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THE SYNTHESIS OF HOMOPROTOBERBERINES

M. SHAMMA and M. J. HILLMAN
Department of Chemistry, The Pennsylvania State University,
University Park, Pennsylvania 16802

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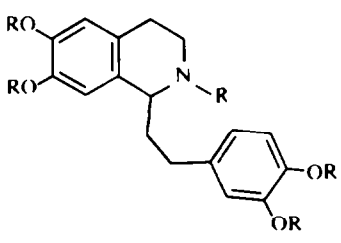
Abstract—Three approaches to the homoprotoberberines have been developed. Mannich condensation of amine **7** with formaldehyde gave homoprotoberberine **9**. In the homophthalide approach, treatment of amino lactones **13** and **14** with base gave lactam alcohols **15** and **16**, which could in turn be converted to amino alcohols **18** and **19**. Furthermore, lactam alcohols **15** and **16** underwent catalytic hydrogenolysis to lactam **20**. Reduction of **20** with LAH furnished homoprotoberberine base **21**. In the Dieckmann sequence, cyclization of diester **24** afforded α-amino ketone **25** which was readily reduced to the homoprotoberberine alcohol **26**. The homoprotoberberine bases prepared were found to be *cis* B/C fused. Homoprotoberberines unsubstituted at C-9 undergo catalytic hydrogenolysis with cleavage of the N_7—C_8 bond.

A VARIETY of alkaloids related to the 1-phenylethyl-1,2,3,4-tetrahydroisoquinoline unit **1** have been isolated in recent years.[1-6] Conspicuously absent from this group of natural products, however, are the homoprotoberberines (**2**) which would contain one carbon more than the regular protoberberine bases (**3**). Although the existence of homoprotoberberines was postulated in 1965,[7] compounds possessing this tetracyclic framework have yet to be isolated from natural sources. Nevertheless, with other "homo" alkaloids having been found in plants, there was sufficient justification for investigating synthetic approaches to the homoprotoberberines.



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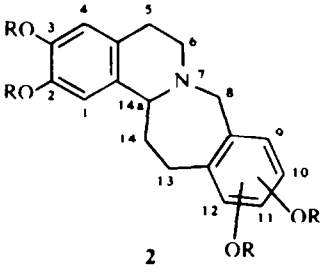

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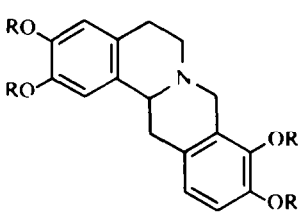

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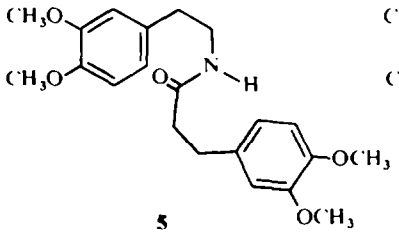
The Mannich approach[8]

A classical method for the preparation of protoberberines involves a Mannich type condensation of a 1-benzyltetrahydroisoquinoline with formaldehyde in the presence of acid. It was, therefore, only logical to assume that a 1-phenylethyltetrahydroisoquinoline would cyclize in like manner with formaldehyde to furnish a homoprotoberberine.

The acid chloride of 3-(3′,4′-dimethoxyphenyl)propionic acid (**4**) was, therefore, condensed with β-(3,4-dimethoxyphenyl)ethylamine to afford the amide **5**. Bischler–Napieralski cyclization with phosphorus oxychloride gave the imminium salt **6** which

was reduced directly with sodium borohydride to furnish the desired 1-(3',4'-dimethoxyphenylethyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**7**). When the hydrochloride salt of **7** was refluxed with aqueous formaldehyde, two products were obtained, the N-methyl-1-phenylethyltetrahydroisoquinoline **8** and the desired homoprotoberberine **9**, in 31% and 20% yield, respectively.



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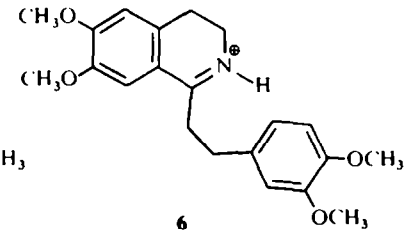

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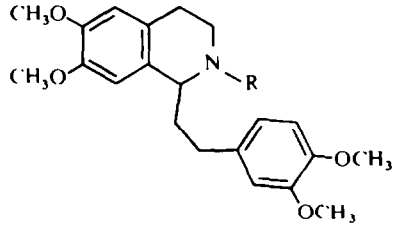
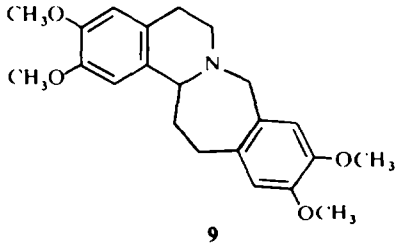


7; R = H
8; R = CH_3



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The homophthalideisoquinoline approach

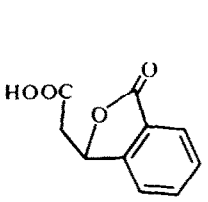
Functionalization at C-13. An approach to the homoprotoberberine skeleton which led to functionalization at C-13 was through the condensation of the acid chloride of the known phthalide-3-acetic acid (**10**) with β-(3,4-dimethoxyphenyl) ethylamine to yield the amide lactone **11**. Bischler–Napieralski cyclization with PPE provided the imine **12** which when reduced with Adams catalyst furnished a diastereoisomeric mixture of homophthalideisoquinolines **13** and **14**. TLC indicated that the product was approximately a 1 : 1 mixture of diastereoisomers, although the spots were too close to allow for an actual separation of the two compounds.

Since the hydrogen of a secondary amine is acidic, it was reasonable to expect that the amide anions of **13** and **14** would attack the lactone carbonyl intramolecularly and generate two different tetracyclic lactams. When the amine lactones **13** and **14** were treated with methanolic potassium hydroxide, a 47% yield of a diastereoisomeric mixture of tetracyclic lactams **15** and **16** was obtained. Preparative TLC indicated that the lactam isomer of lower R_f (0·52) predominated over the isomer of higher R_f (0·65) in the ratio of 7 : 1.

