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THE SYNTHESIS OF (±)-MESEMBRINE[1]

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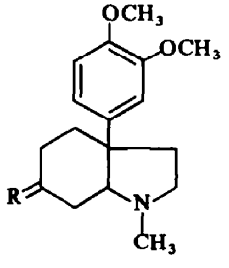
Abstract—The nitrostyrene **4** was condensed with butadiene to the nitrocyclohexene **5**. Ketone **7**, obtained by a Nef reaction on **5** followed by preferential catalytic reduction, was alkylated with allyl bromide to yield olefin **8**. Reduction with LAH, followed by acetylation afforded the olefin acetate **11**. The acid acetate **13**, formed by OsO_4–$NaIO_4$ oxidation of **11** to the aldehyde acetate **12** and further oxidation of **12** with silver oxide, was converted to the amide **14**. LAH reduction gave the amino alcohol **15**. The N-formyl amide **15a** was oxidized to the ketone **16**. Bromination to **17**, followed by dehydrobromination, produced the eneone **18**. Epoxidation to **19** was carried out with Clorox, and reduction of **19** using chromous acetate gave the β-hydroxyketone **20**. Further reduction with $NaBH_4$ afforded the desired diol **21**. Preferential oxidation with Pt/air, followed by acid catalyzed dehydration, finally yielded (±)-mesembrine (1).

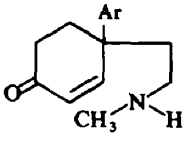
STRUCTURE **1** for mesembrine, the main alkaloid from *Sceletium tortuosum* N. E. Br., formerly *Mesembrianthemum tortuosum*, of the family Azoaceae, was first arrived at by Popelak *et al.* through a series of chemical transformation on the alkaloid, and the synthesis of the degradation product mesembrane **2**.[2, 3]

Since mesembrine is a β-amino ketone, the best synthetic approach to the alkaloid seemed to be the preparation of the precursor **3**. It was felt that if this molecule could be synthesized, it would immediately undergo an intramolecular Michael type reaction to yield mesembrine.[4]

The starting material was the nitrostyrene **4** which was prepared from veratraldehyde and nitromethane.[5] Diene condensation was accomplished with butadiene to give the nitrocyclohexene **5** in good yield, and a Nef reaction was then run on the



1: R = O
2: R = 2H



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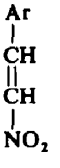
Ar = 3,4-Dimethoxyphenyl



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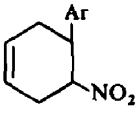

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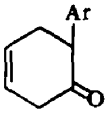
sodium salt of **5** to obtain the ketone **6**.[6] Considerable difficulty was originally encountered with the Nef reaction in that intractable oils were obtained that could only be crystallized after long standing in the cold. However, after it was realized that solutions of the sodium salt of **5** were sensitive to both heat and oxygen, considerable improvement of the yield was achieved. It was later found that extraction of the crude

Nef product with both acid and base removes materials which apparently retard crystallization. When these refinements were incorporated in the original procedure, an 80% yield of high purity material was realized. Hydrogenation of the Nef product over 5% Pd/C preferentially reduced the double bond to give the ketone **7**.

At this stage it was necessary to introduce a side chain at the tertiary carbon atom of compound **7**. Ideally, this chain was to consist of two carbons and a functional group which could easily be converted to an amine. The first system used was chloroacetonitrile and potassium t-butoxide as the condensing agent, but no material could be obtained that corresponded to the desired product. A series of alkylating agents were then tried, namely, bromoethyl acetate, bromoacetic acid, N-methylenimine and bromoethylamine.[7] Again no desired product could be isolated. Finally, reaction of ketone **7** with allyl bromide and either NaH or $NaNH_2$ as the condensing agent gave the monoalkylated product **8** in high yield. The difficulty in alkylation is not unusual in systems of this type since Okada encountered the same difficulty with the ketone **9**.[8] Confirmation of the position of alkylation was accomplished by the preparation of a piperonylidene derivative of **8**.



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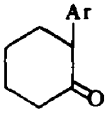

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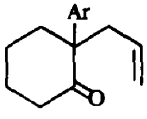

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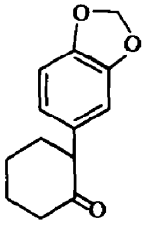

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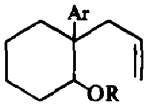
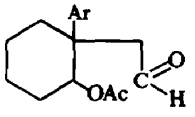
The ketone **8** was now reduced with LAH to yield the alcohol **10** and the latter compound esterified with acetic anhydride and pyridine to the acetate **11**. In an attempt to prepare the aldehyde **12** the useful oxidizing system consisting of catalytic quantities of OsO_4 and two molar equivalents of $NaIO_4$ was utilized.[9] This oxidizing mixture was sufficiently mild because a high yield of the desired compound **12** was obtained.



