared as AB quartets centered at δ 5.98 (J=1.3 Hz) and δ 6.15 (J=1.3 Hz), respectively. Two ortho- protons from the aromatic ring D gave rise to two doublets at δ 6.91 and 7.69 with J=8.3 Hz, whereas protons from aromatic ring A gave singlets at δ 6.70 and 7.42. In the mass spectrum, the $[M+1]^+$ ion was detected at *m/z* 442 in addition to the base peak at *m/z* 176 which is characteristic of the dihydroisoquinolinium ion (20).



SCHEME 1

Reductive desulfurization of lactam **4** with Raney nickel in THF at reflux in the presence of 1% NaOH resulted in a mixture of two compounds: the expected 8-oxostylopine [**5**] and 8-oxocoptisine [**6**]. The formation of dehydrolactam **6** is in agreement with the sometimes observed course of Raney nickel desulfurization of a compound which possess an α-hydrogen next to the thioacetal group (21). Analytically pure **5** and **6** were obtained after column chromatography and their structures were confirmed by spectroscopic methods. The ir spectrum of lactam **5**, mp 250–252°, revealed an absorption band at 1640 cm^{-1} (C=O), while for the dehydrolactam **6**, mp 289–291°, two bands were observed at 1660 (C=O) and 1620 (C=C) cm^{-1}. In the ^{1}H-nmr spectrum of compound **5**, the presence of the six methylene protons was manifested as multiplets within the ranges δ 2.70–2.93, 3.07–3.14, and 4.73–4.79, and the methine proton gave a multiplet at δ 4.92–4.97. The protons of one of the methylenedioxy substituents gave rise to an AB quartet centered at δ 6.12 (J=1.3 Hz), while those of the other one gave a singlet at δ 5.96. The four protons from the aromatic rings were represented as multiplets at δ 6.66–6.69 and 6.85–6.88. In the mass spectrum, the M^+ ion is detected at *m/z* 337, and the base peak at *m/z* 134 corresponds to the methylenedioxytropolonic ion, formed from the M^+ ion in a retro-Diels-Alder reaction

followed by loss of CO. 8-Oxostylopine [**5**] was previously described by Shono and coworkers who reported a new electroreductive reaction applicable to the synthesis of berbine-type compounds but did not give any characteristics of compound **5** (22).

In the ^{1}H-nmr spectrum of dehydrolactam **6**, protons from the methylene group of ring B appeared as two triplets at δ 2.88 and 4.27 with J=6.1 Hz. Methylenedioxy protons gave rise to two 2-proton singlets at δ 6.00 and 6.21. The aromatic protons from ring A could be seen as two singlets at δ 6.73 and 7.19, whereas those of ring D appeared as two doublets at δ 7.03 and 7.15 (J=8.3 Hz), respectively. The vinylic proton gave rise to a singlet at δ 6.70. In the mass spectrum of **6** the M^+ ion at *m/z* 335 was also the base peak.

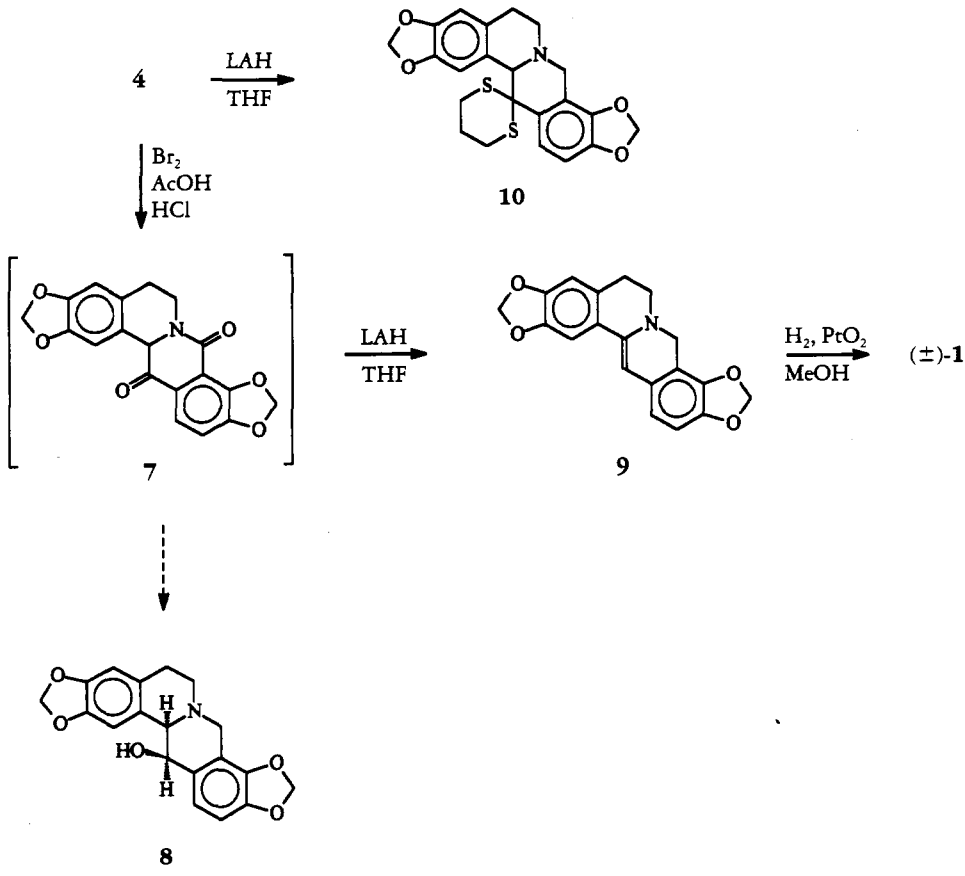
The reduction of the mixture of both lactams **5** and **6** with $LiAlH_4$ in THF led to the formation of racemic stylopine [**1**], yield 40%, mp 216–218°. In the literature, the following mp values have been recorded for the racemic form of this compound: 228–229° (7), 217–218° (8), 194–195° (9), 213–215° (10), and 198–200° (11). The ir, ^{1}H-nmr and mass spectra of our synthetic stylopine [**1**] corresponded to those reported in the literature (9,11,20).