Alternatively, when the imine **12** was reduced with $NaBH_4$ in absolute ethanol, a 25% overall yield of the mixture of diastereoisomeric lactams **15** and **16** was recorded. In this case, the isomer ratio was 10 : 1 in favor of the lower R_f isomer.

Stuart models clearly indicate that the amino lactone **13** would have fewer steric obstacles to overcome in cyclizing to the lactam alcohol **15** than would the diastereo-

isomeric amino lactone **14** in forming the corresponding lactam alcohol **16**. Consequently, the lactam alcohol of higher R_f, which was obtained as the minor product, can be assigned structure **16**; while the lower R_f and major product must be represented by expression **15**.



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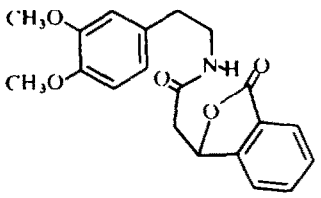

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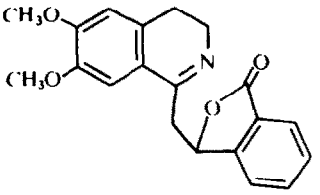

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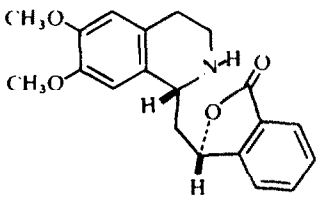

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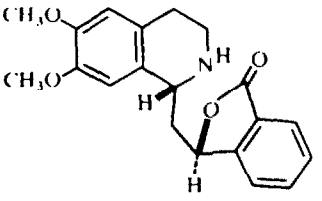

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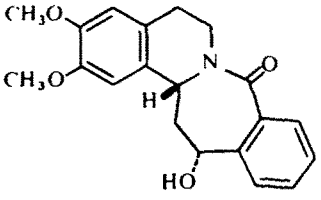

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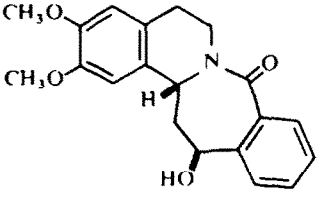

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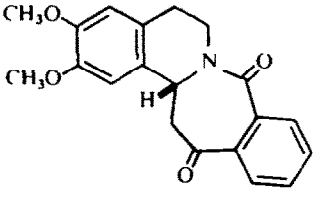
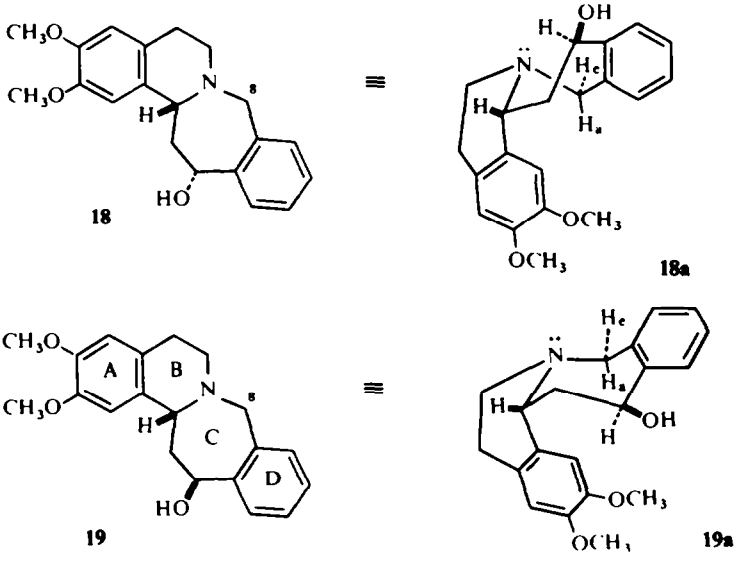


17

The keto lactam **17** could be readily obtained through Sarett oxidation of the mixture of lactam alcohols **15** and **16**. Reduction of this keto lactam with $NaBH_4$ gave the higher R_f lactam alcohol **16** preferentially over **15** in the ratio of at least 10:1, the overall yield being 97%. Alternatively, hydrogenation of the keto lactam **17** with Adams catalyst afforded a mixture of lactam alcohols with the higher R_f compound **16** predominating in the ratio of about 3:2. Both lactam alcohols exhibited lactam CO absorptions in the IR between 6·13 and 6·23 μ, but the diastereoisomer of lower R_f, namely **15**, exhibited more free OH at 2·78 μ.

The lactam alcohols **15** and **16** were then reduced individually with LAH to form

homoprotoberberines **18** and **19** respectively. Since pseudo first order rates of methiodide formation in acetonitrile solution had been used to study the stereochemistry of quinolizidine systems,[9] this physical method was applied in the present instance. Amine **18** was found to quaternize very quickly at a rate of $2{\cdot}3 \times 10^{-2}\text{sec}^{-1}$, while isomer **19** reacted at the even faster rate of $3{\cdot}1 \times 10^{-2}\text{sec}^{-1}$. Since the rate of quaternization under identical experimental conditions for a *cis* B/C fused protoberberine is around $3 \times 10^{-2}\text{sec}^{-1}$, while it is close to $5 \times 10^{-3}\text{sec}^{-1}$ for a *trans* fused analog,[9] it is safe to assume that both isomers **18** and **19** are *cis* B/C fused. The absence of Bohlmann bands[10] in the IR spectra of the two amines added further support to these stereochemical conclusions. Accordingly, compound **18** can be assigned the probable twist-boat conformation **18a**, and compound **19** the probable pseudo-chair conformation **19a** in which the nitrogen is less hindered sterically to approach of methyl iodide.