10: R = H
11: R = acetyl



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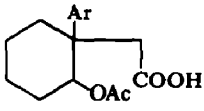

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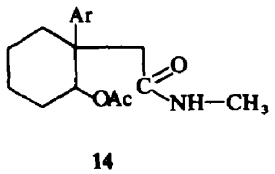
However, difficulties were encountered when the oxidation of the olefin was attempted on a large scale. The yield was observed to decrease constantly as the amount of **11** was increased above 5 g. The procedure was then changed from the original literature directions which called for the addition of solid $NaIO_4$ in small amounts to a solution of the substrate olefin and catalytic amounts of OsO_4. Instead, a dilute solution of the oxidant in water was added to the olefin through a capillary

tip over approximately 10 hr. This method was found to be satisfactory for quantities of olefin weighing up to 50 grams.

It was now necessary to convert the aldehyde **12** to an N-methylamino derivative. The reaction sequence of choice for performing this transformation consisted first of oxidation of the aldehyde **12** with silver oxide to give a 93% yield of the acid **13**. The acid chloride obtained from the oxalyl chloride treatment of **13** was then reacted immediately with methylamine for a quantitative yield of the amide **14**. Subsequent reduction with LAH readily afforded the amino alcohol **15**, and the amino function was further protected by acetylation and formation of the amide alcohol **15a**. Jones oxidation of this amide alcohol afforded the amide ketone **16**. α-Bromination of



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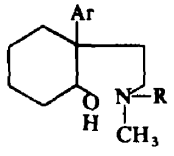
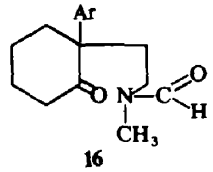


15 : R = H
15a: R = formyl



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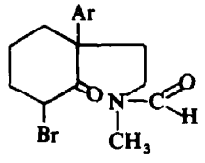
16 by means of phenyltrimethylammonium tribromide,[10] followed by dehydrohalogenation of the bromoketone **17** with $CaCO_3$ in refluxing dimethylformamide yielded the key eneone **18**. The problem was now to rearrange this compound to the desired eneone 3, and this transformation was achieved by the following sequence.

The epoxy ketone **19** obtained by Clorox oxidation[11] of eneone **18** was reduced with chromous acetate[12] and the crude reaction mixture obtained was separated by preparative TLC. The main component proved to be the hydroxy ketone **20**.



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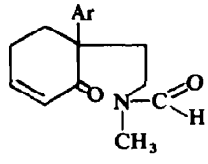

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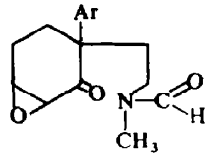

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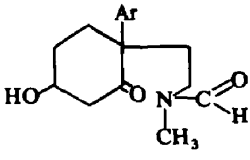

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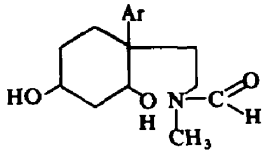

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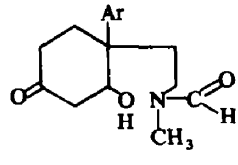

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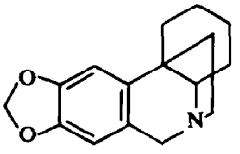
In fact, when a sample of compound **20** was subjected to mild acid dehydration a quantitative yield of the known eneone **18** was obtained. The diol **21**, produced by $NaBH_4$ reduction **20**, was found to be stable to $NaIO_4$, and must therefore be a 1,3-diol.

It was now necessary to oxidize preferentially the alcohol group *gamma* to the quaternary carbon in diol **21**. There are only a limited number of methods available for the preferential oxidation of the less hindered alcohol in a diol system, but the system Pt/air was eminently simple and selective.[13] After three days reaction of the diol **21** with Pt/air in ethyl acetate, the IR spectrum of the crude mixture indicated the development of carbonyl absorption. Subsequent acid catalyzed dehydration of the ketoalcohol **22** was accompanied by hydrolysis of the formyl function. When the reaction mixture was made basic with sodium bicarbonate, (±)-mesembrine (**1**) was obtained without the actual isolation of the eneone precursor **3**. The synthetic sample compared favorably with natural mesembrine in its IR spectra in $CHCl_3$ and CS_2 solution, and its NMR spectrum and thin layer chromatograms in ten different solvent systems.

