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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DXLVIII[1]

SYNTHESIS OF A HASUBANAN RING SYSTEM FROM THE BENZYLISOQUINOLINE RETICULINE[2]

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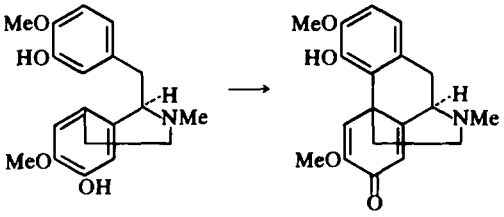
Abstract—The synthesis of a cepharamine analogue (**19**) from reticuline (**1**) by phenolic oxidation is reported. Reticuline was converted into the methine base (**13b**), whose dihydro compound (**14c**) was oxidised to the seco-morphinandienone (**17b**). Michael-type cyclization of **17b**, followed by an isomerization of the enone (**18**) gave the cepharamine-type compound (**19**).

The synthesis of natural products via routes which are operable, or thought to be operable in Nature is very fascinating to synthetic chemists. Since biogenetic mechanisms have been elucidated and plausible biosynthetic mechanisms have also been proposed, an attempt to reproduce biogenesis in the laboratory can be initiated. Phenol oxidation plays an important role in the biosynthesis of alkaloids, especially isoquinoline and related structures,[3] as shown in the biogenesis of salutaridine (**2**) from reticuline (**1**).[4]



1 2

CHART 1

We have also investigated the total synthesis of natural products by phenol oxidation based on their biogenesis,[5] and here wish to report the synthesis of a cepharamine analogue (**19**) by phenol oxidation, although the route was not followed in the biogenetic pattern.

Cepharamine, an alkaloid from *Stephania cepharantha*, has been assigned the benzindolizine structure (**6**) by chemical and spectroscopic methods[6] and by total synthesis.[7] Bases having this ring system are called "hasubanan" alkaloids.[8] The biogenesis of hasubanan alkaloids have been explained by rearrangement of the phenol oxidation products (**2** or **5**) from reticuline (**1**) or protosinomenine (**4**) type precursors.[3]

Battersby[9] and Franck,[10] independently, found that treatment of the morphinandienol (**8**) with acid gave the enone (**9**), but not a hasubanan type compound. Moreover, in light of the biogenetic pattern, we synthesised the proerythrinadienone (**11**) from the phenolic benzylisoquinoline (**10**) which was treated with acid to give the similar enone (**12**).[11]

Since this fact suggests that the C_9—N bond in morphinandienone and proerythrinadienone would be stable under acid conditions, we investigated the synthesis of a compound having a hasubanan ring system by a route in which the C_9—N bond would be formed in final step. Thus, a retro-Michael reaction of cepharamine isomer (**3**), a key intermediate to cepharamine (**6**), would afford the open-chain dienone (**7**), named tentatively as seco-morphinandienone. Therefore, the synthesis of **7** by phenol oxidation, which had succeeded in the conversion of reticuline (**1**) into the morphinandienones,[3,5,12] was examined.

The most promising starting materials for the dienone (**7**) would be dihydrostilbenes (**14**), because the cross-conjugated α-methoxy-γ-phenylcyclohexadienones could be easily prepared by phenol oxidation.[5,12] Reticuline (**1**) was treated with ethyl chlorocarbonate in a two-phase system with chloroform and aqueous sodium hydroxide at room temperature[13] to give the stilbene (**13a**) as an oil in good yield. The UV spectrum indicated the *trans*-stilbene chromophore[14] at 325 nm and the NMR spectrum lacked the ABX pattern[15] characteristic of the styrene group of the other possible product (**15**). Catalytic reduction of the stilbene (**13a**) proceeded smoothly to afford the dihydrostilbene (**14a**), which on mild hydrolysis with 10% sodium hydroxide solution yielded the diphenolic urethane. The NMR spectrum showing no C–ethyl group proved the product to be structure (**14b**), and not structure (**16**).

