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AN IMPROVED PHOTOCHEMICAL APORPHINE SYNTHESIS

NEW SYNTHESES OF DICENTRINE AND CASSAMERIDINE

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Abstract—An improved non-oxidative photochemical synthesis of aporphine derivatives has been developed, in which *o*-halobenzylidenetetrahydroisoquinolines are irradiated in the presence of potassium t-butoxide. The yield (72%) of one such product, N-carbethoxynorneolitsine (**25**) is the highest ever reported for any cyclization producing the aporphine ring system. Compound **25** was converted in two steps to cassameridine (**4**), confirming the suggested structure of this oxoaporphine. The natural bases dehydrodicentrine (**26**) and dicentrine (**3**) were also synthesized using the improved photochemical approach.

We recently reported novel syntheses of the aporphine bases nuciferine (**1**) and glaucine (**2**) in which the key step involved a nonoxidative photocyclization of a halogenated stilbene-type precursor.[1] We now report further applications of this method to the syntheses of dicentrine (**3**) and the rare oxoaporphine cassameridine (**4**),[2] as well as a greatly improved procedure for carrying out the critical photocyclization step.

RESULTS

An improved photocyclization of 6′*-halo-*1*-benzylidene-*2*-carbethoxy-*1,2,3,4*-tetrahydroisoquinolines.* In our earlier paper, we described syntheses of the precursors (**5** and **6**) of nuciferine (**1**) and glaucine (**2**) by the irradiation of the 6′-halo-isoquinoline derivatives **7** and **8** in methanol solution in the presence of calcium carbonate. The calcium carbonate was used as an acid scavenger for hydrogen halide formed by aromatization of the presumed dihydrophenanthrene intermediates (**9** and **10**).[1]