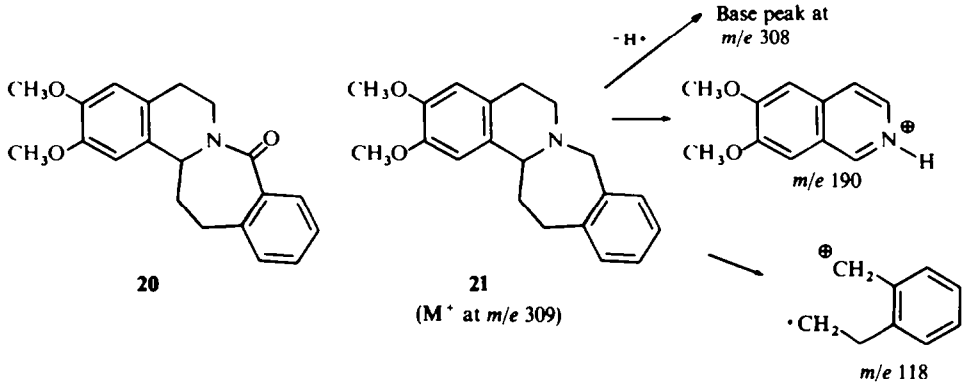


Interlocking evidence for the stereochemical assignments was afforded by the NMR spectra of homoprotoberberine alcohols **18** and **19**. The C-8 equatorial hydrogen of species **19** is appreciably more deshielded than the corresponding equatorial hydrogen of **18**. Specifically, the C-8 methylene protons of **18** appear at δ 4·24 in an AB pattern with an ics of 28 Hz and $J_{a,e}$ 14·5 Hz, whereas for isomer **19** they are at δ 4·81 with an ics of 79 Hz and $J_{a,e}$ 14 Hz. Conformation **19a** is considerably more rigid than **18a**, with the result that the C-8 equatorial hydrogen in **19a** is held more firmly in the plane of the aromatic D ring and is more subject to deshielding.

To obtain the lactam **20**, a mixture of lactam alcohols **15** and **16**, derived from a potassium hydroxide in methanol cyclization of the amine lactones **13** and **14**, was hydrogenolyzed in ethanolic perchloric acid with 5% Pd–C and hydrogen. In addition to the lactam **20**, the product contained a residue of the unhydrogenolyzed high R_f lactam alcohol **16** that could be separated by chromatography. No residual low R_f

lactam alcohol **15** was ever observed, so that this isomer must suffer hydrogenolysis at a faster rate.

Reduction of the lactam **20** to the crystalline homoprotoberberine **21** was accomplished by refluxing with LAH in THF. The mass spectrum of **21** shows a strong molecular ion at *m/e* 309 ($C_{20}H_{23}O_2N$) which is only slightly less intense than the base peak at *m/e* 308 corresponding to $(M\text{-}1)^+$. Strong peaks are also found at *m/e* 190 and 118.



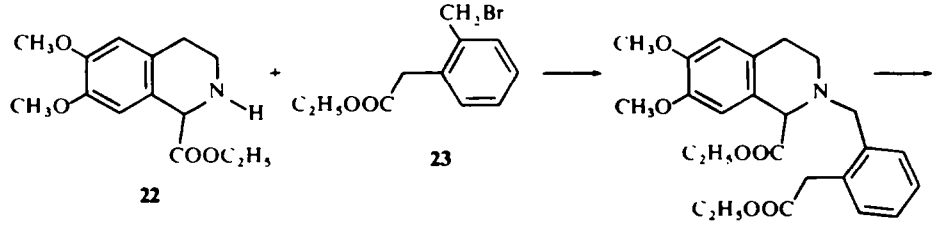
20 **21** (M^+ at *m/e* 309)

The rate of methiodide formation for base **21** was found to be $3{\cdot}4 \times 10^{-2}\,sec^{-1}$. This very fast rate indicates a *cis* B/C fusion, and this conclusion is again reinforced by the lack of Bohlmann bands in the IR spectrum of **21**.

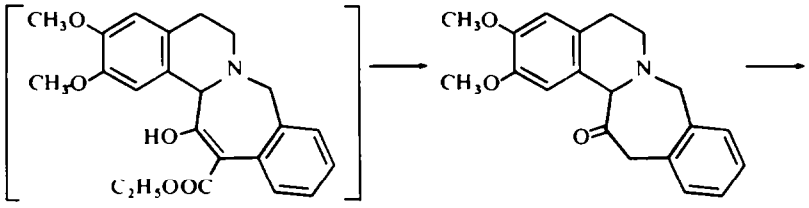
The Dieckmann approach

Functionalization at C-14. Condensation of the amino ester **22** with ethyl 2-bromomethylphenyl acetate (**23**) gave rise to the diester **24**. Dieckmann cyclization of the material with sodium hydride in benzene, followed by hydrolysis and decarboxylation, afforded the desired amino ketone **25**. Reduction with Adams catalyst then gave the 14-hydroxyhomoprotoberberine **26**. The pseudo first order rate of methiodide formation for the amino alcohol **26** was very fast, $1{\cdot}5 \times 10^{-2}\,sec^{-1}$, corresponding to a *cis* B/C ring fusion. The lack of Bohlmann bands in the IR spectrum supported this assignment.

Since the homoprotoberberine bases prepared in the present study are *cis* B/C fused, it appears that the favored ring fusion for this class of heterocycles is *cis*.



22 **23** **24**



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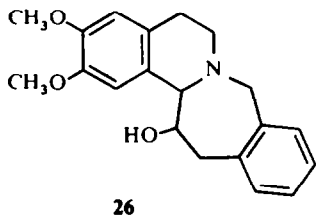
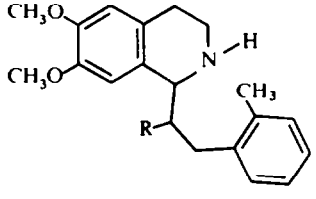


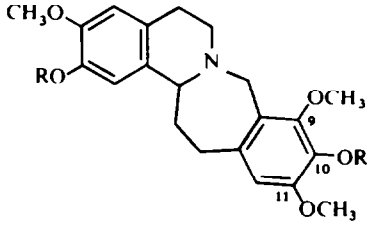
26

Hydrogenolysis of homoprotoberberines. When the homoprotoberberine alcohols **18** and **19** or the homoprotoberberine **21** were stirred under a hydrogen atmosphere with 5% Pd–C in ethanolic perchloric acid, the tricyclic base **27** was obtained. As structural proof, an independent synthesis of **27**, described in the Experimental, was carried out, and the two materials were found to be identical in all respects.

In like fashion, the 14-hydroxyhomoprotoberberine base **26** could be hydrogenolyzed to the crystalline secondary amine **28**. However, the homoprotoberberines **29** and **30** did not undergo catalytic hydrogenolysis. It may be argued, therefore, that for steric reasons hydrogenolysis of a homoprotoberberine will not occur when a substituent is present at C-9.