Phenol oxidation of the diphenolic urethane (**14b**)

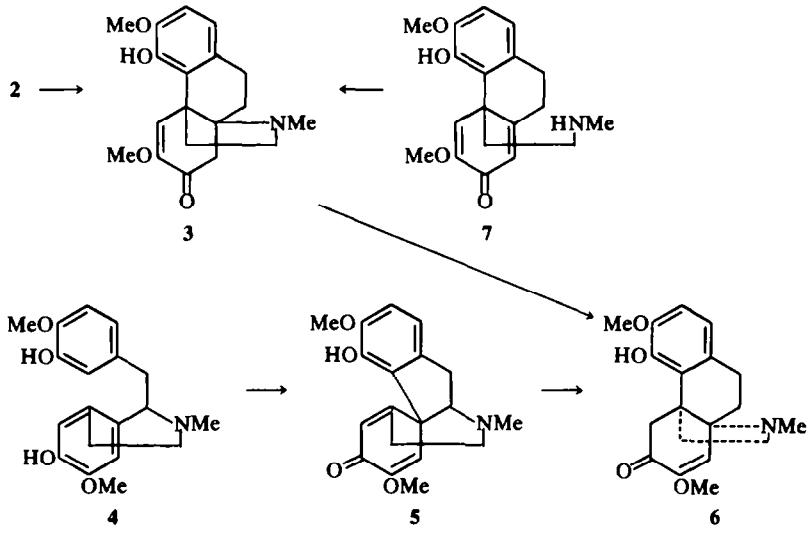


CHART 2

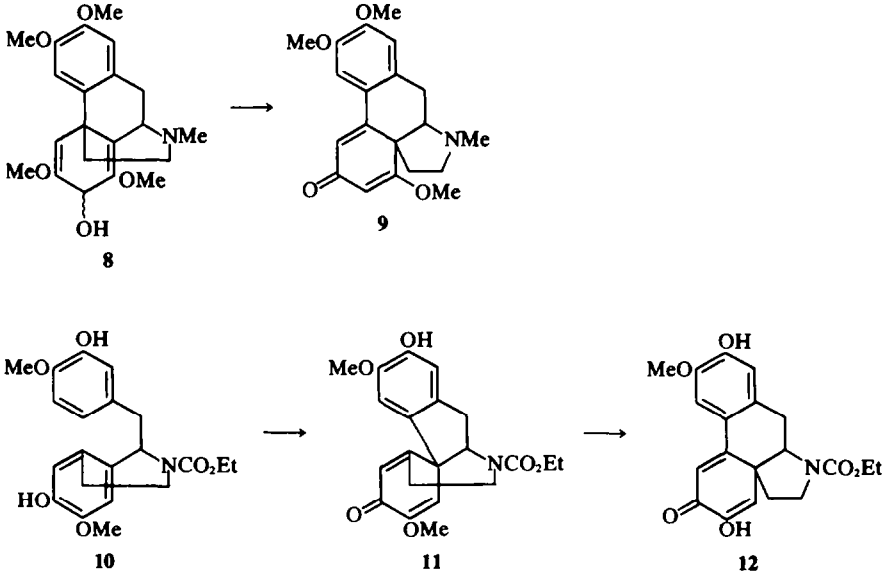
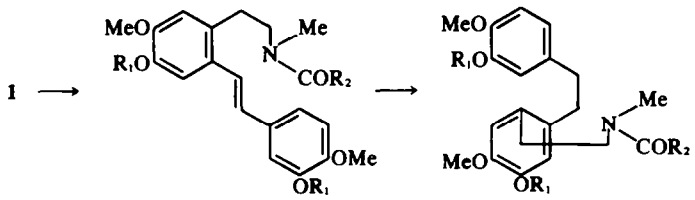


CHART 3

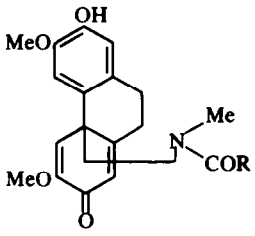
with a two-phase oxidizing system using potassium ferricyanide, aqueous bicarbonate, and chloroform[12] gave the dienone (**17a**) coupled at the *para–para* position in 5% yield, whereas use of vanadium oxychloride[16] as an oxidant raised the yield of the dienone (**17a**) to 26%. The IR and UV spectra showed the cross-conjugated α-methoxycyclohexadienone system, which was supported by NMR spectroscopy.[17] However, hydrolysis of the urethane group to the secondary amine (**18**), which could immediately give the cyclohexenone (**19**) by Michael addition, resulted in failure with recovery of starting material.