The hydrolytic removal of the dithiane masking group in lactam **4**, and the subsequent reduction of the 8,13-dioxo compound **7**, should afford another alkaloid from the protoberberine group, 13-hydroxystylopine [**8**]. This alkaloid was isolated by Jeffs and Scharver from *Corydalis ophiocarpa* in 1975 (23). Although the chemistry of 8,13-dioxoberbines has been throughly investigated by Shamma and others (24), there is not much literature data on 8,13-dioxostylopine [**7**] itself.

For the hydrolysis of the dithiane masking group in lactam **4**, bromine in a mixture of HOAc and HCl was used. The resulting 8,13-dioxo compound **7** could not be fully characterized due to its instability. Therefore, the crude reaction product was reduced with $LiAlH_4$ to obtain dihydrocoptisine [**9**], apparently a dehydration product, not the expected 13-hydroxystylopine [**8**]. The structure of **9** was confirmed on the basis of ir, hrms, and ^{1}H-nmr spectra, and by catalytic hydrogenation, which gave stylopine [**1**] quantitatively (Scheme 2).

Another approach to the synthesis of 13-hydroxystylopine [**8**] from lactam **4** involved $LiAlH_4$ reduction prior to dithiane hydrolysis. This reduction was performed either in Et_2O at room temperature or in refluxing THF to give compound **10** in 52% yield, mp 179–180°. Dithiane **10** showed weak absorption bands in the ir spectrum at 2920, 2900, and 2800 cm^{-1}, characteristic of -CH and =CH. The ^{1}H-nmr spectrum indicated the presence of signals of four methylene protons from the nitrogen-containing ring B along with six protons from the dithiane ring as five multiplets at δ 1.79–1.92, 2.15–2.23, 2.40–2.76, 3.11–3.17, and 3.28–3.33. Two methylene protons from ring C gave rise to two doublets at δ 3.87 and 4.05 with J=15.4 Hz. The methine proton was represented by a singlet at δ 4.19 whereas the protons of one of the methylenedioxy substituents appeared as an AB quartet centered at δ 5.94 (J=1.4 Hz), with the other one as a singlet occurring at δ 5.95. Two ortho- protons from the aromatic ring D were seen as two doublets at δ 6.73 and 7.82, respectively (J=8.0 Hz). Protons from the aromatic ring A gave two singlets at δ 6.65 and 7.67. In the mass spectrum, the M^+ ion could be detected at *m/z* 427 in addition to the base peak at *m/z* 174, which is characteristic of the isoquinolinium ion (20), and the ion at *m/z* 148 may correspond to methylenedioxycyclooctatrienyl ion $[C_9H_8O_2]^+$ derived from the lower part of the molecule.

Hydrolysis of the dithiane grouping in compound **10** proved to be difficult. Therefore, dihydro derivative **9** seems to be the best intermediate in the synthesis of 13-hydroxystylopine [**8**] to date (23).



