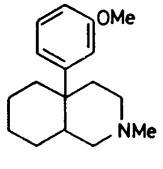
Synthesis of Morphine Analogues. Part 1. Synthesis of Some 5-Benzyl-2-methyloctahydroisoquinolines

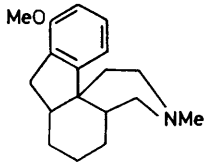
By **John R. Lindsay Smith,*** **Richard O. C. Norman,** and **Malcolm E. Rose,** Department of Chemistry, The University of York, Heslington, York YO1 5DD
Adrian C. W. Curran, Reckitt and Colman Ltd., Dansom Lane, Kingston-upon-Hull HU8 7DS

The synthesis of 5-benzyl-2-methyl-1,2,3,4,6,7,8,8a-octahydroisoquinolines from 3,4-dihydrocoumarin is described.

REPORTS [1] of the analgesic activity of 4a-aryldecahydroisoquinolines such as (1) caused us to consider whether more rigid compounds, derived from linking the aryl moiety to the isoquinoline nucleus, might have increased activity associated with their closer relationship to the morphine skeleton. Thus, compound (2) was considered a worthwhile synthetic objective, and we report here the synthesis, and attempted cyclisation, of the octahydroisoquinolines (10) and (12) by an annelation route that resembles that recently reported by Schultz and Lucci [2] for the preparation of a 5-aryloxyoctahydroisoquinolone (Scheme 1).



(1)

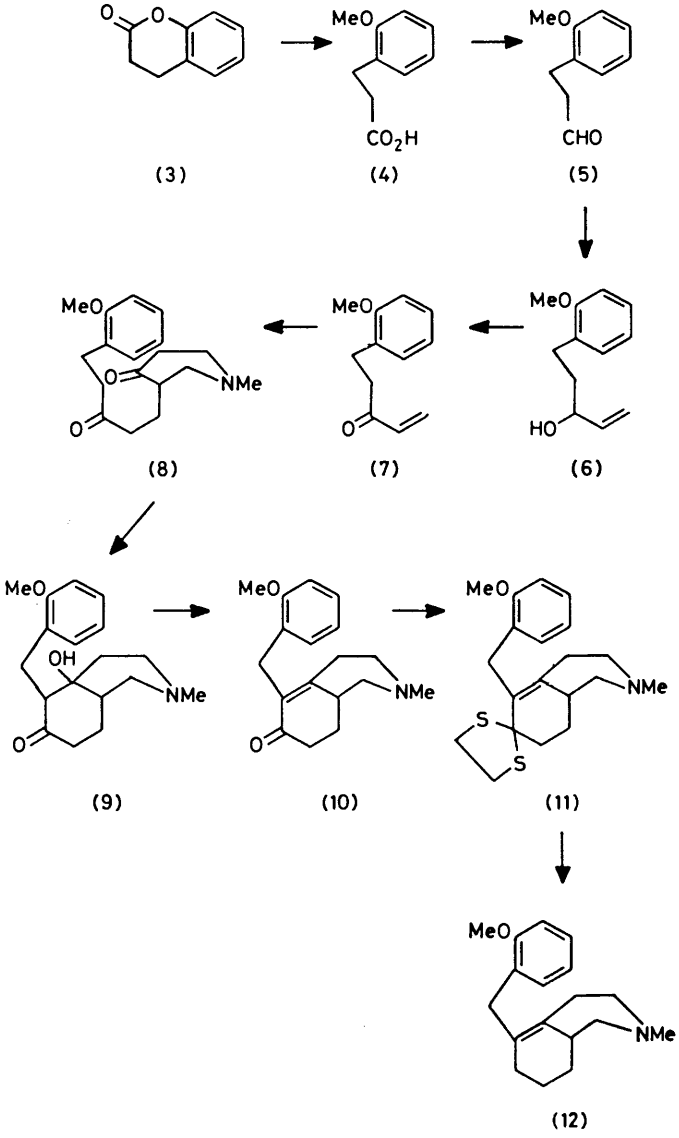


(2)

