Design of the Substrate for Oxidative Phenol Coupling. An Efficient Synthesis of the c-Homoerythrinan Skeleton [1]

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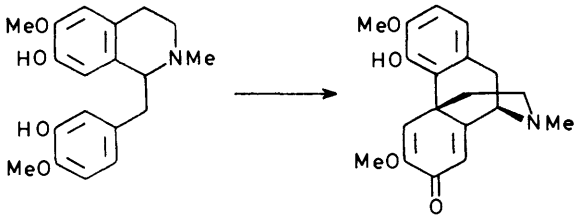
Attention is drawn to the importance of conformational interactions in the cyclisation step of intramolecular phenolic coupling reactions. Careful design of the substrate molecule to minimise these interactions should result in better yields for this important strategy of natural product synthesis. The hypothesis is supported by the contrast in the behaviour of the 1-phenethylquinoline (5) and the 1-phenylacetamidoquinoline (8): when these diphenols were oxidised under identical conditions, (5) gave a complex intractable mixture whereas (8) gave in 67% yield the dienone (23) with the c-homoerythrinan skeleton.

OXIDATIVE coupling of phenols is a key step in living systems for generating rather complex structures from comparatively simple ones.[2] Thus reticuline (1) is oxidised in the opium poppy to salutaridine (2), and a well defined sequence of straightforward reduction, tautomerism, and hydrolysis reactions results in the

[1] Preliminary communications, E. McDonald and A. Suksamrarn, *Tetrahedron Letters*, 1975, 4421, 4425.

[2] See 'Oxidative Phenol Coupling,' ed. A. R. Battersby and W. I. Taylor, Dekker, New York, 1969.

biosynthesis of morphine (3).[3] In principle, oxidation of phenols should be a powerful synthetic tool *in vitro*



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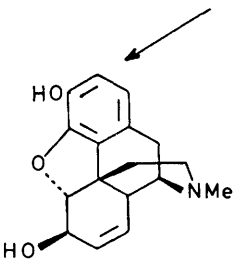
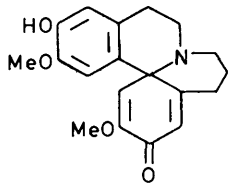


(3)

and much effort has been spent on biomimetic synthesis of a wide variety of natural products along these lines.[4] Unfortunately, yields are usually poor * [though 0.002% for the oxidation [5] of reticuline (1) to salutaridine (2) is exceptionally low], but the recent introduction of new reagents for non-phenolic,[6] monophenolic [7] and diphenolic [8] oxidative couplings [particularly with $VOCl_3$, VOF_3, $Tl(O_2CCF_3)_3$] coupled with a renewed emphasis on *N*-protection (as $\geqslant N\rightarrow BH_3$,[7a] $\geqslant NCO_2Et$,[8c] $\geqslant NCHO$,[6a-c] or $\geqslant NCOCF_3$)[7a,8b,c] offers considerable hope for the future. In this paper we draw attention to a third factor,[1] the removal of conformational interactions in the transition state for cyclisation, by suitable design of the substrate molecule.

c-Homoerysodienone (4) was required in connection with synthetic and biosynthetic studies [9] on the *Schellhammera* alkaloids. We reasoned that oxidative cyclisation of the diphenol (5) should afford the dienone (4), but inspection of molecular models revealed a set of



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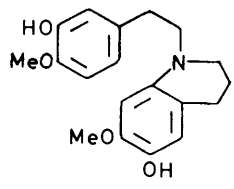