SCHEME 2

Stylopine [**1**] is an interesting compound because of its biological activity. It belongs to the most active group of alkaloids tested against Gram-positive and Gram-negative bacteria at 1 mg/liter concentration (25). Neuropsychopharmacological studies using (*S*)(−)-**1** with mice and rats have indicated this methylenedioxy-substituted tertiary base to possess antipsychotic and neuroleptic activity (26). Several tetrahydroisoquinolines have been investigated for their in vitro affinities for rat brain α-adrenoceptors. Among these, (*S*)-(−)-stylopine [**1**] was the most potent inhibitor of [^{3}H]WB4101-binding to α_1-adrenoceptors, more so than to α_2-adrenoceptors (27,28). The effects of 36 tetrahydroisoquinolines on [^{3}H]QNB (quinuclidinyl benzilate) binding to the muscarinic receptors of the rat brain were investigated by receptor binding in vitro. The affinities of stylopine [**1**] were relatively high (29). During the determination of the trypanocidal activity of isoquinoline alkaloids in mice, stylopine [**1**] was found to be fairly toxic (30).

In comparison with other methods of the total synthesis of stylopine [**1**], the strategy described here based on addition of lithiated 1,3-dithiane to 3,4-dihydroisoquinoline is one of the shortest. There is the possibility of obtaining other members of alkaloids of the protoberberine group by using suitably substituted aromatic aldehydes and 3,4-dihydroisoquinolines as substrates.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on a Kofler block and are uncorrected.

Ir spectra were taken in KBr pellets on a Perkin-Elmer 180. High-resolution ms measurements were performed on a JEOL JMS-D-100 by peak matching (resolution=8000) using perfluorokerosene as the reference standard. Ei mass spectra were measured on Hewlett Packard 5987A. ^{1}H-nmr spectra were recorded in $CDCl_3$ solution on Varian Gemini 300, using TMS as internal standard. The purity of all compounds prepared was checked by tlc on precoated plates (Merck, Si gel 60 F_{254}). Merck Si gel 60 (200–300 mesh) was used for cc.

LACTAM **4**.—*n*-Butyllithium (2.2 mmol) was added to a solution of diisopropylamine (0.22 g, 2.2 mmol) in dry THF (4 ml) at 0° under an Ar atmosphere and kept at this temperature for 10 min. The solution was cooled to −76° and dithiane **3** (13) (0.61 g, 2.1 mmol) in THF (4 ml) was introduced dropwise, yielding a violet-colored reaction mixture. The carbanion solution was kept for 30 min at −76° and a suspension of imine **2** (12)-boron trifluoride complex [prepared by treating the imine **2** (0.42 g, 2.4 mmol) in THF (4 ml) with 1.2 equivalents of boron trifluoride etherate at −76° for 20 min (19)] was added. The color of the reaction mixture changed to yellow. The reaction mixture was stirred for 2 h at −76° and then poured onto 10% K_2CO_3 (ca. 10 ml). Phases were separated and the aqueous one was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated to give 1.0 g of a yellow solid. Crystallization from CH_2Cl_2/Et_2O gave 0.51 g of the product **4**, mp 267–268°. The mother liquors were chromatographed on Si gel (1:10) with CH_2Cl_2/MeOH to give an additional 0.1 g of lactam (yield 66%). Ir (KBr) ν max 3400 (br) water of crystallization, 1650 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.75–2.01 (3H, m, SCH_2), 2.30–2.52 (3H, m, SCH_2), 2.67 (1H, ddd, J_{gem}=15.1 Hz, J_{vic}=J_{vic}=2.5 Hz, H-5), 2.90 (1H, ddd, J_{gem}=12.6 Hz, J_{vic}=12.6 Hz, J_{vic}=2.8 Hz, H-6), 3.49 (1H, ddd, J_{gem}=15.1 Hz, J_{vic}=12.6 Hz, J_{vic}=4.5 Hz, H-5), 4.92 (1H, ddd, J_{gem}=12.6 Hz, J_{vic}=4.5 Hz, J_{vic}=2.1 Hz, H-6), 4.97 (1H, s, H-14), 5.98 (2H, ABq, J=1.3 Hz, OCH_2O), 6.15 (2H, ABq, J=1.3 Hz, OCH_2O), 6.70 (1H, s, H-1 or H-4), 6.91 (1H, d, J=8.3 Hz, H-11 or H-12), 7.42 (1H, s, H-1 or H-4), 7.69 (1H, d, J=8.3 Hz, H-11 or H-12); eims (70 eV) *m/z* [M+1]$^+$ 442 (90), 208 (7), 176 (100), 174 (17); *anal.*, found, C 56.79, H 4.38, N 2.91, $C_{22}H_{19}NO_5S_2\times3/2\ H_2O$ requires C 56.40, H 4.73, N 2.99%.