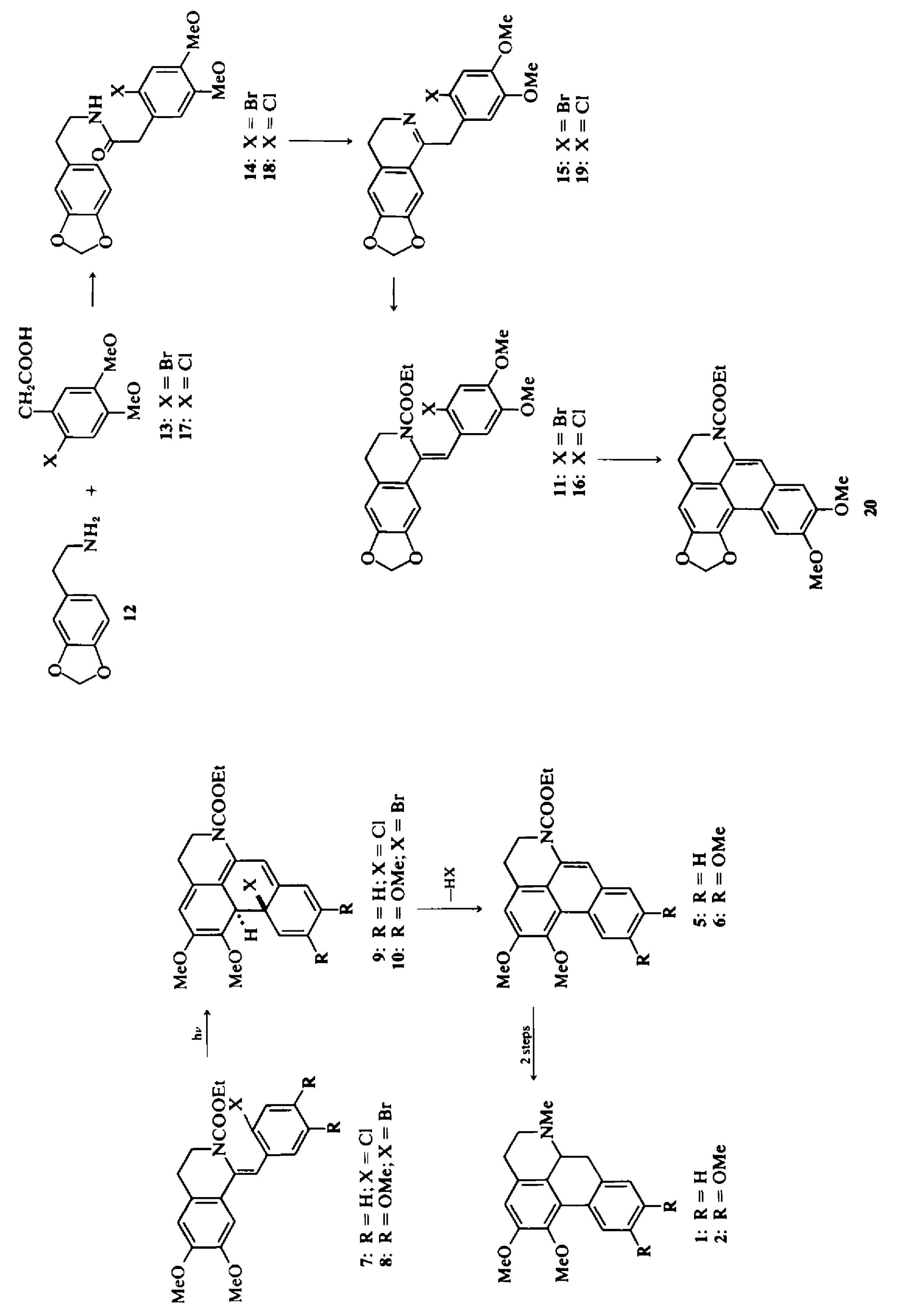
In the course of extending our general method to the synthesis of other aporphines and related alkaloids, the bromo stilbene **11** was prepared starting from homopiperonylamine (**12**) and 6-bromohomoveratric acid (**13**) *via* the corresponding amide (**14**) and dihydroisoquinoline (**15**). Similarly, the analogous chlorostilbene **16** was prepared from 6-chlorohomoveratric acid (**17**) *via* intermediates **18** and **19**. It was found that excellent results were obtained in the cyclization step when bromide **11** was irradiated in 20% t-butyl alcohol-benzene in the presence of potassium t-butoxide as the base. On a half gram scale, the reaction was completed in 6·5 hr, and the cyclization product, N-carbethoxydehydronordicentrine (**20**) was isolated in 56% yield. A comparable irradiation of the corresponding chlorostilbene **16** required 14 hr, and gave the product **20** in appreciably lower yield (44%).

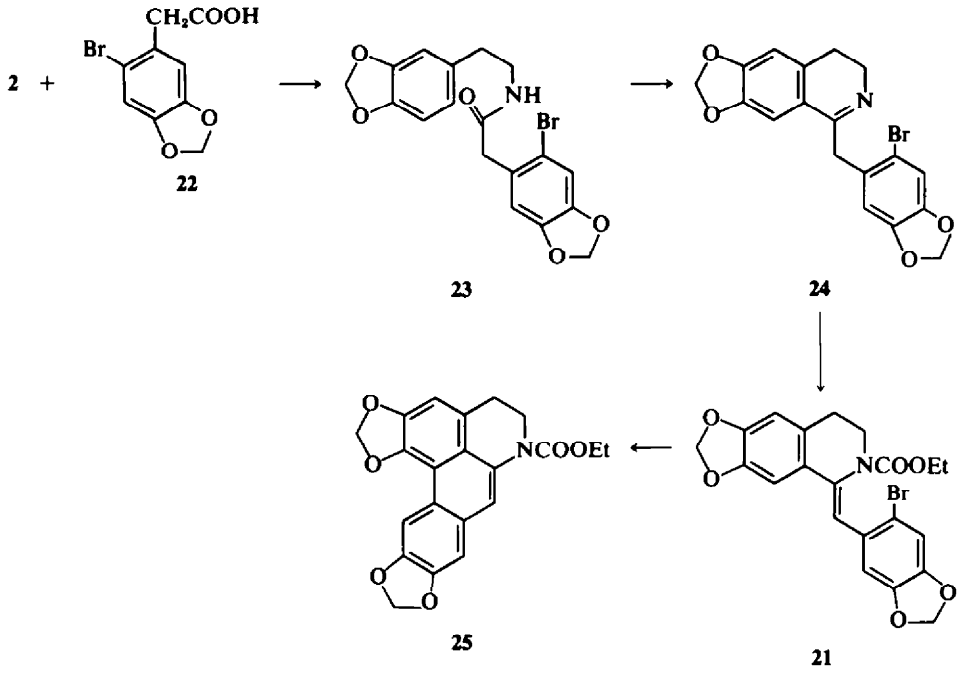
The superiority of the t-butyl alcohol-t-butoxide system was shown by using it in the irradiation of the known bromostilbene **8**, when N-carbethoxydehydronorglaucine (**6**) was isolated in 59% yield. The same conversion was reported previously in only 24% yield using the methanol and calcium carbonate system.[1]