27; R = H
28; R = OH



29; R = H
30; R = CH_3

EXPERIMENTAL

All IR spectra were taken in $CHCl_3$. The NMR solvent was $CDCl_3$ unless stated otherwise; the spectra were obtained at 60 MHz. The mass spectra were run on an A.E.I. MS-902 spectrometer at 70 eV. TLC was on Merck Silica Gel-254. The pseudo first order rates of methiodide formation were run at 25° in purified MeCN soln on 3 mg of sample.[9] Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

N-(3,4-Dimethoxyphenylethyl)-β-(3',4'-dimethoxyphenyl)propionamide (**5**)

A suspension of 3-(3',4'-dimethoxyphenyl)propionic acid [11] (33·5 g, 0·16 mole) in anhyd ether (1 l.) was stirred overnight with 10 drops pyridine and purified thionyl chloride (116 ml, 1·60 mole). The solvent was evaporated and the remaining crude acid chloride taken up in $CHCl_3$ (600 ml). The $CHCl_3$ soln was added

dropwise to a mixture of β-(3,4-dimethoxyphenyl)ethylamine (29 g, 0·160 mole), chloroform (600 ml), Na_2CO_3 (170 g, 1·60 mole), and water (800 ml). Stirring was continued for 1 hr. The $CHCl_3$ layer was separated, washed, dried and evaporated to dryness. The crude, oily amide thus obtained crystallized on trituration with ether. After recrystallization from benzene–light petroleum, white crystals were obtained, 44·7 g (75%), m.p. 98–99°. (Found: C, 67·63; H, 7·41. Calcd for $C_{21}H_{27}O_5N$: C, 67·54; H, 7·29%).

1-(3′,4′-*Dimethoxyphenylethyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline Salt* (**6**)

The above amide (3·00 g, 8·05 mmol), $POCl_3$ (3 ml) and dry benzene (120 ml) were refluxed for 2½ hr. The solvent was removed, and the remaining yellow crystalline material was collected and washed with ether, 3·78 g. This material, a mixture of hydrochloride and hydrophosphate salts, was sufficiently pure for further work.

1-(3′,4′-*Dimethoxyphenylethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**7**) hydrochloride

The above imminium salt (3·78 g) in MeOH (100 ml) was chilled in an ice-bath. $NaBH_4$ (3·0 g, 0·080 mole) was added in small portions with stirring. The yellow color of the imine rapidly faded and stirring was continued for an hr. The excess borohydride was decomposed with glacial AcOH and the solvent removed. The residue was taken up in a $CHCl_3$-water mixture and the $CHCl_3$ separated, washed, dried and evaporated to give the free base (3·08 g) as a white foam. This secondary amine was dissolved in $CHCl_3$, and gaseous HCl was bubbled in. The solvent was removed and trituration with ether gave 2·42 g (77%) hydrochloride salt. Recrystallization from EtOH-ether gave white crystals, m.p. 185–186°. λ_{max}^{EtOH} 281, 232 and 210 (log ε 3·75, 1·14 and 4·35) for hydrochloride salt. (Found: C, 62·44; H, 7·21. Calcd for $C_{21}H_{28}O_4N \cdot \frac{1}{2}H_2O$: C, 62·60; H, 7·25%).

1-(3′,4′-*Dimethoxyphenylethyl*)-2-*methyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**8**) *and* 2,3,10,11-*tetramethoxyhomotetrahydroprotoberberine* (**9**)

The above hydrochloride salt (100 mg, 0·254 mmol) was dissolved in water (2·6 ml) and 37%aq formaldehyde (2 ml). The mixture was refluxed for 6 hr, cooled, made basic with NH_4OH, and extracted into $CHCl_3$. The $CHCl_3$ was separated, washed, dried, and evaporated to give 105 mg of a yellow oil. Preparative TLC (MeOH) gave predominantly two compounds, **8** and **9**, R_f 0·42 (29 mg) and R_f 0·62 (19 mg) respectively.

Compound **8** exhibited λ_{max}^{EtOH} 281, 227 and 208 mμ (log ε 3·68, 4·07 and 4·30). Mass spectrum, M^+ *m/e* 371 for $C_{22}H_{29}O_4N$, base peak *m/e* 206.

Compound **9** exhibited λ_{max}^{EtOH} 282, 225 sh and 210 mμ (log ε 3·75, 4·20 and 4·34). Mass spectrum, M^+ *m/e* 369 for $C_{22}H_{27}O_4N$. Other intense peaks *m/e* 368, 192, 190 and 178 (base); NMR δ 3·83, 3·86, 3·88 and 3·88 (s, 12H, Ar-O-CH_3), δ 4·23 (AB, ics 33 Hz, J = 15 Hz, 2H, C-8 methylene), δ 6·55, 6·57, 6·72 and 6·79 (s, 4H, Ar-H).

N-(3,4-*Dimethoxyphenylethyl*)*phthalideacetamide* (**11**)

A suspension of **10**[12] (17·30 g, 0·0902 mole) in anhydrous ether (700 ml) was stirred overnight with 4 drops pyridine and purified thionyl chloride (65 ml, 0·902 mole). The solvent was removed and the remaining crude acid chloride taken up in $CHCl_3$. This soln was added dropwise to a mixture of β-(3,4-dimethoxyphenyl)ethylamine, (16·35 g, 0·0902 mole), chloroform (350 ml), Na_2CO_3 (95·5 g, 0·902 mole), and water (600 ml). Stirring was continued for 1 hr, the $CHCl_3$ layer was separated, washed, dried and evaporated to dryness. The crude, oily amide thus obtained crystallized from ether. Recrystallization from MeOH-ether gave white crystals, 26·4 g (83%), m.p. 102·5–103·5, IR 2·90, 5·65 and 5·99 μ. (Found: C, 67·52; H, 6·17. Calcd for $C_{20}H_{21}O_5N$: C, 67·59; H, 5·96%).

1-(α-*Phthalidemethyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (**12**)

Amide **11** (30·3 g, 0·0855 mole), dry chloroform (1100 ml), and PPE[13] (152 g) were refluxed for 12 hr in a 2-liter flask fitted with a condenser topped with a drying tube. The solvent was removed and the PPE hydrolyzed with ice-water (1 l.). The aqueous soln was washed with ether. Basification with conc NH_4OH caused **12** to precipitate, 22·8 g (79%). An analytical sample recrystallized from benzene melted 176–177°, λ_{max}^{EtOH} 310, 282 and 274 mμ (log ε 3·87, 3·92 and 3·93). (Found: C, 71·22; H, 5·78. Calcd for $C_{20}H_{19}O_4N$: C, 71·20; H, 5·68%).