3-(2-Methoxyphenyl)propanoic acid (4) was obtained by methylation with dimethyl sulphate of the dianion from the hydrolysis of 3,4-dihydrocoumarin. In the initial methylation the required compound (4) and its methyl ester were formed in the proportions 20 : 80, but alkaline hydrolysis of this mixture followed by work-up gave a 95% overall yield of (4) in a 'one-pot' reaction. The conversion of the arylpropanoic acid into its acid chloride and catalytic reduction with 5% palladium–barium sulphate (Rosenmund reduction [3]) gave 3-(2-methoxyphenyl)propanal (5) in 85% yield. An alternative reduction of the acid chloride with tri-t-butoxyaluminium hydride [4] was unsatisfactory, giving 8% of the aldehyde (5) and 40% of the corresponding alcohol.

The allylic alcohol (6) was obtained from a Grignard reaction of the aldehyde (5) with vinylmagnesium bromide; the yield varied between 50 and 67%, the remainder of the aldehyde being accounted for as the trimer (13). Oxidation of the allylic alcohol with Jones reagent resulted in quantitative conversion of (6) into (7) with an overall yield of (7), based on the starting dihydrocoumarin, of greater than 40%. The alternative one-step reaction of the lithium salt of (4) with vinyl-lithium gave none of the enone (7).

The pyrrolidine enamine of 1-methyl-4-piperidone reacted with (7) by 1,4-addition followed by an internal aldol condensation to give (9) in 67% yield. That the reaction proceeded beyond the Michael addition and that the product was not the uncyclised isomeric dione (8)

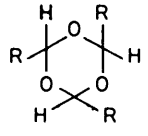


SCHEME 1

was shown by ^{13}C n.m.r. spectroscopy, for the product contained only one carbonyl carbon (213.5 p.p.m.), and one tertiary alcohol α-carbon (73.6 p.p.m.). This

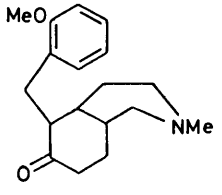
conclusion was confirmed by the mass and i.r. spectra. Treatment of the hydroxy-ketone (9) with aqueous alcoholic potassium hydroxide gave an almost quantitative yield of the enone (10). The same conversion was also achieved by use of acidic reagents, for example polyphosphoric or trifluoroacetic acid.

We found that the best method for reducing the enone (10) to the alkene (12) (overall yield 55%) involved the formation of the cyclic dithioacetal (11) and hydrogenolysis with Raney nickel.[5] Three alternative methods gave lower yields of the required product together with other materials. Thus reduction of the dithioacetal with titanium(IV) chloride and lithium aluminium hydride [6] gave four products of which the major one was (12), but the yield was low and purification difficult. Direct reduction of (10) by use of aluminium trichloride and lithium aluminium hydride, a method that has been reported to reduce αβ-unsatu-

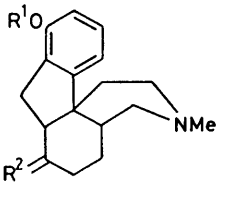


R = 2-methoxyphenethyl

(13)



(14)



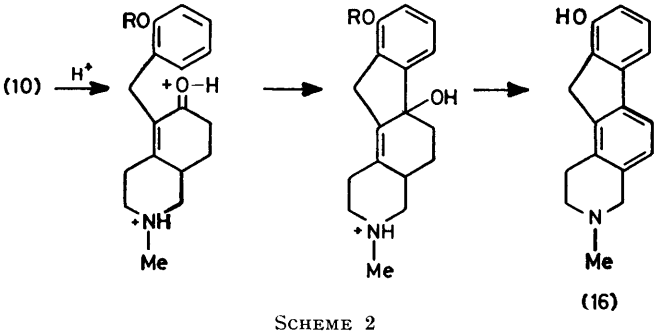
(15) a; R^1 = Me or H, R^2 = O

b; R^1 = Me or H, R^2 = CH_2S | CH_2S

c; R^1 = H, R^2 = 2H

rated ketones to alkenes without migration of the double bond,[7] gave a mixture that contained mainly the ketone (14). A modified Wolff–Kishner reduction which has been reported to give alkenes from the hydrazones of αβ-unsaturated ketones with potassium t-butoxide,[8] and also a recent method with sodium hydride in dimethyl sulphoxide,[9] failed; the enone (10) was re-formed from unchanged hydrazone during work-up.