Finally, the bromostilbene **21** was prepared from homopiperonylamine (**12**) and 6-bromohomopiperonylic acid (**22**) *via* the corresponding amide (**23**) and dihydroisoquinoline (**24**). Photocyclization of **21** in the t-butyl alcohol-t-butoxide system gave N-carbethoxydehydronorneolitsine (**25**) in an unexpectedly high yield (72%).

Conversion of the photolysis products into dehydrodicentrine, dicentrine, and cassameridine. The general procedure described earlier for the conversion of urethane **6** into glaucine (**2**)[1] was applicable without difficulty in the dicentrine series. Thus, reduction of urethane **20** with lithium aluminum hydride in the presence of aluminum chloride gave the naturally occurring base dehydrodicentrine (**26**)[3] in 78% yield. Reduction of **26** with amalgamated zinc and hydrochloric acid afforded (±)-dicentrine (**3**) in 80% yield.

Similarly, lithium aluminum hydride-aluminum chloride reduction of urethane **25** gave dehydroneolitsine (**27**) in 68% yield. Dehydroneolitsine has not been described previously, but it may confidently be predicted to eventually be found in nature. Peracetic acid oxidation[4] of **27** afforded cassameridine (**4**). The infrared spectrum of synthetic **4** was identical with that of authentic **4**,


12
13: X = Br
17: X = Cl
14: X = Br
18: X = Cl
15: X = Br
19: X = Cl
11: X = Br
16: X = Cl
20
7: R = H; X = Cl
8: R = OMe; X = Br
hν
9: R = H; X = Cl
10: R = OMe; X = Br
−HX
5: R = H
6: R = OMe
2 steps
1: R = H
2: R = OMe



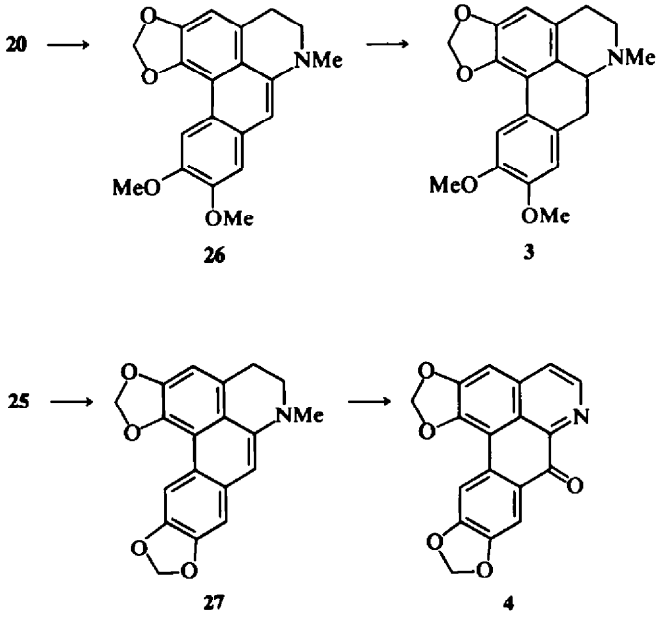
isolated earlier in our laboratory only in trace amounts.[2] Thus, this synthesis confirms the structure of cassameridine which was originally suggested only on the basis of ultraviolet and mass spectral data.[2,*]

*See ref. 8 for a recent independent synthesis of 4 by a different route.