Diastereoisomeric mixture of 1-(α-*phthalidemethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**13** and **14**)

A suspension of **12** (14·48 g, 0·0431 mole) and PtO_2 (1 g) in EtOH (280 ml) under H_2 was shaken for

5 hr. The usual workup gave a diastereoisomeric mixture of **13** and **14** (13·4 g, 92%). The material was used without further treatment. A sample purified by preparative TLC (MeOH-ether 1:1, R_f 0·54) showed IR absorption at 5·68 μ. Mass spectrum, M^+ *m/e* 339 for $C_{20}H_{21}O_4N$, base peak *m/e* 192.

Diastereoisomeric mixture of 2,3-*dimethoxy*-8-*oxo*-13-*hydroxyhomotetrahydroprotoberberines* (**15** and **16**)

Method A. A diastereoisomeric mixture of **13** and **14** (13·4 g, 0·039 mole) was dissolved in MeOH (700 ml). KOH (2·66 g, 0·0474 mole) was added and the soln stirred for 2½ days under N_2. The solvent was evaporated after acidification with glacial AcOH, and the residue taken up in $CHCl_3$. The $CHCl_3$ soln was washed and dried. Evaporation and then trituration with ether gave whitish crystals. Recrystallization from EtOH-ether afforded 6·27 g (47%) of **15** and **16** as white crystals, m.p. 241·5–242·5°. Preparative TLC (EtOAc-acetone 1:1) showed this material to be a mixture of diastereoisomers, with the lower R_f isomer **15** predominating by about 7:1. (Found: C, 71·05; H, 6·31. Calcd for $C_{20}H_{21}O_4N$: C, 70·78; H, 6·24%).

Method B. The imine lactone **12** (7·60 g, 0·023 mole) dissolved in EtOH (700 ml) was treated in portions with $NaBH_4$ (8·55 g, 0·23 mole), and stirred under N_2 for 2½ days. Excess borohydride was destroyed with glacial AcOH. The solvent was removed and the residue dissolved in $CHCl_3$. The $CHCl_3$ layer was washed and dried. Evaporation and trituration with ether gave whitish crystals. Recrystallization from EtOH-ether afforded 1·87 g (25%) of **15** and **16**. Preparative TLC EtOAc-acetone: 1:1) showed this material to be a mixture of diastereoisomers, with the lower R_f isomer **15** predominating by about 10:1.

2,3-*Dimethoxy*-8,13-*dioxohomotetrahydropratoberberine* (**17**)

Chromium trioxide (1·03 g, 0·0103 mole) was added with stirring to dry pyridine (100 ml) in a 500 ml flask that was chilled in an ice-bath. A diastereoisomeric mixture of **15** and **16** (1·03 g, 3·03 mmol) in dry pyridine (25 ml) was added to the CrO_3-pyridine complex in one portion, and stirring in the ice-bath was continued for 1 hr. After standing at room temp. for 22 hr, the pyridine was removed below 35°. The dark brown solid which resulted was dissolved in $CHCl_3$ and the inorganic material removed by filtration. The $CHCl_3$ layer was washed and dried. Evaporation and trituration with EtOH gave crystals, 0·725 g. Recrystallization from EtOH gave the keto lactam **17** as white crystals, m.p. 210–212°, 571 mg (55%), λ_{max}^{EtOH} 286 mμ (log ε 3·78), IR 5·92 and 6·12 μ. Mass spectrum M^+ *m/e* 337 for $C_{20}H_{19}O_4N$; other intense peaks *m/e* 191 (base) and 176. NMR δ 3·75 and 3·84 (s, 6H, $ArOCH_3$), δ 6·51 and 6·64 (s, 2H, ArH), δ 7·2–8·0 (m, 4H, ArH).

Sodium borohydride reduction of keto lactam **17**

Keto lactam **17** (63 mg, 0·187 mmol) was suspended in EtOH (10 ml). $NaBH_4$ (45 mg, 0·94 mmol) was added, and the reaction stirred at room temp. for 4 hr. Glacial AcOH was added and the solvent removed *in vacuo*. The residue was taken up in $CHCl_3$ and water. The $CHCl_3$ layer was separated, washed and dried. Evaporation gave 61 mg (97%) of a white crystalline material which was shown by TLC (EtOAc-acetone 1:1) to be almost exclusively the high R_f lactam alcohol isomer **16**. The isomer ratio was at least 10 to 1 in favor of this isomer.

Catalytic reduction of keto lactam **17**

A soln of **17** (95 mg, 0·28 mmol) in EtOH (250 ml) was hydrogenated overnight using 209 mg PtO_2. Work-up gave alcohols **15** and **16** in essentially quantitative yield. Preparative TLC (EtOAc-acetone 1:1) showed this material to be a mixture of diastereoisomers with the high R_f isomer **16** predominating in the ratio of 3:2.

Isolation of (±)-2,3-*dimethoxy*-8-*oxo*-13-α-*hydroxy*-14a-β-H-*homotetrahydroprotoberberine* (**15**)

The low R_f (R_f 0·52) lactam alcohol (**15**) was obtained by preparative TLC (EtOAc-acetone 1:1) of the diastereoisomeric mixture obtained from methods A or B. White crystals, m.p. 218–219·5°, λ_{max}^{EtOH} 280 and 228 mμ (log ε 3·63 and 4·05), IR 2·78, 2·95, 6·13 and 6·22 μ. Mass spectrum M^+ *m/e* 339, other intense peaks *m/e* 321, 310, 192 (base), 176, 133 and 131; NMR (pyridine-d_5) δ 3·74 and 3·76 (s, 6H, $ArOCH_3$), δ 6·68 and 6·81 (s, 2H, ArH), δ 7·2–8·2 (m, ArH and Py-H).