We were unsuccessful in our attempts to cyclise to (2) or (15) any of the compounds (10), (11), and (12) with the acidic reagents commonly used for related cyclisations in the syntheses of benzomorphans [10] and morphinans.[11] Thus (10) with polyphosphoric acid or phosphoric acid at 150 °C gave a low yield of a product which, although not fully characterised, had spectra (mass, n.m.r., i.r.) consistent with its being (16) and which presumably arose by cyclisation onto the carbonyl rather than the alkene double bond (Scheme 2). Un-

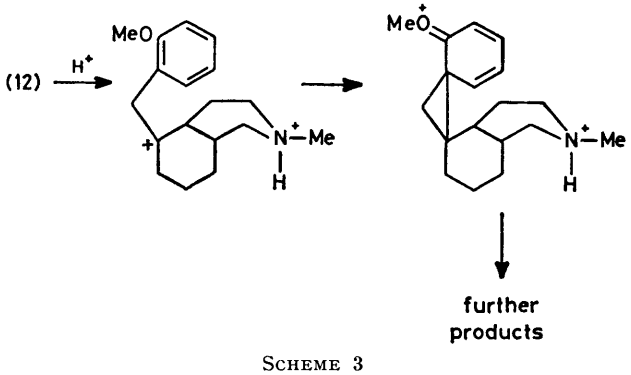


SCHEME 2

fortunately the cyclic dithioacetal group was unstable to the strongly acidic reaction conditions (88% phosphoric acid at 140—150 °C), and (11) gave the same product as (10). When (12) was treated with 88% phosphoric acid at 140 °C, 48% hydrobromic acid at 136 °C, or boron trifluoride–ether complex in trifluoroacetic acid at 110 °C, a large number of products was obtained and mass-spectral analysis showed the absence of ions expected from (2). We suspect that acid, helped by the $+M$ effect of the methoxy group, promotes the undesirable cyclisation to a three-membered ring (Scheme 3). It is noteworthy that attempts to cyclise 1,4-dienes to five-membered rings by ionic reactions likewise result in cyclopropane derivatives.[12]

The attempted cyclisation of (12) with mercury(II) acetate [13,14] followed by reduction with sodium borohydride gave mercury and an almost quantitative recovery of starting material; presumably these arise from aromatic mercuriation of the methoxyphenyl ring.[14] Oxidation of (12) with palladium(II) acetate, under conditions that are known to cause cyclisation of 3-phenylpropenes,[15] gave the expected deposit of palladium metal, but the organic products were intractable polar materials.

The hydroxy-ketone (9) was completely devoid of analgesic activity in the phenylquinone writhing [16] and the rat tail pressure [17] antinociceptive tests.



SCHEME 3

EXPERIMENTAL

I.r. spectra (liquid film or nujol mull) were recorded on Pye–Unicam SP200 and SP1025 spectrometers. ^{1}H N.m.r. spectra for deuteriochloroform solutions were obtained with

Varian A-60A or JEOL 100 MHz spectrometers and ^{13}C n.m.r. spectra with a JEOL JNM-FX60 F.T. spectrometer. Tetramethylsilane was used as internal standard. Routine low-resolution mass spectra were measured on A.E.I. MS9, MS12, and MS30 spectrometers, and accurate mass measurements were made by the P.C.M.U. (Harwell, U.K.). T.l.c. was carried out on silica gel GF_{254} (Merck) and for column chromatography 80—200 mesh silica gel (Fisons Scientific Apparatus Ltd.) was used.

Materials.—All the commercial materials were of reagent grade and obtained from Aldrich Chemical Co. Ltd., B.D.H. Ltd., Koch–Light Ltd., Fisons Scientific Apparatus Ltd., or Johnson Matthey Chemicals Ltd. The nitrogen gas (British Oxygen white spot) was dried by passing it through concentrated sulphuric acid followed by silica gel and potassium hydroxide pellets.