†See ref. 1 for the case in support of the intermediacy of such a dihydrophenanthrene.

DISCUSSION

On the basis of the examples studied so far, the substitution of potassium t-butoxide for calcium carbonate as the base in the non-oxidative photochemical aporphine cyclization greatly improves the yield of aporphine derivative obtained. The major factor in this improved yield is probably the fact that the photochemical intermediate (i.e. **10**)† can smoothly undergo a concerted E2 elimination in the presence of t-butoxide, but can decompose



only solvolytically (E1) in the presence of calcium carbonate, which functions only in preventing the solution from becoming acidic and thus decomposing the enamide starting material. The high yield (72%) of **25** from **21** is particularly worthy of note, since it represents the highest yield ever recorded for an aporphine-forming cyclization by any procedure.†

During the course of our study, an independent synthesis of cassameridine (**4**) was reported in preliminary form.[6] This synthesis, which differs from that reported here, is patterned after Taylor's synthesis of liriodenine.[7] Although a direct comparison of samples has not been made, the NMR of **4** reported in this communication is essentially the same as that of our material.

EXPERIMENTAL

All m.ps were determined in open tubes using a Thomas-Hoover Uni-melt apparatus and are uncorrected. UV spectra were measured in 95% EtOH (unless otherwise noted) with a Perkin-Elmer Model 202 spectrophotometer. IR spectra were recorded in KBr with a Perkin-Elmer Model 137 spectrophotometer. Mass spectra were determined using a Perkin-Elmer Model 270B instrument. The NMR spectra were obtained in $CDCl_3$ (unless otherwise noted) using a Varian A-60 instrument, except that of **4**, which was obtained using the Varian HA-100 model; chemical shifts are reported as ppm (δ) downfield from tetramethylsilane. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

N-(3',4'-Methylenedioxyphenethyl)-6-chlorohomoveratramide (**18**). A mixture of **17**[8] (5·0 g, 0·021 mole), **12** (4·1 g, 0·025 mole) and tetralin (50 ml) was refluxed for 1·5 hr in a Dean-Stark apparatus. After cooling, the ppt was filtered off, washed with dil HCl, dil ammonia, and water. Crystallization of the dried powder from EtOH gave amide **18** (5·5 g, 67%) as plates, m.p. 133–135°. The analytical sample, m.p. 136·5–137·5°, was crystallized from MeOH. (Found: C, 60·18; H, 5·54; Cl, 9·61; N, 3·83. Calcd. for $C_{19}H_{20}ClNO_5$: C, 60·40; H, 5·34; Cl, 9·38; N, 3·71%).

N-Carbethoxy-1-(6'-chloro-3',4'-dimethoxybenzylidene)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**16**). A soln of amide **18** (5·0 g, 0·0133 mole) in polyphosphate ester[9] (50 ml) was heated at 99° for 24 hr. The soln was poured into cold water and the mixture was made basic with ammonia. The precipitated dihydroisoquinoline (**19**) was filtered, dried, and dissolved in chloroform (30 ml). 20% Na_2CO_3 aq (50 ml) and a soln of ethyl chloroformate (5·0 g, 0·046 g) in chloroform (20 ml) were added with cooling. After stirring for 2 hr, the organic layer was washed with dil HCl, followed by water. Evaporation of the dried solution, followed by crystallization from EtOH, gave **16** (3·56 g, 62%) as almost white prisms, m.p. 206–207°. The *trans* configuration may be assigned to **16** on the basis of the triplet at δ 0·87 in its NMR spectrum;[1] ν 1705 cm^{-1}, 1505; λ_{max} 222 mμ (log ϵ 4·78), 298 (4·51), 335 (4·70). The analytical sample, m.p. 208·5–209·5°, was recrystallized from chloroform-methanol. (Found: C, 60·99; H, 5·40; Cl, 8·46; N, 3·15. Calcd. for $C_{22}H_{22}ClNO_6$: C, 61·19; H, 5·13; Cl, 8·21; N, 3·24%).