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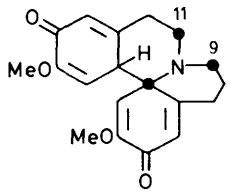
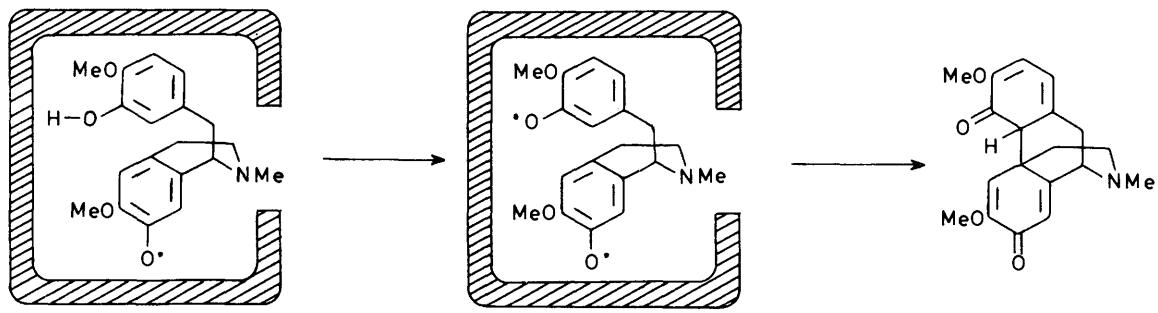


(6)

three 1,3-diaxial interactions between the substituents at the marked atoms in the intermediate (6). We

* *In vivo* the transformation (1) ⟶ (2) probably involves the enzyme-bound radicals (i) and (ii) held in a conformation which ensures that coupling is exclusively *ortho,para* to generate (iii) which can easily aromatise to (2). We emphasise that the radical



(i) (ii) (iii)

(i) is not only extensively delocalised but also sterically hindered survive unchanged until the second electron-transfer step [*cf.* W. A. Waters, *J. Chem. Soc.* (*B*), 1971, 2026].

[3] See (*a*) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 1965, 2423; (*b*) A. R. Battersby, D. M. Foulkes, and R. Binks, *ibid.*, p. 3323; (*c*) G. Blaschke, H. I. Parker, and H. Rapport, *J. Amer. Chem. Soc.*, 1967, **89**, 1540; (*d*) A. R. Battersby, J. A. Martin, and E. Brockmann-Hanssen, *J. Chem. Soc.* (*C*), 1967, 1785, and references cited therein.

[4] For a recent review see T. Kametani, *Bio-organic Chem.*, 1974, **3**, 430.

[5] D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1967, 128.

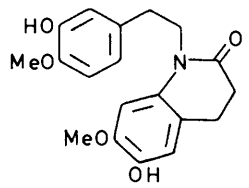
[6] (*a*) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1973, **95**, 6861; (*b*) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *ibid.*, 1975, **97**, 5622; (*c*) S. M. Kupchan, O. P. Dhingra, C. K. Kim, and V. Kamsewaran, *J. Org. Chem.*, 1976, **41**, 4047; (*d*) A. S. Kende and L. S. Liebeskind, *J. Amer. Chem. Soc.*, 1976, **98**, 267; (*e*) R. E. Damon, R. H. Schlessinger, and J. F. Blount, *J. Org. Chem.*, 1976, **41**, 3772; (*f*) A. McKillop, A. G. Turrell, and E. C. Taylor, *J. Org. Chem.*, 1977, **42**, 764.

[7] (*a*) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Amer. Chem. Soc.*, 1973, **95**, 612; (*b*) U. Palmquist, A. Nilsson, V. D. Parker, and A. Ronlán, *ibid.*, 1976, **98**, 2571; (*c*) S. M. Kupchan, O. P. Dhingra, and C. K. Kim, *J. Org. Chem.*, 1976, **41**, 4049.

[8] (*a*) M. A. Schwartz, R. A. Holton, and S. W. Scott, *J. Amer. Chem. Soc.*, 1969, **91**, 2800; (*b*) M. A. Schwartz and R. A. Holton, *ibid.*, 1970, **92**, 1090; (*c*) M. A. Schwartz and I. S. Mami, *ibid.* 1975, **97**, 1239.