Isolation of (±)-2,3-*dimethoxy*-8-*oxo*-13-β-*hydroxy*-14a-β-H-*homotetrahydroprotoberberine* (**16**)

The high R_f (R_f 0·65) lactam alcohol **16** was obtained by preparative TLC (EtOAc-actone 1:1) of material obtained from the $NaBH_4$ reduction of **17**. White crystals, m.p. 264–265°, λ_{max}^{EtOH} 281 and 228 mμ (log ε 3·71 and 4·19); IR 2·77, 2·98, 6·17 and 6·23 μ. Mass spectrum M^+ *m/e* 339 for $C_{20}H_{21}O_4N$, other

intense peaks *m/e* 321, 310, 192 (base), 176, 133 and 131; NMR (pyridine-d_5) δ 3·69 and 3·75 (s, 6H, $ArOMe_3$), δ 6·66 and 6·78 (s, 2H, ArH), δ 7·0–7·8 (m, ArH and Py-H); this spectrum was difficult to integrate due to the insolubility of the compound.

Diastereoisomeric mixture of 2,3-*dimethoxy*-13-*hydroxyhomotetrahydroprotoberberines* **18** *and* **19**

A diastereoisomeric mixture (2·23 g, 6·58 mmol) of lactam alcohols **15** and **16** was suspended in dry THF (100 ml) and added portionwise to LAH (1·25 g, 32·9 mmol) in dry THF (60 ml). After refluxing for 8 hr, excess hydride was decomposed with Na_2SO_4 aq, the inorganic material removed and the THF evaporated. The residue was taken up in $CHCl_3$, washed and evaporated. Trituration with ether have 1·79 g (84%) of **18** and **19**. An analytical sample was recrystallized from MeOH, m.p. 207·5–209·5°. (Found: C, 73·02; H, 7·27. Calcd for $C_{20}H_{23}O_3N \cdot \frac{1}{4}CH_3OH$: C, 72·95; H, 7·26%).

LAH *reduction of lactam alcohol* **15**

The low R_f lactam alcohol **15** (93 mg, 0·27 mmol) was reduced with LAH as described to give 105 mg of a yellow solid. Preparative TLC (ether–MeOH 4:1, R_f 0·64) gave the pure diastereoisomer **18** as pale yellow crystals, m.p. 198–202°, 72 mg (79%), λ_{max}^{EtOH} 284 and 281 mμ (log ε 3·62 and 3·61), mass spectrum M^+ *m/e* 325 for $C_{20}H_{23}O_3N$, other intense peaks *m/e* 324, 308, 192 (base), 176, 119 and 117; NMR (pyridine-d_5) δ 3·68, 3·68 (s, 6H, $ArOCH_3$), δ 4·24, (AB, ics 28 Hz, *J* 14·5 Hz, 2H, C-8 methylene protons), δ 6·64, 6·74 and 6·74 (s, 3H, ArH), δ 7·0–8·2 (m, ArH and Py-H). Pseudo first order rate of methiodide formation $2·3 \times 10^{-2}$ sec^{-1}.

LAH *reduction of lactam alcohol* **16**

The high R_f lactam alcohol **16** (100 mg, 0·295 mmol) was reduced with LAH as described above to give 105 mg of a yellow solid. Preparative TLC (ether–MeOH 4:1, R_f 0·70) gave the pure **19** as pale yellow crystals, m.p. 185–188°, 77 mg (80%), λ_{max}^{EtOH} 282 and 286 mμ (log ε 3·61 and 3·61), mass spectrum M^+ *m/e* 325 for $C_{20}H_{23}O_3N$, other intense peaks *m/e* 324, 308, 192 (base), 176, 119 and 117; NMR (pyridine-d_5) δ 3·65 and 3·80 (s, 6H, $ArOCH_3$), δ 4·81 (AX, ics 79 Hz, *J* 14 Hz, 2H, C-8 methylene protons), δ 6·68 and 6·89 (s, 2H, ArH), δ 7·1–7·8 (m, ArH and Py-H). Pseudo first order rate of methiodide formation $3·1 \times 10^{-2}$sec^{-1}.

Hydrogenolysis of diastereoisomeric mixture of 2,3-*dimethoxy*-13-*hydroxyhomotetrahydroprotoberberines* **18** *and* **19**

A mixture of **18** and **19** (99 mg, 0·30 mmol) was dissolved in EtOH (25 ml) and hydrogenated overnight with 200 mg 5% Pd/C and 0·1 ml 72% perchloric acid. One ml of conc NH_4OH was then added and the mixture filtered. The usual work-up gave 84 mg of an oil. Preparative TLC (MeOH–ether 1:1, R_f 0·52) gave 55 mg (58%) of **27** as a colorless oil which was identical with an authentic sample prepared as indicated below.

Independent synthesis of compound **27**

(a) N-(3,4-*Dimethoxyphenylethyl*)-β-(2′-*methylphenyl*)*proprionamide*. A suspension of 3-(2′-methylphenyl)-propionic acid[14] (7·89 g, 0·0482 mole) in dry ether (300 ml) was stirred overnight with 4 drops pyridine and thionyl chloride (35 ml, 0·482 mole). The solvent was removed and the crude acid chloride taken up in $CHCl_3$. The $CHCl_3$ soln was added dropwise to a mixture of β-(3,4-dimethoxyphenyl)ethylamine (8·73 g, 0·0482 mole), $CHCl_3$ (250 ml), Na_2CO_3 (51 g, 0·48 mole), and ice-water (400 ml). Stirring was continued for 1 hr, the $CHCl_3$ layer separated, washed with 10% HCl aq, dried, and evaporated. The oily amide crystallized readily from ether to give 12·80 g (81%) crystals. An analytical sample recrystallized from benzene–light petroleum melted 89–90°. (Found: C, 73·37; H, 7·77. Calcd for $C_{20}H_{25}O_3N$: C, 73·37; H, 7·70%).

(b) 1-(2′-*Methylphenylethyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline salt*. The above amide (3·02 g, 9·24 mmol), $POCl_3$ (3 ml) and dry benzene (120 ml) was refluxed for 2½ hr. The solvent was removed and the yellow crystalline material was collected, washed with ether, 3·87 g. The dihydroisoquinoline thus obtained, a mixture of hydrochloride and hydrophosphate salts, was sufficiently pure for further work.

(c) 1-(2′-*Methylphenylethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**27**). The above imminium salt (3·87 g) in MeOH (100 ml) was chilled in an ice-bath. $NaBH_4$ (3·50 g, 0·0924 mole) was added in small portions with stirring. The yellow color of the imine rapidly faded and stirring was continued for an additional hr. The excess borohydride was decomposed with glacial AcOH and the solvent removed. The residue was taken up in ether and water and the ether separated, washed, dried, and evaporated to

give 1·97 g (68% based on starting amide) of the free base. An analytical sample of the hydrochloride recrystallized from ethanol melted 207–210°. (Found: C, 67·36; H, 7·45. Calcd for $C_{20}H_{26}O_2NCl \cdot \frac{1}{2}H_2O$: C, 67·31; H, 7·63%).