Since the urethane resisted hydrolysis, the N-trifluoroacetyl protecting group, which is easily removed with weak alkali,[18,19] was chosen. Reticuline (**1**) was treated with an excess of trifluoroacetic anhydride in a sealed tube at 160° to give the stilbene (**13b**), which exhibited the *trans*-stilbene chromophore in the UV spectrum. Reduction with Adams' catalyst in ethanol afforded the diphenolic amide (**14c**), showing no ethyl group in its NMR

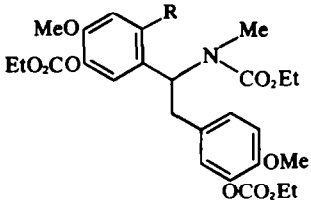


13a: $R_1 = CO_2Et$, $R_2 = OEt$
13b: $R_1 = H$, $R_2 = CF_3$

14a: $R_1 = CO_2Et$, $R_2 = OEt$
14b: $R_1 = H$, $R_2 = OEt$
14c: $R_1 = H$, $R_2 = CF_3$



17a: R = OEt
17b: $R = CF_3$



15: $R = -CH=CH_2$
16: R = —Et

CHART 4

spectrum. Phenol oxidation of this amide with vanadium oxychloride[16] in ether at 0° gave the dienone (**17b**) coupled at the *para–para* position in 26·3% yield, which showed a typical cross-conjugated α-methoxycyclohexadienone system[17] in its IR and UV spectra. The NMR spectrum indicated the presence of two aromatic and two olefinic protons with the expected three methyl resonances.

Before hydrolysis of the amide group and cyclization to the enone system, we calculated the electron density at the β-olefinic carbon of acrolein and α-methoxyacrolein by the LCAO method,[20] as there are two possibilities for cyclization at the C-5 and C-8a positions in an intramolecular Michael addition. The electron density (*ca* 2·1) in α-methoxyacrolein showed a value twice that (*ca* 0·95) in acrolein, which indicated that a Michael addition was likely to occur at the C-8a position. A similar type of intramolecular addition has been reported in the synthesis of the crinan system by Franck[21] as shown in Chart 5.

Hydrolysis of the amide with methanolic potassium carbonate solution afforded, in quantitative yield, the enone (M^+, *m/e* 329), the IR (ν_{max} 1679 and 1625 cm^{-1}) and UV [λ_{max} 257 and 283 sh nm (log ϵ 3·74 and 3·505)] spectra of which indicated the product to have a α-methoxylated enone system. The NMR spectrum (δ) showed an enolic O–Me resonance at 3·58 ppm and an olefinic proton at 5·80 ppm. Thus the above spectroscopic data were similar to those of dihydroorientalinone (**21**)[22] and dihydrokreysiginone (**22**).[23] Therefore, the product was assigned structure (**18**), and the possible alternative structure (**20**) was ruled out.

Treatment of enone (**10**) with methanolic hydrochloric acid solution at room temperature[24] gave a mixture of the starting enone and cepharamine analogue (**19**), which could be separated by alumina chromatography. The IR (ν_{max} 1678 and 1625 cm^{-1}) and UV [λ_{max} 255 and 287 sh (log ϵ 3·87 and 3·775)] spectra of **19** were similar to those of **18**; but the NMR spectrum showed clear differences: an N–Me at 2·41, an enolic O–Me at 3·65, an O–Me at 3·84, an olefinic proton at 5·64 and two aromatic protons at 6·65 and 6·56 ppm. The chemical shifts of N–Me, enolic O–Me and olefinic protons are very similar to those of cepharamine (**6**).[6]