[9] E. McDonald and A. Suksamrarn, preceding paper.

expected that these interactions would raise the energy of the transition state for cyclisation and therefore favour *inter*molecular coupling leading eventually to



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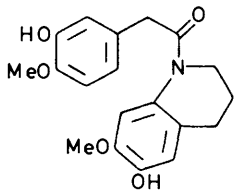
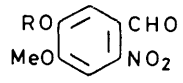
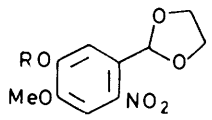


(8)

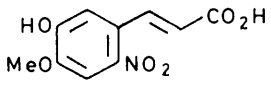
polymeric products. (The majority of oxidative phenol couplings are reported to give a low yield of monomeric products together with intractable unidentified polymer.) However, if one of the sp^3-hybridized carbon atoms C-9 and -11 were replaced by an sp^2-hybridized atom, *two* of the three troublesome interactions would be



(9) R = Me
(12) R = H



(10) R = Me
(11) R = H



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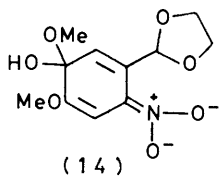
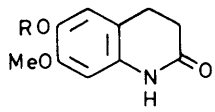


(14)

removed. We therefore decided to prepare the diphenolic amides (7) and (8) and the corresponding amine (5) and to compare their behaviour in reactions with one-electron oxidants.

Selective demethylation of 6-nitroveratraldehyde [10] (9) was achieved in *ca.* 70% overall yield *via* alkaline hydrolysis [11] of the ethylene acetal (10) to (11); deprotection of (11) gave 6-nitroisovanillin (12). This highly effective sequence was devised because (*a*) nitration of isovanillin itself gives a mixture of isomers; [12] and (*b*) alkaline treatment of 6-nitroveratraldehyde (9), or the corresponding cinnamic acid, gave complex mixtures of products. Knoevenagel condensation of 6-nitroisovanillin (12) with malonic acid gave the cinnamic acid (13). Massive reversible shifts (*ca.* 90 nm) in the long wavelength u.v. absorptions of (11), (12), and (13) on adding alkali proved that demethylation had occurred specifically *para* to the nitro-group [clearly *via* the intermediate (14)].

Reductive cyclisation of the nitrocinnamic acid (13) to dihydroisoquinolone (15) was achieved by catalytic hydrogenation in the presence of HCl, and benzylation of (15) gave the protected lactam (16) in 80% overall yield from the aldehyde (12). Methylation of the sodium salt of (16) in dimethylformamide by methyl iodide gave the expected *N*-methyl derivative, but attempted alkylation using the phenethyl mesylate (17) resulted in elimination rather than substitution and only the styrene (18) was isolated. Although other routes to the amide

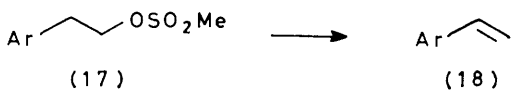


(15) R = H
(16) R = CH_2Ph

(7) can be envisaged we turned instead to the synthesis of the isomeric amide (8).

Reduction of the lactam (16) with $LiAlH_4$ gave the tetrahydroquinoline (19), and this was condensed with the phenylacetic acid [13] (20) using dicyclohexylcarbodiimide in CH_2Cl_2 at 0—5 °C to produce the protected amide (21). Reduction of (21) by $LiAlH_4$ gave the amine (22), and hydrogenolysis of (21) and (22) afforded the crystalline diphenolic substrates (8) and (5) required for comparative oxidation studies.

The partition coefficients of the diphenolic amide (8) between equal volumes of chloroform and aqueous 5% $NaHCO_3$ and Na_2CO_3 were *ca.* 30 and 1, respectively.