3-(2-*Methoxyphenyl*)*propanoic Acid* (4).—3,4-Dihydrocoumarin (6.0 g) was added to stirred aq. 3M-KOH (120 cm^3) and the mixture was heated to reflux for 0.5 h; the solution was then homogeneous, and dimethyl sulphate (36 g) was added at a rate such as to maintain gentle reflux. The mixture was then refluxed again for 0.5 h before addition of solid KOH (26.7 g) and refluxing for a further 1.0 h. The solution was poured into ice-cold aq. 4M-HCl (120 cm^3) and the liberated acid (4) was collected by filtration (6.93 g, 95%); m.p. 87.5—88.5 °C (from petroleum, b.p. 60—80 °C) (lit.,[18] 87—89 °C); τ 0.2 (1 H, s, exchangeable, CO_2H), 2.6—3.4 (4 H, m, ArH), 6.2 (3 H, s, OCH_3), and 6.9—7.5 (4 H, m, $ArCH_2CH_2$).

3-(2-*Methoxyphenyl*)*propanal* (5).—3-(2-Methoxyphenyl)-propanoyl chloride(13.1 g, 92%) [b.p. 92—95 °C at 0.6 mmHg (lit.,[19] 165 °C at 40 mmHg)] was prepared from the acid (4) (12.8 g) and thionyl chloride (10.3 cm^3). 5% Palladium–$BaSO_4$ (1.5 g) was added to a vigorously stirred solution of the acid chloride (10.1 g) in dry xylene (50 cm^3) and hydrogen was passed through the mixture as it was heated to reflux. After 5 h, when the exit gases contained negligible HCl, the mixture was cooled and filtered. The filtrate was combined with washings (diethyl ether) from the catalyst and concentrated under vacuum. Vacuum distillation gave the aldehyde (5) (7.67 g, 92%), b.p. 124—126 °C at 14 mmHg (lit.,[19] 260 °C at 760 mmHg); τ 0.25 (1 H, t, CHO), 2.6—3.4 (4 H, m, ArH), 6.2 (3 H, s, OCH_3), and 6.9—7.5 (4 H, m, $ArCH_2CH_2$). The 4-nitrophenylhydrazone derivative had m.p. 121—126 °C (lit.,[19] 126—127 °C).

An alternative reduction of the acid chloride (1.12 g) by the method of Brown and Subba Rao [20] by use of lithium tri-t-butoxyaluminium hydride [20] gave a mixture (0.58 g) which contained two major products (by t.l.c. analysis in diethyl ether). The mixture had $\nu_{max.}$ 3 700br (OH stretch) and 1 720 (C=O stretch), τ 0.3 (t, CHO), 2.6—3.4 (m, ArH), 4.75 (exchangeable, OH), 6.25 (s, OCH_3), 6.4 (t with D_2O exchange, CH_2OH), 6.9—7.5 (m, $ArCH_2CH_2CH_2OH$ and $ArCH_2CH_2CHO$), and 8.15 (m, $ArCH_2CH_2CH_2OH$). The proportions of the aldehyde (5) and the corresponding alcohol were 1 : 5 (^1H n.m.r. spectroscopy).