2,3-*Dimethoxy*-8-*oxohomotetrahydroprotoberberine* (**20**)

To lactam alcohols **16** and **17** (3·04 g, 8·98 mmol), prepared according to Method A above, in EtOH (250 ml), 5% Pd/C (1·05 g) and 72% perchloric acid (0·6 ml) was added. The mixture was hydrogenated overnight. NH_4OH (conc. 1·6 ml) was added, the soln filtered, and the EtOH removed. The colorless oil obtained from the work-up was redissolved in $CHCl_3$ and fractionated through an alumina column (75 g of aluminum oxide, pH 7·3). The eluate gave the desired lactam **20**, 2·32 g (80%), and 0·270 g of unhydrogenolyzed high R_f lactam alcohol **16**. Both compounds crystallized upon trituration with ether. Recrystallization from benzene–light petroleum gave **20** as crystals, m.p. 159·5–161°, λ_{max}^{EtOH} 281 and 227 mμ (log ε 3·67 and 4·14), IR 6·18 μ; mass spectrum M^+ and base peak at *m/e* 323. (Found: C, 73·83; H, 6·58. Calcd for $C_{20}H_{21}O_3N$: C, 74·28; H, 6·55%).

2,3-*Dimethoxyhomotetrahydroprotoberberine* (**21**)

Lactam **20** (302 mg, 0·934 mmol) in dry THF (40 ml) was added to LAH (354 mg, 9·34 mmol) in dry THF (100 ml). The mixture was refluxed for 8 hr. Excess reagent was decomposed with a satd Na_2SO_4 aq, the inorganic material removed by filtration, and the THF evaporated. Work-up gave 307 mg of a pale yellow solid. Preparative TLC (ether, R_f 0·44) furnished **21** as crystals, m.p. 152–154°, 248 mg (86%), λ_{max}^{EtOH} 285, 281 and 230 sh (log ε 3·66, 3·66 and 3·98); NMR δ 3·78 and 3·84 (s, 6H, ArOMe), δ 4·20 (AB, ics 32 Hz, *J* 14·5 Hz, 2H, C-8 methylene protons), δ 6·53, 6·57, 7·15, 7·15, 7·15 and 7·15 (s, 6H, ArH); mass spectrum M^+ *m/e* 309 for $C_{20}H_{23}O_2N$, other intense peaks *m/e* 308 (base), 294, 192, 191, 190 and 118. Rate of methiodide formation $3·4 \times 10^{-2} sec^{-1}$.

Hydrogenolysis of 2,3-*dimethoxyhomotetrahydroprotoberberine* (**21**)

Compound **21** (68 mg, 0·22 mmol) in EtOH (25 ml) was hydrogenated overnight with 5% Pd/C (106 mg) and 72% perchloric acid (0·1 ml). Conc. NH_4OH (1 ml) was added and the mixture filtered. Work-up gave 66 mg of an oil. Preparative TLC (MeOH–ether 1 : 1), R_f 0·52) furnished **27** (35 mg, 51%) as a colorless oil.

Ethyl N-(3,4-*dimethoxyphenylethyl*)*oxamate*

The Grussner and Matsuo[15,16] procedures were modified as follows: Diethyl oxalate (130 g, 0·889 mole) was cooled, hydrolyzed with ice water (1500 ml), basified with conc. NH_4OH, and extracted into $CHCl_3$. dropwise, and the mixture heated for an additional hr. The oxamate distilled at 210°/1·5 mm as an oil which crystallized on standing. Recrystallization from benzene–light petroleum gave 33·1 g (67%) white crystals, m.p. 66·5–67·5°.

1-*Carbethoxy*-3,4-*dihydro*-6,7-*dimethoxyisoquinoline*

This PPE procedure has advantages over those previously published.[15–17] A mixture of the above oxamate (33·10 g, 0·118 mole) and PPE (116 g) was heated with stirring at 115–120° for 3 hr. The mixture was cooled, hydrolyzed with ice water (1500 ml), basified with conc. NH_4OH, and extracted into $CHCl_3$. The $CHCl_3$ was washed with water, dried, and evaporated to a brown oil which crystallized upon trituration with ether. The white crystalline imine (18·66 g (60%), m.p. 81·5–83° (Lit. 79–80°)) was sufficiently pure for further work.

1-*Carbethoxy*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**22**)

The preceding imine (18·66 g, 0·0709 mole) was dissolved in EtOH (270 ml) and hydrogenated using PtO_2 (1 g). After 2 hr, the soln was filtered and evaporated. The residue gave 18·64 g (99%) of the secondary amine as a pale yellow oil. Material so obtained is sufficiently pure for further work, but must be used immediately to avoid decomposition. It can be stored as the oxalate salt;[15] and the free base regenerated using liquid ammonia.

Ethyl 2-*bromomethylphenylacetate* (**23**)

3-Isochromanone[18] (8·45 g, 0·0572 mole) in abs. EtOH (140 ml) was chilled to −10°. After anhyd HBr (60 g) had been bubbled in, the flask was stoppered and allowed to stand at room temp. for 6 days. The solvent was removed and the residue taken up in $CHCl_3$. The soln was washed with ice-water and

$NaHCO_3$aq and then dried. After evaporation of the solvent, the residue was dissolved in the minimum amount of benzene and passed through an alumina column (pH 7·3). The benzene was evaporated below 40°. The product was a light brown liquid, 12·14 g (83%), IR 5·78 μ.

1-Carbethoxy-2-(2'-carbethoxymethyl)benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**24**)

A mixture of bromoester **23** (12·13 g, 0·0474 mole) and amino-ester **22** (12·50 g, 0·0474 mole) was refluxed in MeCN (700 ml) for 15 hr. The residue from the work-up was dissolved in benzene and passed through an alumina column (pH 7·3). The benzene was removed, and the residue recrystallized from cyclohexane, m.p. 92·5–93·5°, 16·50 g (79%), λ_{max}^{EtOH} 286, 282 and 211 mμ (log ε 3·58, 3·56 and 4·36), IR 5·78 μ. (Found: 67·64; H, 7·25. Calcd for $C_{25}H_{31}O_6N$: C, 68·01; H, 7·08%).