Although the synthesis of cepharamine analogue

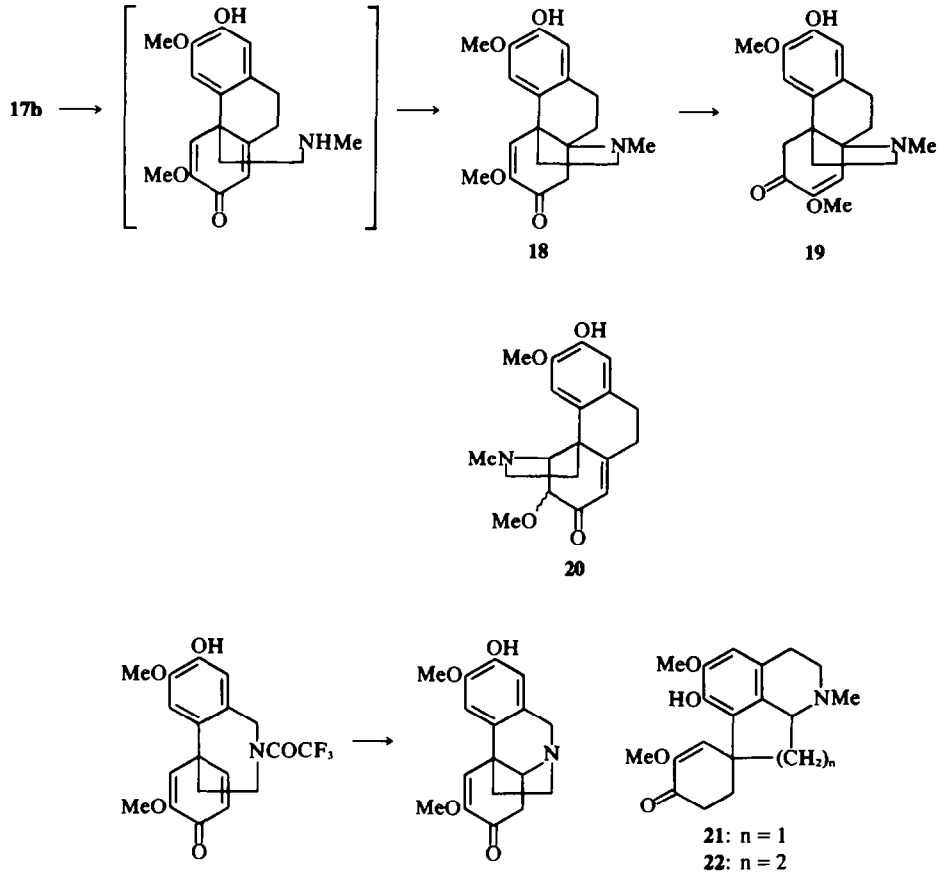


CHART 5

(19) is of interest as a biogenetic model for the hasubanan ring system, the reaction is defective in that the phenol oxidation forms unnatural compounds, which are coupled *para* to a phenolic OH group.

EXPERIMENTAL

M.p.s are uncorrected and were determined on a Yanagimoto microapparatus (MP-S2). IR spectra were measured with a Hitachi EPI-3 and UV spectra with a Hitachi 124 spectrometer. NMR spectra were recorded on a Hitachi H-60 spectrometer using TMS as an internal standard. The mass spectra were taken with a Hitachi RMU-7.

2' - (β - N - *Ethoxycarbonyl* - N - *methyl*) *aminoethyl* - 3,5' - *diethoxycarbonyloxy* - 4,4' - *dimethoxystilbene* (**13a**). To a mixture of ethyl chlorocarbonate (0·434 g; 4 m mol) and KOH (0·322 g; 4 m mol) in 0·3 ml water was added a soln of **1** (0·329 g; 1 m mol) in 20 ml $CHCl_3$ at room temp, and the mixture was stirred for 1 h. The organic layer was separated, washed successively with 10% HCl and water, dried (Na_2SO_4), and concentrated *in vacuo* to afford 0·434 g of an oil, which was further purified by silica gel chromatography to give **13a** (400 mg; 73·5%): IR ν_{max} ($CHCl_3$) 1755, 1680 cm^{-1}; UV λ_{max} (MeOH) 283, 325 nm; NMR ($CDCl_3$) δ7·28–6·57 (7H, m, aromatic and olefinic H), 4·27 (6H, q, J = 7 Hz, 3 × CH_2CH_3), 3·73 and 3·70 (3H, each s, OCH_3), 2·76 (3H, s, NCH_3), 1·3 ppm (9H, t, J 7 Hz, 3 × CH_2CH_3); *m/e* 545 (M^+, parent). (Calc. for $C_{28}H_{35}NO_{10}$: C, 61·64; H, 6·47; N, 2·57. Found: C, 61·42; H, 6·21; N, 2·78%).