The stereochemical problem involved in the synthesis of mesembrine was never considered a difficult one. Since mesembrane (**2**) had been synthesized[3] by a route somewhat similar to that used for the preparation of crinane (**23**)[14] it was known that



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mesembrane had to be *cis* fused. It follows that mesembrine also must have a *cis* junction.[15] The synthetic scheme described in the present paper bears some analogies to the crinane and mesembrane syntheses, and also leads to *cis* fusion.

EXPERIMENTAL

Standard experimental procedure. All IR spectra were recorded in $CHCl_3$ on either a Beckman IR-5 or an IR-5a spectrophotometer NMR spectra were measured on a Varian A-60 spectrometer in $CDCl_3$ solution using TMS as an internal standard. The mass spectra were obtained with a single focus Nuclide 12-90-Gl. 1 mass spectrometer. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. All m.ps are uncorrected.

6-(3,4-Dimethoxyphenyl)-3-cyclohexen-1-one (**6**). A soln of 23·8 g (0·091 mole) of **5** was prepared in 600 ml hot, deoxygenated 95% EtOH. All subsequent operations were carried out under a N_2 atm. The soln was then added all at once to EtONa aq prepared from 5·10 g (0·217 moles) Na in 150 ml abs EtOH. The resulting soln was rapidly cooled in an ice bath and allowed to stand for ½ hr at room temp. The soln was then added over 1½ hr with vigorous stirring to an ice cold soln of 120 ml conc HCl, 400 ml distilled water, 300 ml 95% EtOH and 1·8 g urea. The soln was stirred an additional hr at 0° and ½ hr at room temp. The reaction mixture was diluted with an equal volume of water and after saturation with CH_2Cl_2, extracted with five 200 ml portions of the same solvent. The extracts were washed with sat $NaHCO_3$ aq and water, dried over $MgSO_4$, and evaporated *in vacuo* to give 20 g of a dark yellow oil. The oil was purified for an analytical sample by slow crystallization from EtOH and sublimation at 100° (1 mm) to yield white crystals, m.p. 73·5–75·0°, λ_{max} 5·82 and 6·09 μ. (Found: C, 72·67; H, 7·18. Calc. for $C_{14}H_{16}O_3$: C, 72·39; H, 6·94%).

2-(3,4-Dimethoxyphenyl)cyclohexanone (**7**). A soln of 40 g (0·17 mole) of **6** was made in 250 ml abs EtOH. To this was added 1·0 g 5% Pd/C. The mixture was hydrogenated at an initial press of 40 psi with shaking on a Parr hydrogenator until the theoretical amount of H_2 was consumed (approximately 3 hr). The mixture was then filtered through Filter Cel and evaporation of the filtrate *in vacuo* gave 39 g of an orange oil.

The above procedure was repeated 3 times and the combined products dissolved in 4 l. of ether. The soln was then washed successively with 10% NaOH aq, 10% HCl and water until each separate washing was substantially free from color. The organic layer was then dried over $MgSO_4$, filtered and evaporated *in vacuo* to give an oil. The oil was triturated with cold ether to give a solid which was filtered off, washed with a minimum amount of cold ether and air-dried to yield 84 g (70%) of a light yellow solid. An analytical sample was prepared by sublimation at 100° (1 mm) to give white crystals, m.p. 65° (lit. 68–70°).

2-*Allyl*-2-(3,4-*dimethoxyphenyl*)*cyclohexanone* (**8**). A soln of 54 g (0·20 mole) of **7** in 500 ml benzene was added dropwise with 12 g (0·25 mole) 50% NaH in 100 ml refluxing benzene. The mixture was refluxed an additional 10 hr and then a soln of 22 ml (0·25 moles allyl bromide in 100 ml benzene) was added dropwise and the whole refluxed overnight. The mixture was then cooled and water was added cautiously to destroy the excess NaH. The benzene layer was diluted with 2 l. ether, washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil, 60 g (95%). An analytical sample was prepared by chromatography on Baker's acidic alumina. The IR spectrum exhibited peaks at 5·88 and 6·10 μ; the NMR spectrum revealed vinylic absorption from 4·6–5·3 ppm. (Found: C, 74·46; H, 8·26. Calc. for $C_{17}H_{22}O_3$: C, 74·42; H, 8·08%).