DESULFURIZATION OF LACTAM **4** WITH RANEY NICKEL.—To a suspension of lactam **4** (0.22 g, 0.5 mmol) in THF (30 ml) and 1% NaOH (5.3 ml) Raney nickel W-2 (ca. 1.5 g) was added and the mixture was stirred at reflux for 3 h and then an additional ca. 1.5 g of Raney nickel were added. Reflux was continued for 1.5 h and then the reaction mixture was left overnight with stirring at room temperature. On the next day, the reaction mixture was filtered through Celite and the catalyst was washed with $CHCl_3$. The organic filtrates were combined and evaporated *in vacuo*. The resulting yellow solid was crystallized from $MeOH/CH_2Cl_2$, giving yellow needles (0.13 g, 76%), mp 264–266° and 280–282°, being a mixture of two compounds: 8-oxostylopine [**5**] and 8-oxocoptisine [**6**]. Analytical samples of pure **5** and **6** were obtained after two cc separations on Si gel (1:20) with CH_2Cl_2 as eluent.

8-Oxostylopine [**5**].—Mp 250–252°; ir (KBr) ν max 1640 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 2.70–2.93 (4H, m, CH_2), 3.07–3.14 (1H, m, CH_2), 4.73–4.79 (1H, m, CH_2), 4.92–4.97 (1H, m, H-14), 5.96 (2H, s, OCH_2O), 6.12 (2H, ABq, J=1.3 Hz, OCH_2O), 6.66–6.69 (3H, m, Ar-H), 6.85–6.88 (1H, m, Ar-H); eims (70 eV) *m/z* [M]$^+$ 337 (21), 322 (4), 162 (56), 134 (100); hrms *m/z* [M]$^+$ 337.0951 ($C_{19}H_{15}NO_5$ requires 337.0949).

8-Oxocoptisine [**6**].—Mp 289–291°; ir (KBr) ν max 1660 (C=O), 1620 (C=C) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 2.88 (2H, t, J=6.1 Hz, $ArCH_2$), 4.27 (2H, t, J=6.1 Hz, $ArCH_2CH_2N$), 6.00 (2H, s, OCH_2O), 6.21 (2H, s, OCH_2O), 6.70 (1H, s, CH=C), 6.73 (1H, s, H-1 or H-4), 7.03 (1H, d, J=8.3 Hz, H-11 or H-12), 7.15 (1H, d, J=8.3 Hz, H-11 or H-12), 7.19 (1H, s, H-1 or H-4); eims (70 eV) *m/z* [M]$^+$ 335 (100), 320 (80); hrms *m/z* [M]$^+$ 335.0794 ($C_{19}H_{13}NO_5$ requires 335.0793).

STYLOPINE [**1**].—A mixture of compounds **5** and **6** (0.13 g, 0.39 mmol) was dissolved in dry THF (50 ml) and $LiAlH_4$ (0.14 g) was added. The mixture was stirred at reflux for 1.5 h, cooled and then the excess of reducing agent was decomposed with H_2O and 20% NaOH. The organic layer was decanted and the inorganic residue was extracted with Et_2O until a Dragendorff test was negative. The combined organic extracts were dried (Na_2SO_4) and evaporated to give 0.13 g of an oily residue. This was chromatographed on Si gel (1:20) with CH_2Cl_2 to give 0.05 g (40%) of stylopine [**1**], which was crystallized from CH_2Cl_2/Et_2O, mp 216–218° [lit. 228–229° (7), 217–218° (8), 194–195° (9), 213–215° (10), 198–200° (11)]; ir (KBr) ν max 2920, 2800, 2750 (Ar-H, C-H), 1500, 1480, 1460 (C=C, C-N) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 2.57–2.84 (3H, m, CH_2), 3.05–3.26 (3H, m, CH_2), 3.53 (1H, d, J=15.0 Hz, H-8), 3.54–3.59 (1H, m, H-14), 4.10 (1H, d, J=15.0 Hz, H-8′), 5.92 (2H, s, OCH_2O), 5.94 (2H, ABq, J=1.4 Hz, OCH_2O), 6.59 (1H, s, H-1 or H-4), 6.62 (1H, d, J=8.0 Hz, H-11 or H-12), 6.68 (1H, d, J=8.0 Hz, H-11 or H-12), 6.72 (1H, s, H-1 or H-4); eims (70 eV) *m/z* [M]$^+$ 323 (9), 174 (52), 148 (100); hrms *m/z* [M]$^+$ 323.1167 ($C_{19}H_{17}NO_4$ requires 323.1167).