N-(3',4'-Methylenedioxyphenethyl)-6-bromohomoveratramide (**14**). This amide (colorless needles, m.p. 157–158°) was prepared in 56% yield from amine **12** and **13**[10] as described above for its chloro analog **18**. (Found: C, 54·00; H, 4·74; N, 3·32. Calcd. for $C_{19}H_{20}BrNO_5$: C, 54·04; H, 4·77; N, 3·32%).

N-Carbethoxy-1-(6'-bromo-3',4'-dimethoxybenzylidene-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**11**). A mixture of amide **14** (1·895 g), $POCl_3$ (3 ml) and dry chloroform (30 ml) was stirred for 1 hr at room temp and then refluxed for 2·5 hr. Evaporation *in vacuo*, followed by washing with ether, gave **15** hydrochloride (2·143 g, ~ 100%), which was used without further purification as follows. A soln of ethyl chloroformate (5 g) in chloroform (20 ml) was added dropwise over 20 min to a cooled and stirred mixture of **15** hydrochloride (5·520 g), chloroform (80 ml) and 10% Na_2CO_3 aq (80 ml). After stirring for a further 3 hr, the organic layer was washed with water and 5% HCl, dried and evaporated *in vacuo*. Trituration of the residue with EtOH gave colorless crystals of **11** (4·542 g, 78%), m.p. 202–205°. Recrystallization from $CHCl_3$–EtOH gave colorless prisms, m.p. 210–211°. (Found: C, 55·21; H, 4·70; N, 3·14. Calcd. for $C_{22}H_{22}BrNO_6$: C, 55·47; H, 4·66; N, 2·94%).

B. *Directly from amide* **14**. The direct conversion of **14** (1·05 g) to **11** (0·593 g, 53%, m.p. 208–209°) without isolation of **15** was carried out as described above for the synthesis of **16** from **18**.

N-Carbethoxydehydronordicentrine (**20**)

A. *From bromourethane* **11**. A mixture of **11** (0·500 g), t-BuOK (0·45 g), t-BuOH (50 ml) and benzene (200 ml) was stirred under N_2 at room temp for 6·5 hr, while irradiated (Corex filter) by a Hanovia 450 W lamp. After dilution with water, the washed, dried, and concentrated benzene phase was chromatographed on silica (15 g). Elution with chloroform, followed by crystallization from MeOH, gave the pale yellow product **20** (0·232 g, 56%), m.p. 198–201°; $\lambda_{max}^{dioxane}$ 241 mμ (log ϵ 4·56), 263 (4·80), 272 (5·04), 326 (4·33), 339 (4·35), 360 (3·88), 384 (3·78). The analytical sample, m.p. 201–203°, was crystallized from $CHCl_3$–MeOH. (Found: C, 66·54; H, 5·52; N, 3·53. Calcd. for $C_{22}H_{21}NO_6$: C, 66·83; H, 5·35; N, 3·54%).

B. *From chlorourethane* **16**. An exactly similar reaction to that described above was carried out starting with **16** (0·500 g); an irradiation time of 14 hr was necessary, as indicated by TLC and UV monitoring of the reaction. Compound **20** (0·200 g, m.p. 195–199°) was obtained in 44% yield.

N-Carbethoxydehydronorglaucine (**6**). Starting with the known **8**[1] (0·500 g), photocyclization was carried out exactly as in the preparation of **20** (see above), except that an irradiation time of 29·5 hr was required. The product **6** (0·244 g, 59%) formed prisms (MeOH), m.p. 159–161° (lit.[1] m.p. 162–163°).