2' - (β - N - *Ethoxycarbonyl* - N - *methyl*) *aminoethyl* - 3,5' - *diethoxycarbonyloxy* - 4,4' - *dimethoxydihydrostilbene* (**14a**). To a soln of **13a** (0·4 g, 0·73 m mol) in 20 ml EtOH, PtO_2 (200 mg) was added. The mixture was shaken in a current of H_2 at room temp. After a calculated amount of H_2 had been absorbed, the mixture was worked up and purified by silica gel chromatography to give **14a** (0·340 g; 84·5%) as a syrup; IR ν_{max} ($CHCl_3$) 1760, 1680 cm^{-1}; UV λ_{max} (MeOH) 277 nm; *m/e* 547 (M^+); NMR ($CDCl_3$) δ 7·15–6·61 (5H, m, aromatic H), 4·27 (6H, q, J = 7 Hz, 3 × CH_2CH_3), 3·75 (6H, s, 2 × OCH_3), 2·81 (3H, s, NCH_3), 1·23 ppm (9H, t, J = 7 Hz, 3 × CH_2CH_3). Calc. for $C_{28}H_{37}NO_{10}$: C, 61·41; H, 6·51; N, 2·56. Found: C, 61·61; H, 6·81; N, 2·63%.

2'-(β-*Ethoxycarbonyl* - N - *methyl*) *aminoethyl*-3,5'-*dihydroxy* - 4,4' - *dimethoxydihydrostilbene* (**14b**). A mixture of **14a** (0·546 g; 1 m mol) and 10 ml 10% NaOH was heated on a hot water-bath for 4 h. Ammonium acetate was added to the mixture and the ppt was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to give a dark brown syrup. Chromatography on silica gel gave **14b** (0·24 g; 69·5%) as a

syrup, the structure of which was established by the following data: IR ν_{max} ($CHCl_3$) 3500, 1675 cm^{-1}; NMR ($CDCl_3$) δ4·05 (2H, q, J = 7 Hz, CH_2CH_3), 3·79 (6H, s, $2\times OCH_3$), 2·80 (3H, s, NCH_3), 1·20 ppm (3H, t, J = 7 Hz, CH_2CH_3); *m/e* 403 (M^+). Calc. for $C_{22}H_{29}NO_6$: C, 65·49; H, 7·25; N, 3·47. Found: C, 65·45; H, 7·31; N, 3·45%.

Phenol oxidation of **14b** *by vanadium oxychloride.* To a soln of **14b** (1·426 g; 3·5 m mol) in 10 ml ether $VOCl_3$ (1·23 g; 6·5 mol) in 10 ml ether was added with stirring under N_2 with ice-cooling. Stirring was continued for 3 h, and the mixture was refluxed for 6 h. Water was added and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to give a dark brown syrup, which was chromatographed on silica gel with chloroform to afford the crude dienone **17a** (0·99 g). Rechromatography on silica gel with n-hexane–$CHCl_3$ (10:90 v/v) gave 0·33 g (23·4%) of **17a**; IR ν_{max} ($CHCl_3$) 3500, 1680, 1670, 1645, 1625 cm^{-1} UV λ_{max} (EtOH) 316, 280, 248 nm; NMR ($CDCl_3$) δ6·82–6·25 (4H, m, aromatic and olefinic H), 4·08 (2H, q, J = 7 Hz, CH_2CH_3), 3·23, 3·64 (6H, each s, $2\times OCH_3$), 2·78 (3H, s, NCH_3), 1·20 ppm (3H, t, J = 7 Hz, CH_2CH_3); *m/e* 401 (M^+).

Phenol oxidation of **14a** *by potassium ferricyanide.* To a mixture of **14b** (1·223 g; 3 m mol) in 50 ml $CHCl_3$ and $NaHCO_3$ (4 g) in 75 ml water a soln of $K_3Fe(CN)_6$ (2·3 g; 7 m mol) in 75 ml water was added with stirring at room temp during 5 h. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated to give 1·2 g of a brown gummy material, which was chromatographed on silica gel. Elution with EtOH–$CHCl_3$ (1:99 v/v) gave **17a** (0·06 g; 5%) as a brown oil, which was identical with the above sample.

2′ - (β - N - *Trifluoroacetyl* - N - *methyl*)*aminoethyl* - 3,5′ - *dihydroxy* - 4,4′ - *dimethoxystilbene* (**13b**). A mixture of **1** (7 g; 21 m mol) and 20 ml trifluoroacetic anhydride was heated in a sealed tube at 160° for 6 h. After cooling, the mixture was dissolved in $CHCl_3$. Evaporation of the solvent *in vacuo* gave a mixture of **13b** and the ditrifluoroacetate of **13b** as an oil, which was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to afford **13b** (8·9 g; 96%): IR ν_{max} ($CHCl_3$) 3450, 1680 cm^{-1}; UV λ_{max} (MeOH) 295, 325, (sh) nm; NMR ($CDCl_3$) δ7·12–6·66 (7H, m, aromatic and olefinic H), 3·80 (6H, s, $2\times OCH_3$), 2·91 ppm (3H, s, NCH_3); *m/e* 425 (M^+). Calc. for $C_{21}H_{22}F_3NO_5$: C, 59·29; H, 5·17; N, 3·29. Found: C, 59·26; H, 4·97; N, 3·22%.