A piperonylidene derivative was prepared, m.p. 135–137°; λ_{max} 6·00 μ. (Found: C, 73·92; H, 6·53. Calc. for $C_{25}H_{26}O_5$: C, 73·86; H, 6·45%).

2-*Allyl*-2-(3,4-*dimethoxyphenyl*)*cyclohexanol* (**10**). To a mixture of 6·0 g (0·16 mole) LAH in 500 ml dry ether, a soln of 44 g (0·16 mole) of **8** in 750 ml dry ether was added dropwise with stirring. The heterogeneous mixture was stirred an additional 2 hr and water was then cautiously added to destroy the excess LAH. The Li and Al salts were filtered off and washed with ether. The combined filtrates were evaporated under N_2 to a small volume and cooled in an ice bath. The ppt formed was filtered off and washed with a minimum amount of cold ether. The filtrates were combined and the process repeated. The combined solids amounted to 31 g (70%), m.p. 115–116·5; λ_{max} 2·88 and 6·11 μ. (Found: C, 74·00; H, 8·95. Calc. for $C_{17}H_{24}O_3$; C, 73·88; H, 8·75%).

2-*Allyl*-2-(3,4-*dimethoxyphenyl*)*cyclohexyl acetate* (**11**). A soln of 30 g (0·11 mole) of **10** in 100 ml dry pyridine and 40 ml Ac_2O was refluxed for 2 hr. The soln was then poured into ice water and allowed to stand for 15 min. It was then extracted with $CHCl_3$. The organic layer was washed with 10% HCl and water, dried over $MgSO_4$ and evaporated *in vacuo* to give 32 g (92%) of a light yellow oil. A sample was purified for analysis by chromatography on Baker's acidic alumina. The IR spectrum exhibited peaks at 5·80 and 6·10 μ. (Found: C, 71·93; H, 8·22. Calc. for $C_{19}H_{26}O_4$: C, 71·67; H, 8·23%).

2-*Acetoxy*-1-(3,4-*dimethoxyphenyl*)*cyclohexaneacetaldehyde* (**12**). A soln of 28 g (0·09 mole) of **11** was prepared in 540 ml pure dioxan. To this was added 2·0 g (7·8 mmoles) OsO_4. The soln was stirred in the dark for 15 min in order to allow the osmate ester to form. The soln was then diluted with 180 ml distilled water. To this was added a soln of 46 g (0·21 moles) $NaIO_4$ in 320 ml distilled water over 10 hr. The mixture was then stirred overnight in the dark. The salts were filtered and the filter cake washed with dry ether. The filtrate was diluted with 4 l. of ether, washed with 10% $Na_2S \cdot 9H_2O$ soln until the aqueous washings were free from ppt or color and then washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to an oil. The oil was triturated with cold ether and the solid obtained was filtered and washed with cold ether. The filtrates were combined and the process repeated to give a total of 22 g (79%) of a white solid, m.p. 94–95°; λ_{max} 3·72 and 5·85 μ. (Found: C, 67·45; H, 7·51. Calc. for $C_{18}H_{24}O_5$: C, 67·48; H, 7·55%).

2-*Acetoxy*-1-(3,4-*dimethoxyphenyl*)*cyclohexaneacetic acid* (**13**). To a soln of 9·5 g (0·03 mole) of **12** in 150 ml abs EtOH, a soln of 11 g (0·07 mole) $AgNO_3$ in 15 ml distilled water was added. To this was added dropwise with stirring 150 ml of a KOH soln (21 g KOH dissolved in 350 ml water). The heterogeneous mixture was stirred an additional 2 hr. The mixture was then filtered and the Ag salts washed with an equal volume of water. The basic soln was extracted several times with ether and the washings discarded. The soln was now made acidic with conc HCl and extracted well with $CHCl_3$. The extracts were washed once with a small volume of water, dried over $MgSO_4$, and evaporated *in vacuo* to yield an oil. Trituration with cold ether gave 9·3 g (93%) of a white solid, m.p. 137–140°; λ_{max} 2·91, 5·80 and 5·88 μ. (Found: C, 64·90; H, 7·41. Calc. for $C_{18}H_{24}O_6$: C, 64·27; H, 7·19%).