3-*Hydroxy*-5-(2-*methoxyphenyl*)*pent*-1-*ene* (6).—The aldehyde (5) (8.2 g) in dry tetrahydrofuran–diethyl ether (3.5 and 13.5 cm^3, respectively) was added slowly to a stirred solution of vinylmagnesium bromide [21] [prepared from vinyl bromide (13.7 g)] in dry tetrahydrofuran (17 cm^3) cooled in an ice–salt bath. The mixture was warmed to room temperature and after 15 h it was heated to 50—60 °C for 1 h; it was then added to sat. aq. NH_4Cl (100 cm^3). Extraction with ether, followed by drying ($MgSO_4$) and evaporation, gave a pale yellow viscous liquid. Column chromatography (diethyl ether) gave two products; first 2,4,6-*tri*-(2-*methoxybenzyl*)-1,3,5-*trioxan* (2.5—4.1 g, 30—50%), m.p. 87—89 °C (Found: C, 73.25; H, 7.55. $C_{30}H_{36}O_4$ requires C, 73.15: H, 7.3%); τ 2.6—3.3 (12 H, m, ArH), 5.15 (3 H, t, OCHO), 6.2 (9 H, s, OCH_3), 7.2 (6 H, t, $ArCH_2CH_2$), and 7.95 (6 H, m, $ArCH_2CH_2$), δ_C 157.4 (C_{Ar}–OCH_3), 129.8—110.1 (5 C_{Ar}), 101.2 (OCHO), 55.1 (OCH_3), 33.9 ($ArCH_2$), and 24.4 ($ArCH_2CH_2$) (all resonances gave the expected couplings in the off-resonance spectrum), *m/e* (11 eV) 492 (M^+); and secondly 3-*hydroxy*-5-(2-*methoxyphenyl*)*pent*-1-*ene* (4) (4.8—6.4 g, 50—67%), b.p. 112—114 °C at 1 mmHg; $\nu_{max.}$ 3 400br cm^{-1} (OH stretch), τ 2.6—3.3 (4 H, m, ArH), 3.7—5.0 (3 H, m, $CH=CH_2$), 5.9 (1 H, d of t with D_2O exchange, CHOH), 6.2 (3 H, s, OCH_3), 7.15 (2 H, t, $ArCH_2$), and 8.1 (3 H, m, CH_2CHOH and exchangeable OH), *m/e* 192.115 0 (M^+, 13%) ($C_{12}H_{16}O_2$ requires 192.115 1), 174 (12), 160 (19.5), 159 (20.5), 121 (92), 91 (100), and 77 (40).

5-(2-*Methoxyphenyl*)*pent*-1-*en*-3-*one* (7).—Jones reagent [22] was added dropwise to a cooled, stirred solution of the alcohol (6) (5.2 g) in acetone (100 cm^3) until the solution exhibited a permanent orange colour. Excess of oxidant was removed with propan-2-ol, the mixture was concentrated under vacuum, and the residue was dissolved in the minimum of water. Extraction with ether, followed by drying ($MgSO_4$) and removal of solvent, gave the *enone* (7) (5.2 g, 100%) as a colourless liquid; τ 2.7—4.4 (7 H, m, ArH and $CH=CH_2$), 6.2 (3 H, s, OCH_3), and 7.0—7.3 (4 H, s, $ArCH_2CH_2$), δ_C 200.6 (CO), 157.4 (C_{Ar}–OCH_3), 136.5 ($CH=CH_2$), 130.0—110.1 (5 C_{Ar} and $CH=CH_2$), 55.1 (OCH_3), and 39.6 and 25.3 ($ArCH_2$ and $ArCH_2CH_2CO$) (all resonances gave the expected couplings in the off-resonance spectrum), *m/e* 190.099 4 (M^+, 32.5%) ($C_{12}H_{14}O_2$ requires 190.099 2), 159 (32.5), 121 (70.5), 91 (100), and 55 (41).

Attempted Synthesis of the Enone (7) *from* (4) *with Vinyllithium.*—Vinyl-lithium [22] (0.19 g) in tetrahydrofuran (5 cm^3) was added to the lithium salt of (4) (0.94 g) suspended in dry tetrahydrofuran (10 cm^3) and the mixture was stirred until it became homogeneous. It was then poured over ice (50 g) and extracted with diethyl ether. The aqueous layer was acidified (HCl) and re-extracted with diethyl ether. The ethereal solutions were combined and worked up to give the starting material (4) (0.8 g, 91%). There was no evidence for the enone (7) in the reaction mixture.

4a-*Hydroxy*-5-(2-*methoxybenzyl*)-2-*methyl*-6-*oxodecahydroisoquinoline* (9).—The pyrrolidine enamine of 1-methyl-4-piperidone [23] (5 g) was added slowly with stirring to the enone (7) (5 g) in dry benzene (30 cm^3) under dry nitrogen. After 15 h stirring, water was added to the mixture and the precipitated solid wax removed by filtration. The filtrate was diluted with water and extracted with dichloromethane, and the organic solution was dried (Na_2SO_4) and concentrated under vacuum. The residue and filtered solid were combined to give (9) (5.36 g, 67%), m.p. 187—189 °C (from propan-2-ol) (Found: C, 71.4; H, 8.3; N, 4.65. $C_{18}H_{25}NO_3$ requires C, 71.3; H, 8.25; N, 4.6%); $\nu_{max.}$ 3 200br (OH stretch), 1 700 cm^{-1} (C=O stretch), τ 2.7—3.4 (4 H, m, ArH), 6.3 (3 H, s, OCH_3), and 7.0—8.5 (18 H, m, NCH_3, CH, and CH_2), δ_C 213.5 (C=O), 157.2 (C_{Ar}–OCH_3), 130.0—110.3 (5 C_{Ar}), 73.6 (COH), 63.0 (COCH), 56.5 (CH_2), 55.1 (OCH_3), 50.2 (CH_2), 46.0 (NCH_3), and 37.1—25.7 (5 C, CH_2 and CH) (all resonances