2′ - (β - *Trifluoroacetyl* - *N* - *methyl*)*aminoethyl* - 3,5′ - *dihydroxy* - 4,4′ - *dimethoxydihydrostilbene* (**14c**). A mixture of **13b** (5 g; 12 m mol) and PtO_2 (1 g) in 300 ml EtOH was shaken a current of H_2 at room temp for 4 h. After removal of the catalyst by filtration, the solvent was distilled to afford a viscous oil, which was purified by silica gel chromatography to give **14b** (3·2 g; 64·5%) IR ν_{max} ($CHCl_3$) 3480, 1685 cm^{-1}; UV λ_{max} (MeOH) 284 nm; NMR ($CDCl_3$) δ6·78–6·55 (5H, m, aromatic H), 3·82 ppm (6H, s, $2\times OCH_3$); *m/e* 427 (M^+). Calc. for $C_{21}H_{24}F_3NO_5$: C, 59·01; H, 5·62; N, 3·28. Found: C, 59·05; H, 5·36; N, 3·29%.

Phenol oxidation of **14c** *by vanadium oxychloride.* To a soln of **14c** (1·067 g; 2·5 m mol) in 10 ml ether $VOCl_3$ (1·2 g; 6·25 m mol) in 10 ml ether was added with stirring under ice-cooling. The mixture was stirred for 3 h and then refluxed for 5 h. Water was added, and the organic layer was worked up as usual to afford a brown syrup, which was chromatographed on silica gel with $CHCl_3$ to give 0·47 g of crude dienone compound. Rechromatography of this material on silica gel with $CHCl_3$ gave **17b** (0·28 g; 26·4%) as a pale red oil, which was triturated with n-hexane. Recrystallization of the resulting solid from $CHCl_3$–hexane yielded a yellow powder, m.p. 126–128°: IR ν_{max} ($CHCl_3$) 1685, 1665, 1645, 1625 cm^{-1}; UV λ_{max} (MeOH) 255 (log ε 4·288) 2·80 (log ε 4·161) 322 (log ε 3·482) nm; NMR ($CDCl_3$) δ6·88 and 6·68 (2H, each s, aromatic H), 6·38, 6·27 (2H, each s, olefinic H), 3·94, 3·80 (6H, each s, $2\times OCH_3$), 2·97 ppm (3H, s, NCH_3); *m/e* 425 (M^+). Calc. for $C_{21}H_{22}F_3NO_5$: C, 59·29; H, 5·17. Found: C, 59·04; H, 4·88%.

Michael reaction of **17b**. To a soln of **17b** (100 mg; 0·235 m mol) in 40 ml MeOH K_2CO_3 (20 mg) was added with stirring. The color of the soln changed from red to dark brown. The solvent was removed *in vacuo* to give a residue, which was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to afford **18** (70 mg, 90·3%) as a pale yellow oil; IR ν_{max} ($CHCl_3$) 3450, 1679, 1629 cm^{-1}; UV λ_{max} (MeOH) 257 (log ε 3·74), 283sh (log ε 3·505) nm; NMR ($CDCl_3$) δ6·81, 6·60 (2H, each s, aromatic H), 5·80 (1H, s, olefinic H), 3·92, 3·58 (6H, each s, $2\times OCH_3$), 2·25 ppm (3H, s, NCH_3); *m/e* 329 (M^+). Picrate of **18** formed yellow needles (EtOH), m.p. 213–215°. Calc. for $C_{19}H_{23}NO_4.C_6H_3N_3O_7$: C, 53·76; H, 4·69; N, 10·10. Found: C, 53·48; H, 4·98; N, 10·02%.