HYDROLYSIS OF DITHIANE **4**.—To a well-stirred solution of dithiane **4** (0.22 g, 0.5 mmol) in HOAc

(5 ml) containing 18% HCl (0.5 ml), a mixture of bromine (0.02 ml) in HOAc (1 ml) was added at 70°. It was then allowed to cool to room temperature and after 2 h basified with 25% KOH, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated to give a yellow solid (0.11 g) (tlc, mainly one spot). On the basis of the ir and ^{1}H-nmr spectra it was not possible to determine its structure. This solid was then used for further transformation.

A suspension of the yellow compound (0.1 g) in dry THF (40 ml) and $LiAlH_4$ (0.1 g) was refluxed for 2 h and allowed to cool to room temperature. The excess of the reducing agent was decomposed with H_2O and 20% NaOH. The organic layer was decanted and the inorganic residue was extracted with Et_2O until a Dragendorff test was negative. The combined organic extracts were dried (Na_2SO_4) and evaporated to give 0.09 g of an oily compound. Cc (1:20) with CH_2Cl_2 eluted 0.07 g of a substance, which after crystallization from Et_2O, afforded dihydrocoptisine [**9**], 35 mg (22% yield, based on **4**), mp 215° (dec) [lit. 175–179° (31), 194–196° (23)]; ir (KBr) ν max 2920, 2900, 2780 (Ar-H, C-H), 1580 (C=C from dehydrolactam ring), 1500, 1490, 1480, 1460 (C=C, C-N) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 2.87 (2H, t, J=6.0 Hz, CH_2), 3.11 (2H, t, J=6.0 Hz, CH_2), 4.24 (2H, s, CH_2), 5.92 (2H, s, OCH_2O), 5.94 (2H, s, OCH_2O), 5.98 (1H, s, C=CH), 6.50 (1H, d, J=8.0 Hz, H-11 or H-12), 6.58 (1H, s, H-1 or H-4), 6.64 (1H, d, J=8.0 Hz, H-11 or H-12), 7.16 (1H, s, H-1 or H-4); eims (70 eV) *m/z* [M]$^+$ 321 (20), 320 (80), 319 (100); hrms *m/z* [M]$^+$ 321.0998 ($C_{19}H_{15}NO_4$ requires 321.1000).

Hydrogenation of dihydrocoptisine [**9**].—A solution containing dihydrocoptisine [**9**] (0.02 g, 0.06 mmol) in MeOH (20 ml) was hydrogenated at atmospheric pressure in the presence of PtO_2 catalyst (5 mg) for 3 h. The solution was filtered and the filtrate was concentrated under vacuum affording 0.019 g of solid, mp 219–222°, identical by tlc and ^{1}H-nmr data to stylopine [**1**].

REDUCTION OF LACTAM **4**.—A suspension of lactam **4** (0.44 g, 1.0 mmol) in dry THF (50 ml) and $LiAlH_4$ (0.44 g), was refluxed for 2 h. The reaction mixture was cooled to room temperature, and the excess of the reducing agent decomposed with H_2O and 20% NaOH. The organic layer was decanted and the inorganic residue was extracted with Et_2O until a Dragendorff test was negative. The combined organic extracts were dried (Na_2SO_4) and evaporated to give 0.41 g of a yellow foam. It was chromatographed on Si gel (1:20) with C_6H_6 to give compound **10**, 0.22 g (52%) in the form of a slightly yellow foam. Mp 179–180°; ir (KBr) ν max 2920, 2900, 2800 (C=C, C-N) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.79–1.92 (2H, m, CH_2), 2.15–2.23 (1H, m, CH_2), 2.40–2.76 (5H, m, CH_2), 3.11–3.17 (1H, m, CH_2), 3.28–3.33 (1H, m, CH_2), 3.87 (1H, d, J=15.4 Hz, H-8), 4.05 (1H, d, J=15.4 Hz, H-8), 4.19 (1H, s, H-14), 5.94 (2H, ABq, J=1.4 Hz, OCH_2O), 5.95 (2H, s, OCH_2O), 6.65 (1H, s, H-1 or H-4), 6.73 (1H, d, J=8.0 Hz, H-11 or H-12), 7.67 (1H, s, H-1 or H-4), 7.82 (1H, d, J=8.0 Hz, H-11 or H-12); eims (70 eV) *m/z* [M]$^+$ 427 (1), 320 (3), 174 (100), 148 (28); *anal.*, found, C 61.50, H 5.05, N 3.09, $C_{22}H_{21}NO_4S_2$ requires C 61.81, H 4.95, N 3.28%.

ACKNOWLEDGMENTS

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