N-(3',4'-Methylenedioxyphenethyl)-6-bromo-3,4-methylenedioxyphenylacetamide (**23**). A soln of $SOCl_2$ (10·8 g) in benzene (25 ml) was added to a stirred mixture of **22**[11] (23·2 g), Et_3N (7·9 g) and benzene (100 ml) at room temp. After 0·5 hr, a soln of Et_3N (8 g) and **12** (15·0 g) in benzene (50 ml) was added. After stirring for 30 min, additional Et_3N (20 ml) was added. After a further 15 min, the Et_3N.HCl was removed by filtration. Work-up of the filtrate for neutral material in the normal way, followed by

†Excellent and practical procedures for the homolytic photocyclization of a number of iodobenzyltetrahydroisoquinolines, including some iodobenzylidenetetrahydroisoquinolines, have been reported since the completion of our work.[5]

crystallization from $CHCl_3$–MeOH, gave white plates of amide **23** (22·3 g, 62%), m.p. 156–158°. Recrystallized material melted at 159–160°. (Found: C, 52·91; H, 4·11; Br, 19·94; N, 3·49. Calcd. for $C_{18}H_{16}BrNO_5$: C, 53·16; H, 3·97; Br, 19·67; N, 3·45%).

N-Carbethoxy-1-(6'-bromo-3',4'-methylenedioxybenzylidene)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**21**). A soln of amide **23** (15·0 g) in polyphosphate ester[11] (50 ml) was heated at 92° for 18 hr, and then poured into cold water (200 ml). NaOH was added until a pH of 10 was reached, then a further 6 g of NaOH and 100 ml chloroform was added (cooling). Ethyl chloroformate (8·0 g) was added to the cold mixture, which was stirred for 1·5 hr. Evaporation of the organic layer and crystallization from $CHCl_3$–MeOH gave yellowish prisms of **21** (11·6 g, 69%), m.p. 183–185·5°. The NMR spectrum of **21** showed a triplet at δ 0·915 indicating the *trans* configuration; λ_{max} 223 (log ε 4·66), 300 (4·32), 333 (4·14). The analytical sample (chloroform–methanol) melted at 186·5–187°. (Found: C, 54·74; H, 4·07; Br, 17·64; N, 3·11. Calcd. for $C_{21}H_{18}BrNO_6$: C, 54·90; H, 3·95; Br, 17·39; N, 3·05%).

N-Carbethoxydehydronorneolitsine (**25**). A mixture of **21** (1·00 g) t-BuOK (0·90 g), t-BuOH (50 ml) and benzene (200 ml) was stirred under N_2 for 21 hr, while irradiated (Corex filter) by a Havovia 450 W lamp. Dilution with water and evaporation of the washed and dried benzene phase gave a solid which crystallized from MeOH, yielding the yellow **25** (0·595 g, 72%), m.p. 198–201°; $\lambda_{max}^{dioxane}$ 264 mμ (log ε 4·99), 270 (4·97), 295 (4·25), 327 (4·32), 340 (4·33), 363 (3·89), 382 (3·83); NMR δ 1·35 (3H, t, J = 7 Hz), 3·12 (2H, t, J = 5 Hz), 4·05 (2H, t, J = 5 Hz), 4·31 (2H, q, J = 7 Hz), 6·07 (2H, s), 6·18 (2H, s), 6·95 (1H, s), 7·13 (1H, s), 7·70 (1H, s), 8·45 (1H, s). The analytical sample, m.p. 206–207°, was recrystallized from $CHCl_3$–MeOH. (Found: C, 66·34; H, 4·30; N, 3·80. Calcd. for $C_{21}H_{17}NO_6$: C, 66·49; H, 4·52; N, 3·69%).