2,3-Dimethoxy-14-oxohomotetrahydroprotoberberine (**25**)

The above diester **24** (3·02 g, 6·86 mmol) was dissolved in dry benzene (300 ml) and refluxed under N_2 for 12 hr with 48% NaH (1·37 g, 27·4 mmole) the benzene was evaporated, 1N HCl (300 ml) added, and the mixture refluxed for 9 hr under N_2. After cooling, the aqueous layer was washed with ether and then basified (pH 9) with solid $NaHCO_3$. The $CHCl_3$ layer was washed with $NaHCO_3$aq and dried. After evaporation of the solvent *in vacuo*, the residue was dissolved in benzene and passed through an alumina column, pH 7·3. Evaporation of the benzene gave 1·64 g (74%) of the α-amino ketone as a pale yellow solid which, because of its instability, was used directly in further work. A sample recrystallized from benzene–light petroleum gave white crystals which melted 143–144·5°, λ_{max}^{EtOH} 284 mμ (log ε 3·56), IR 5·84 μ; mass spectrum M^+ *m/e* 323 for $C_{20}H_{21}O_3N$; the intense peaks are *m/e* 295, 294 (base), 280, 190 and 176; NMR δ 3·80, 3·80 (s, 6H, $ArOCH_3$), δ 3·92 (AX, ics 58 Hz, *J* 12 Hz 2H, C-8 methylene), δ 4·16 (s, 2H, C-13 methylene), δ 4·32 (s, 1H, C-14a methine), δ 6·62, 6·72, 7·14, 7·14, 7·14 and 7·14 (s, 6H, Ar-H).

2,3-Dimethoxy-14-hydroxyhomotetrahydroprotoberberine (**26**)

A suspension of **25** (1·64 g, 5·07 mmol) in EtOH (300 ml) and PtO_2 (352 mg), was hydrogenated for 16 hr. Recrystallization of the product from EtOH gave 1·28 g (78%), m.p. 194–197·5°, λ_{max}^{EtOH} 286, 282 and 212 mμ (log ε 3·59, 3·59 and 4·25); Mass spectrum M^+ *m/e* 325 (base) for $C_{20}H_{23}O_3N$, other intense peaks *m/e* 324, 308, 192, 190 and 105; NMR δ 3·80 and 3·84 (s, 6H, $ArOCH_3$), δ 3·92 (AB, ics 20 Hz, *J* 14·5 Hz, 2H, C-8 methylene), δ 4·3 (s, 1H, C-14a methine), δ 6·56, 6·67, 7·17, 7·17, 7·17 and 7·17 (s, 6H, ArH). Rate of methiodide formation $1·46 \times 10^{-2} sec^{-1}$. (Found: C, 73·14; H, 7·16. Calcd for $C_{20}H_{23}O_3N \cdot \frac{1}{4}C_2H_5OH$: C, 73·08; H, 7·33%).

Hydrogenolysis of 2,3-dimethoxy-14-hydroxyhomotetrahydroprotoberberine (**26**)

The above alcohol **26** (109 mg, 0·335 mmol) in EtOH was hydrogenated overnight with 5% Pd/C (200 mg) and 72% perchloric acid (0·1 ml). Conc. NH_4OH (1 ml) was then added and the mixture worked up to give 93 mg of a colorless oil. Preparative TLC (MeOH–ether 1:1, R_f 0·47) gave **28** (64 mg, 58%), m.p. 95·5–97·5°, λ_{max}^{EtOH} 283 mμ (log ε 3·56); mass spectrum highest peak at *m/e* 309 for $(M - H_2O)^+$. Other intense peaks *m/e* 192 and 105 (base).

Reaction with Ac_2O gave the N,O-diacetyl derivative as an oil, λ_{max}^{EtOH} 284 mμ (log ε 3·52), IR 5·73 and 6·13 μ.

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REFERENCES

[1] A. R. Battersby, R. B. Herbert, L. Mo and F. Šantavý, *J. Chem. Soc.* (C), 1739 (1967)
[2] A. R. Battersby, E. McDonald, M. H. G. Munro and R. Ramage, *Chem. Commun.* 934 (1967)
[3] A. R. Battersby, R. D. Bradbury, R. B. Herbert, M. H. G. Munro and R. Ramage, *Ibid.* 450 (1967)
[4] A. R. Battersby, R. B. Herbert, L. Ipjewska and F. Šantavý, *Ibid.* 228 (1965)
[5] A. C. Barker, A. R. Battersby, E. McDonald, R. Ramage and J. H. Clements, *Ibid.* 390 (1967)

[6] S. R. Johns, J. A. Lamberton and A. A. Sioumis, *Austral. J. Chem.* **22**, 2219 (1969)
[7] A. R. Battersby, R. B. Herbert and F. Šantavý, *Chem. Commun.* 415 (1965)
[8] A description of the Mannich approach has already been given, see A. Brossi, A. I. Rachlin, S. Teitel, M. Shamma and M. J. Hillman, *Experientia* **24**, 766 (1968); and A. Brossi and S. Teitel, *Helv. Chim. Acta* **52**, 1228 (1969)
[9] M. Shamma, C. D. Jones and J. A. Weiss, *Tetrahedron* **25**, 4347 (1969) and references cited
[10] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958)
[11] W. H. Perkin, jun. and R. Robinson, *J. Chem. Soc.* 1080 (1907)
[12] G. A. Page and D. S. Tarbell, *Organic Synthesis* (Edited by N. Rabjohn) Coll. Vol. IV, pp. 136–140. Wiley, New York, N.Y. (1963)
[13] L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, p. 892. Wiley, New York, N.Y. (1967)
[14] Young, *Chem. Ber.* **25**, 2104 (1892)
[15] A. Grussner, E. Jaeger, J. Hellerbach and O. Schnider, *Helv. Chim. Acta* **42**, 2431 (1959)
[16] I. Matsuo, T. Takahashi and S. Ohki, *J. Pharm. Soc. Japan* **83**, 520 (1963)
[17] A. R. Battersby and T. P. Edwards, *J. Chem. Soc.* 1909 (1959)
[18] G. A. Swan, *Ibid.* 1720 (1949)