gave the expected couplings in the off-resonance spectrum and integration showed that all 18 carbon resonances were due to single atoms), *m/e* 303 (M^+, 75%), 164 (100), 126 (46), 121 (39), 91 (58), 58 (40), 57 (38), 44 (59), and 42 (42).

5-(2-*Methoxybenzyl*)-2-*methyl*-1,2,3,4,6,7,8,8a-*octahydro*-6-*oxoisoquinoline* (10).—Aq. KOH (4 g in 8 cm^3) was added dropwise to a solution of the hydroxy-ketone (9) (1 g) in methanol (100 cm^3) under nitrogen. The mixture was refluxed for 2.5 h before being poured into sat. aq. NaCl (250 cm^3). The ethereal extract was dried ($MgSO_4$) and the solvent removed under vacuum to give the liquid *enone* (10) (0.87 g, 92%), τ 2.7—3.4 (4 H, m, ArH), 6.2 (3 H, s, OCH_3), 6.36 (2 H, s, ArCH_2), and 6.9—8.6 (14 H, m, NCH_3, CH, and CH_2), δ_C 198.4 (C=O), 157.4 (C_{Ar}–OCH_3), 156.9 (*C*=C–C=O), 132.1 (C=*C*–C=O), 128.2—109.7 (5 C_{Ar}), 62.7 (ArCH_2), 55.4 (OCH_3), 55.1 (CH_2), 45.7 (NCH_3), 37.8 (=C*C*H), and 36.7—24.0 (4 CH_2), *m/e* 285.172 5, (M^+, 23.5%) ($C_{18}H_{23}NO_2$ requires 285.172 9), 164 (100), 121 (29), 91 (30), 58 (28), 44 (22), and 42 (27).

5-(2-*Methoxybenzyl*)-2-*methyl*-1,2,3,4,6,7,8,8a-*octahydro-isoquinoline* (12).—The cyclic *dithioacetal* (11) was prepared in quantitative yield by the method of Sobti and Dev [5] and had τ 2.7—3.2 (4 H, m, ArH), 6.15 (3 H, s, OCH_3), 6.35 (2 H, s, ArCH_2), 6.75 (4 H, s, SCH_2CH_2S), and 6.9—8.7 (14 H, m, NCH_3, CH, and CH_2), *m/e* 361.152 7 (M^+) ($C_{20}H_{27}NOS_2$ requires 361.153 4). The dithioacetal (1.43 g) in ethanol was added to Raney nickel [prepared [22] from Ni–Al alloy (7 g)] in ethanol to give a total volume of 100 cm^3. The mixture was refluxed for 1.5 h, then the hot solution was filtered and the catalyst was washed successively with ethanol, methanol, and diethyl ether. The combined organic filtrates were concentrated under vacuum to give an oil that on column chromatography ($CHCl_3$–CH_3OH, 4 : 1) gave the *alkene* (12) (0.57 g, 55%) as a colourless liquid, τ 2.7—3.3 (4 H, m, ArH), 6.2 (3 H, s, OCH_3), 6.6 (2 H, s, ArCH_2), and 7.0—8.8 (16 H, m, NCH_3, CH, and CH_2), *m/e* 271.194 3 (M^+, 26.5%) ($C_{18}H_{25}NO$ requires 271.193 6), 150 (78.5), 91 (59), and 58 (100).