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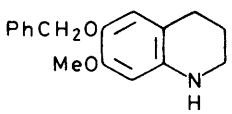

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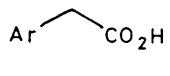

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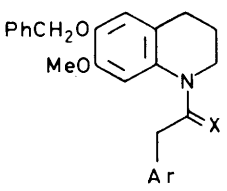
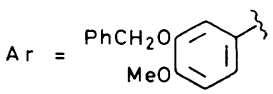


(21) X = O
(22) X = H_2

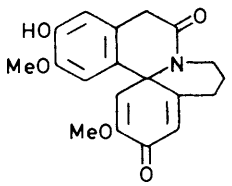


Oxidations were therefore carried out using potassium ferricyanide in the two-phase system chloroform–

[10] J. T. Cassaday and M. T. Bogert, *J. Amer. Chem. Soc.*, 1939, **61**, 2461.
[11] *Cf.* M. Greenwood and R. Robinson, *J. Chem. Soc.*, 1932, 1370.
[12] R. Pschorr and W. Storer, *Ber.*, 1902, **35**, 4393.
[13] A. R. Battersby, R. Binks, R. F. Francis, D. McCaldin, and H. Ramuz, *J. Chem. Soc.*, 1964, 3600.

aqueous 5% $NaHCO_3$, since *inter*molecular coupling (leading eventually to polymer) should be minimised when the diphenol concentration in the aqueous layer is small. These conditions proved remarkably successful and the dienone lactam (23) was obtained reproducibly in high yield (up to 67%). The structure (23) is fully supported by analytical and spectral data (and by the interconversions described in the accompanying paper) but two points deserve special comment. First the appearance of the two aromatic proton signals as singlets in the ^1H n.m.r. spectrum reveals that the dienone (23) has been formed by *para,para*-coupling, and the isomeric dienone (24) could not be detected in the crude reaction product by t.l.c. or n.m.r. The coupling step is therefore highly regiospecific with the least hindered product being formed exclusively. Secondly, a double doublet (1 H) at δ 4.60 has been assigned to one of the protons at C-9. Molecular models reveal that in the rigid dienone (23) this proton is near to the amide carbonyl group in the deshielding region, accounting for its exceptionally low-field signal.

Oxidation of the free base (5) under conditions exactly similar to those used for the amide (8) gave an exceedingly complex mixture of coloured products, and



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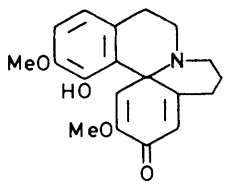


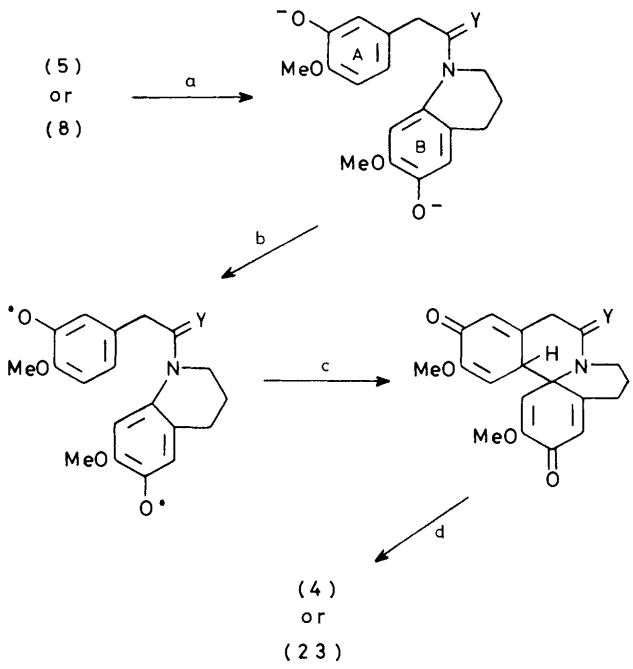
(24)

no dienone was clearly identified. Nor was any improvement noted when iron(III) chloride was used in attempted oxidation of (5).