2-*Acetoxy*-1-(3,4-*dimethoxyphenyl*)*cycloxhexaneacetyl chloride* (*acid chloride of* **13**). To a soln of 31·7 g (0·094 mole) of **13** in 500 ml dry benzene was added 17·0 ml (0·190 mole) oxalylchloride. The soln was stored in the dark for 2 hr and then the benzene and excess reagent were stripped off *in vacuo* with just enough heat to keep the soln fluid. An oil was obtained which exhibited peaks in its IR spectrum at 5·6 and 5·8 μ. The oil was not analyzed but used directly for the next step.

2-*Acetoxy*-1-(3,4-*dimethoxyphenyl*)-N-*methylcyclohexaneacetamide* (**14**). The acid chloride prepared above was redissolved in 300 ml dry benzene and the soln was cooled in an ice bath. Excess methylamine

gas was passed into the soln. The methylamine hydrochloride formed was filtered off and the filtrate evaporated *in vacuo* to give 34·6 g (93%) of a white solid which was analytically pure, m.p. 142–143°; λ_{max} 2·99, 5·82, 6·06 μ; NMR, singlet at 2·42 ppm for $COCH_2$; broad singlet at 2·50 ppm for NCH_3. (Found: C, 65·37; H, 7·56. Calc. for $C_{19}H_{27}NO_5$: C, 65·31; H, 7·79%).

2-(3,4-*Dimethoxyphenyl*)-2-(2-*methylaminoethyl*)*cyclohexanol* (**15**). A soln of 9·4 g (27 mmoles) of **15a** in 100 ml dry 50% THF/dioxan was added dropwise with stirring to a mixture of 2·5 g (66 mmoles) LAH and 20 ml of the same solvent mixture. The heterogeneous mixture was refluxed for an additional 17 hr, cooled in an ice bath and the excess reagent destroyed by water. The inorganic salts were filtered off and the filter cake washed well with THF. The combined filtrates were evaporated *in vacuo* to give 7·1 g (90%) of a colorless oil. Its IR spectrum indicated the absence of any amide or ester absorption and showed intense hydrogen bonding absorption from λ_{max} 3·04–4·2 μ. M^+ *m/e* 293 for $C_{12}H_{27}NO_3$.

N-*Formyl*-2-(3,4-*dimethoxyphenyl*)-2-(2-*methylaminoethyl*)*cyclohexanol* (**15a**). A mixture of 2·5 g of **15**, 10 ml triethylamine and 50 ml ethyl formate was refluxed overnight. The mixture was then evaporated to give 2·5 g (92%) of an oil; λ_{max} 2·90 and 6·09 μ. M^+ *m/e* 321 for $C_{18}H_{27}NO_4$.

N-*Formyl*-2-(3,4-*dimethoxyphenyl*)-2-(2-*methylaminoethyl*)*cyclohexanone* (**16**). A soln of 8·5 g of **15** in 100 ml acetone was oxidized by the dropwise addition with stirring of an equimolar amount of an acidified dichromate soln (made from 14·0 g $Na_2Cr_2O_7 \cdot 2H_2O$ and 11 ml H_2SO_4 diluted to 50 ml with water). The soln was then diluted with water after decanting from the green chromium salts. The soln was extracted with $CHCl_3$ and the extracts were washed with 10% $NaHSO_3$ aq and water, dried over $MgSO_4$ and evaporated *in vacuo* to give an orange oil. The oil was taken up in a small volume of $CHCl_3$ and passed through a short column of Baker's neutral alumina with $CHCl_3$. After evaporation of the eluant *in vacuo*, 6·8 g (80%) of a light yellow oil; λ_{max} 5·92 and 6·09 μ, M^+ *m/e* 319 for $C_{18}H_{25}NO_4$ was obtained.

N-*Formyl*-6-*bromo*-2-(3,4-*dimethoxyphenyl*)2-(2-*methylaminoethyl*)*cyclohexanone* (**17**). A soln of 4·4 g of **16** in 100 ml dry THF was kept at room temp for 19 hr with 5 g phenyltrimethylammonium tribromide. The original deep red soln was now pale yellow in color and the flask was filled with the flocculent ppt of phenyltrimethylammonium bromide. The ppt was filtered off and washed with dry ether. The filtrate was diluted with an equal volume of water and extracted with $CHCl_3$. The extracts were washed well with water, dried over $MgSO_4$ and evaporated *in vacuo* to give 5·7 g of an impure oil. The IR spectrum indicated the presence of an equatorial α-bromo keto group. TLC of the crude material showed that the desired product was contaminated only by the phenyltrimethyl-ammonium bromide. No attempt was made to purify this compound, but it was used directly in the dehydrobromination step; λ_{max} 5·88 and 6·08 μ.