Reduction of the dithioacetal (0.134 g) with titanium(IV) chloride and lithium aluminium hydride by the method of Mukaiyama *et al.*[6] gave a pale yellow liquid (0.084 g) which t.l.c. (methanol) analysis showed to contain four components. Column chromatography (CH_3OH) gave a product (0.02 g) which was shown by ^1H n.m.r. to be mainly the alkene (12).

The direct reduction of the enone (10) (0.2 g) with lithium aluminium hydride and aluminium trichloride by the method of Basu *et al.*[7] gave an oil (0.17 g), $\nu_{max.}$ 1 718 cm^{-1} (sat. C=O stretch), δ_C 211.5 (C=O), 157.2 (C_{Ar}–OCH_3), 131.5—109.8 (5 C_{Ar}), and 61.4—25.7 (11 $C_{aliph.}$). [The spectrum also contained small resonances attributable to the alkene (12).] The mass spectrum contained ions corresponding to the molecular ions of (12) and (14), *m/e* 271 and 287, respectively.

Reduction of the hydrazone of (10) [24] with potassium t-butoxide, by the method of Grundon *et al.*,[8] or with sodium hydride in dimethyl sulphoxide, following the procedure of Szmant *et al.*,[9] was not achieved; work-up gave the enone (10).

Attempted Grewe Cyclisation of (10), (11), *and* (12).—A solution of the enone (10) (0.23 g) in 88% phosphoric acid (2.3 cm^3) was stirred under nitrogen at 150 °C for 24 h, then poured into water and made basic (NH_3). Extraction with ethyl acetate followed by removal of solvent gave a brown solid (0.13 g) which, after column chromatography (methanol), gave an off-white solid showing properties consistent with structure (16) (0.044 g), m.p. 190—200 °C (decomp.); $\nu_{max.}$ 3 400br, 2 950, 1 585, 1 455, 1 305, 1 255, and 790 cm^{-1}, τ 2.6—3.4 (5 H, m, ArH), 4.5 (1 H, br, OH), and 6.2—7.8 (~10H, m, NCH_3 and CH_2), *m/e* 251 (M^+), 250, 208, and 169.

When polyphosphoric acid was used in place of the phosphoric acid, t.l.c. analysis (methanol) showed that the product mixture contained five products, with the major component being the partially characterised material assigned structure (16).

Reaction of the dithioacetal (11) (0.1 g) with 88% H_3PO_4 (2 cm^3) by the method described above gave a mixture (0.034 g) in which the major component was the material assigned structure (16).

Reaction of the alkene (12) (0.046 g) with 88% H_3PO_4 (1 cm^3) under nitrogen at 120 °C for 68 h gave, after work-up as described above (except that chloroform was used instead of ethyl acetate) a brown oil (0.014 g). T.l.c. analysis showed this material to be very polar and mass spectrometry confirmed the absence of materials with the molecular mass of (2) or (15c). Repeating this reaction with 48% hydrobromic acid at 136 °C for 24 h or boron trifluoride–ether in trifluoroacetic acid at 110 °C for 48 h gave similar intractable coloured materials.

Attempted Cyclisation of the Alkene (12) *with Mercury*(II) *Acetate or Palladium*(II) *Acetate*.—(i) The alkene (12) (0.05 g) was treated with mercury(II) acetate (0.059 g) in refluxing dry dichloromethane (1 cm^3) for 15 h. The solvent was then removed in a stream of dry nitrogen and the residue was reduced with sodium borohydride (0.035 g) in methanol (2 cm^3) by the procedure of Lethbridge *et al* [14] The organic solution was separated from the mercury and poured into water, and the mixture was basified (NH_3) and extracted with diethyl ether. Drying ($MgSO_4$) followed by removal of solvent gave the starting material (12) (0.05 g, 100%).

(ii) Palladium(II) acetate (0.043 g) was treated with the alkene (12) (0.05 g) in acetic acid (10 cm^3) for 15 h by the method of Bingham *et al.*[15] The mixture was added to water (20 cm^3) and basified (NH_3) before the organic compounds were separated by extraction with diethyl ether. After drying ($MgSO_4$) and solvent removal a mixture of products (0.025 g) was obtained. One component was the starting material, but t.l.c. analysis (CH_3OH) showed that most of the materials were very polar.

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