Treatment of enone **18** *with methanolic hydrogen chloride.* A stream of dry HCl gas was passed through a soln of **18** (0·110 g; 0·334 m mol) in 1·5 ml MeOH for 1 h. The color of the mixture turned from pale yellow to red. The solvent was evaporated *in vacuo* and the residue was taken up in a small amount of water with cooling. The soln was made basic with 10% Na_2CO_3 and extracted with $CHCl_3$. The solvent was removed to give a mixture of **18** and **19**, in the ratio of 1:4 by NMR analysis. The crude base was chromatographed on alumina with $CHCl_3$. Evaporation of the first eluate **19** (0·023 g; 10·9%) as a syrup; IR ν_{max} ($CHCl_3$) 3480, 1678, 1625 cm^{-1}; UV λ_{max} (MeOH) 255 (log ε 3·87), 287sh (log ε 3·775) nm; NMR ($CDCl_3$) δ6·65, 6·57 (2H, each s, aromatic H), 5·64 (1H, s, olefinic H), 3·84, 3·65 (6H, each s, $2\times OCH_3$), 2·41 ppm (1H, s, NCH_3). Picrate of **19** formed yellow prisms (EtOH), m.p. 218–219°. Calc. for $C_{19}H_{23}NO_4.C_6H_3N_3O_7$: C, 53·76; H, 4·69; N, 10·10. Found: C, 53·51; H, 4·82; N, 10·02%.

Evaporation of the second eluate gave 0·008 g (7·3%) of **18**.

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REFERENCES

[1]Part DXLVII, *Tetrahedron* **30**, 1053 (1974)
[2]A part of this paper was reported as a preliminary communication: T. Kametani, T. Kobari and K. Fukumoto, *Chem. Comm.* 2880 (1972)
[3a]A. R. Battersby, *Oxidative Coupling of Phenols* (Edited by W. I. Taylor and A. R. Battersby) pp. 119–165. Marcel Dekker, New York (1967); [b]T. Kametani and K. Fukumoto, *Phenol Oxidation*. Gihodo, Tokyo (1970)
[4]Ref 3*a*, pp. 128–133, and many refs cited
[5]T. Kametani and K. Fukumoto, *Synthesis* 657 (1972)
[6]M. Tomita and M. Kozuka, *Tetrahedron Letters* 6229 (1966)
[7]Y. Inubushi, M. Kitano and T. Ibuka, *Chem. Pharm. Bull. Tokyo* **19**, 1820 (1971); the review on the syntheses of hasubanan alkaloids was reported by Y. Inubushi, T.

Ibuka and K. Tanaka, *J. Syn. Org. Chem. Japan* p. 98. 30th Aniversary Issue (1972)
[8]M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe and M. Matsui, *Chem. Pharm. Bull. Tokyo* **13**, 538 (1965)
[9]A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber and J. Staunton, *Chem. Comm.* 1214 (1968)
[10]B. Franck and V. Teetz, *Angew. Chem.* **83**, 409 (1971)
[11]T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takahashi and K. Fukumoto, *J. Chem. Soc.* (C), 3315 (1971); *cf* T. Kametani, K. Takahashi, T. Honda, M. Ihara and K. Fukumoto, *Chem. Pharm. Bull. Tokyo* **20**, 1793 (1972)
[12]T. Kametani, A. Kozuka and K. Fukumoto, *J. Chem. Soc.* (C) 1021 (1971), and refs cited
[13]J. Gadamer, *Arch. Pharm.* **259**, 135 (1921)
[14]A. R. Battersby and B. J. Harper, *J. Chem. Soc.* 3526 (1962)
[15]*NMR Spectra Catalog* compiled by N. S. Bhacca, D. P. Hollis, L. F. Johnson and E. A. Pier, Varian Associates, Vol. 2, No. 498 (1963)
[16]M. A. Schwartz and R. A. Holton, *J. Am. Chem. Soc.* **92**, 1090 (1970)
[17]T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, *J. Org. Chem.* **33**, 690 (1968)
[18]H. Newman, *Ibid.* **30**, 1287 (1965)
[19]M. L. Wolfrom and H. B. Bhat, *Chem. Comm.* 146 (1966)
[20]*Cf* J. D. Roberts, *Notes on Molecular Orbital Calculation* Benjamin, New York (1962)
[21]B. Franck and H. J. Lubs, *Angew. Chem.* **80**, 238 (1968)
[22]A. R. Battersby and T. H. Brown, *Chem. Comm.* 170 (1966)
[23]A. R. Battersby, E. McDonald, M. H. G. Munro and R. Ramage, *Ibid.* 934 (1967)
[24]D. H. R. Barton, A. J. Kirby and G. W. Kirby, *J. Chem. Soc.* (C), 929 (1968)