N-*Formyl*-6-(3,4-*dimethoxyphenyl*)-6-(2-*methylaminoethyl*)-2-*cyclohexen*-1-*one* (**18**). A soln of 5·7 of **17** in 90 ml dry DMF was refluxed with stirring for 2 hr with 5 g $CaCO_3$. The mixture was cooled, the solid filtered off and washed with $CHCl_3$. The filtrate was diluted with water and extracted with $CHCl_3$. The extracts were washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The resulting oil was taken up in a small amount of $CHCl_3$ and passed through a short column of Baker's neutral alumina. After evaporation of the eluant *in vacuo*, 3·6 g (79%) of a light yellow oil; λ_{max} 6·04 μ was obtained.

N-*Formyl*-6-(3,4-*dimethoxyphenyl*)-2,3-*epoxy*-6-(2-*methylaminoethyl*)*cyclohexanone* (**19**). A soln of 2·3 g of **18** in 30 ml pyridine was cooled in an ice bath. All at once 25 ml Clorox was added and the soln was kept at 0° for 1 hr. The mixture was poured into an equal volume of ice water, and excess sat $NaHSO_3$ aq was added to destroy the excess reagent. The soln was diluted with more water and extracted with $CHCl_3$. The extracts were washed with cold 10% HCl and with water, dried over $MgSO_4$, and evaporated *in vacuo* to give 2·1 g (90%) of an oil; λ_{max} 5·91 and 6·09 μ. M^+ *m/e* 333 for $C_{18}H_{23}NO_5$.

N-*Formyl*-2-(3,4-*dimethoxyphenyl*)5-*hydroxy*-2-(2-*methylaminoethyl*)*cyclohexanone* (**20**). A soln of 1·8 g of **19** in 100 ml deoxygenated acetone was stirred for 2 hr under N_2 with 3·0 g chromous acetate and a buffer soln prepared from 7·2 g anhyd NaOAc, 25 ml water and 5 ml glacial AcOH (both deoxygenated). The mixture was then diluted with an equal volume of water and *stirred* with five 100 ml portions of $CHCl_3$. The extracts were then washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to a dark oil. The oil was chromatographed by preparative thin layer on Adsorbosil-1 using 2:5 acetone/$CHCl_3$ as the solvent system. This procedure yielded 720 mg (40%) of an oil which exhibited adsorption in the IR at λ_{max} 2·90, 5·90 and 6·00 μ; M^+ *m/e* 335 for $C_{18}H_{25}NO_5$.

N-*Formyl*-4-(3,4-*dimethoxyphenyl*)-4-(2-*methylaminoethyl*)1,3-*cyclohexanediol* (**21**). A soln of 700 mg of **20** in 25 ml abs EtOH was reduced with 700 mg $NaBH_4$ at room temp overnight. The excess reagent was destroyed by the addition of warm water. The soln was then diluted further with water and extracted with $CHCl_3$. The extracts were washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give 670 mg (95%) of an oil; λ_{max} 2·89 and 6·02 μ. M^+ *m/e* 337 for $C_{18}H_{27}NO_5$.

N-Formyl-4-(3,4-dimethoxyphenyl)3-hydroxy-4-(2-methylaminoethyl)cyclohexanone (**22**). A soln of 700 mg of **21** in 150 ml EtOAc was added to 300 mg Pt black and stirred with access for the air for 3 days. The mixture was then filtered through analytical filter paper and the filtrate evaporated *in vacuo* to give 670 mg of an oil which was used directly for the next operation.

(±)-*Mesembrine*. A soln of 670 mg of crude **22** in 25 ml abs EtOH was diluted with 25 ml 10% HCl and refluxed for 4 hr. The soln was cooled and diluted with water. The soln was then extracted with $CHCl_3$ and the extracts were washed with 10% $NaHCO_3$ aq and water, dried over $MgSO_4$ and evaporated *in vacuo* to give 650 mg of an oil which was chromatographed by means of preparative TLC on Adsorbosil-1 using 2:5 acetone/$CHCl_3$ as the solvent system, yielding 357 mg (approximately 50% from the diol **21** stage) of (±)-mesembrine.

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