Dehydrodicentrine (**26**). $AlCl_3$ (0·0852 g) and LAH (0·0563 g) were added to a cooled solution of **20** (0·150 g) in dry ether (50 ml). After stirring for 20 hr at room temp, water was added cautiously. Evaporation of the ether phase and crystallization from MeOH–$CHCl_3$ gave yellow crystals of **26** (0·0995 g, 78%, m.p. 213–215° (lit[3] 218°), identical (TLC, IR) with the natural alkaloid.

(±)-Dicentrine (**3**).* To a well-stirred mixture of amalgamated Zn in HCl (prepared by shaking 0·5 g of Zn dust with 1 ml of 5% $HgCl_2$ for 5 min followed by treatment with 6 ml of 2 N HCl) at 60–70° was added a suspension of **26** (0·068 g) in EtOH (4 ml). After 30 min of additional stirring at 70°, 6 N HCl (2 ml) was added and stirring was continued at 70° for a further 30 min. The soln was decanted, the residue being washed well with water. Basification with ammonia, followed by chloroform extraction, evaporation of the $CHCl_3$, and crystallization from EtOH afforded white needles of **3**, m.p. 178–179° (lit[12] m.p. 178–179°). It was identical in UV, IR ($CHCl_3$ soln) and TLC behavior with naturally derived (+)-dicentrine.

Dehydroneolitsine (**27**). $AlCl_3$ (0·852 g) and LAH (0·563 g) were added to a cooled soln of **25** (1·50 g) in dry ether (250 ml). After stirring for 20 hr at room temp, water was added cautiously. Evaporation of the ether, followed by chromatography on silica ($CHCl_3$ eluent), and crystallization from $CHCl_3$–MeOH gave yellow needles of **27** (0·865 g, 68%), m.p. 197–198°; λ_{max} 262 (log ε 4·97), 305 (3·87), 338 (4·18); NMR δ 2·98 (3H, s), 3·22 (4H, broad s), 5·97 (2H, s), 6·12 (2H, s), 6·43 (1H, s), 6·83 (1H, s), 6·98 (1H, s), 8·38 (1H, s). (Found: C, 71·09; H, 4·85; N, 4·47. Calcd. for $C_{19}H_{15}NO_4$: C, 71·02; H, 4·71; N, 4·36%).

Cassameridine (**4**). Peracetic acid (20 ml of 0·1 M peracetic acid in AcOH) was added in portions to a cooled soln of **27** (0·200 g) in AcOH (50 ml), and the mixture was then allowed to come to room temp. After a further 1 hr, the mixture was basified with aqueous ammonia and extracted with $CHCl_3$. The concentrated extract was chromatographed on silica (1:9 MeOH–$CHCl_3$ eluent), and the eluted product was again chromatographed on neutral alumina ($CHCl_3$ eluent). Crystallization from $CHCl_3$–MeOH gave pure (by TLC) cassameridine (**4**, 0·077 g, 39%), m.p. 301–302° (lit[2] 300°), identical (TLC, IR) with the naturally occurring alkaloid: IR 1500 cm^{-1}, 1470, 1265, 1080; λ_{max} 249 mμ (log ε 4·50), 272 (4·35), 320 (4·16), 349 (4·06), 386 (3·98), 440 (3·91); $\lambda_{max}^{EtOH-HCl}$ 259 mμ (log ε 4·60), 290 (4·51), 380 (4·16), 508 (3·74); NMR (CF_3CO_2H) δ 6·260 (2H, s), 6·645 (2H, s), 7·234 (1H, s), 7·527 (1H, s), 7·900 (1H, s), 8·274 (1H, s), 8·428 and 8·728 (2H, AB_q with J = 5·9 Hz); mass spectrum *m/e* 319·0485. $C_{18}H_9NO_5$ requires *m/e* 319·0481. Like some other oxoaporphines, cassameridine gave rather low combustion results for carbon. (Found: C, 67·00; H, 2·88; N, 4·26. Calcd. for $C_{18}H_9NO_5$: C, 67·72; H, 2·84; N, 4·39%).

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