DISCUSSION

While the superiority of the amide (8) over the corresponding amine (5) as a substrate for oxidative phenolic coupling is exceptionally clear-cut, the mechanistic interpretation of the results remains for the present less certain, because we are studying a multistep reaction. A *possible* mechanistic pathway is outlined (Scheme) to provide a basis for comparing the two reactions.

The deprotonation and oxidation steps (a and b) are dependent respectively on the pK_a and the redox potential of ring B, and these values will vary according to the nature of Y. It is possible therefore that the different results found for (5) and (8) may originate in these primary steps.* However, if an intermediate suitable for cyclisation *can* be generated, then its behaviour will depend on the nature of Y, and for the conformational reasons described in the introduction the ratio of cyclisation (step c) to *inter*molecular reaction should be more favourable when Y = O. Furthermore,



SCHEME

this argument holds *regardless of the mechanistic nature of the oxidative cyclisation.*†

Work is in progress to evaluate further the importance of conformational factors in oxidative phenolic coupling and to apply the principle to the synthesis of natural products.

EXPERIMENTAL

For general directions see preceding paper.[9]

3,4-Dimethoxy-6-nitrobenzaldehyde (9).—To concentrated nitric acid (s. g. 1.42; 30 ml), cooled to 5—10 °C in an ice-bath, was added in small portions finely pulverised veratraldehyde (3.0 g) during 5 min with vigorous stirring. After stirring at room temperature for an additional 1 h the mixture was poured into chipped ice (*ca.* 300 g), and the pale yellow solid was collected, washed with water, and dried in a desiccator; yield 3.60 g (94.4%). Recrystallisation from ethanol gave pale yellow needles, m.p. 134—135° (lit.,[10] 132—133°). This compound was sensitive to light (Found: C, 50.8; H, 4.0; N, 6.8. Calc. for $C_9H_9NO_5$: C, 51.2; H, 4.3; N, 6.65%); $\nu_{max.}$ 1 690, 1 607, 1 575, and 1 332 cm^{-1}; $\lambda_{max.}$ 222 (8 410), 252 (10 329), 261 (10 604), 312 (4 387), and 340 nm (4 662); δ 4.00 (2 × 3 H, s, 2 × CH_3O), 7.38 (1 H, s, ArH), 7.58 (1 H, s, ArH), and 10.36 (1 H, s, CHO), *m/e* 211 (base peak), 181, 164, and 136; *m** 155.26 (211 → 181).

3,4-Dimethoxy-6-nitrobenzaldehyde Ethylene Acetal (10).—A mixture of the nitro-aldehyde (9) (9.6 g) ethylene glycol

* Different results may also arise because (5) and the intermediate derived from it have an unprotected basic nitrogen, whereas (8) has the same nitrogen 'protected' as an amide. However, successful oxidations on tertiary bases under similar conditions *have* been reported.[14]

† Cyclisations which involve pairing of radical cations, radical substitution, or electrophilic substitutions should also be more favourable when Y = O.

[14] *E.g.* A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *J.C.S. Perkin I*, 1974, 1394.

(4 g) and toluene-*p*-sulphonic acid (250 mg) in benzene (60 ml) was heated at reflux for 135 min and the water produced was removed azeotropically (Dean–Stark apparatus). The solvent was evaporated off and the crude product recrystallised from ethyl acetate to give the *acetal* (10) (10.4 g, 89.6%), m.p. 123—124° (Found: C, 51.5; H, 5.2; N, 5.45. $C_{11}H_{13}NO_6$ requires C, 51.75; H, 5.15; N, 5.5%); $\nu_{max.}$ 1 612, 1 580, and 1 335 cm^{-1}; $\lambda_{max.}$ 220 (10 491), 240 (11 079), and 295 nm (4 234); δ 3.90 (3 H, s, CH_3O), 3.94 (3 H, s, CH_3O), 4.03 (4 H, s, OCH_2CH_2O), 6.45 (1 H, s, OCHO), 7.24 (1 H, s, H-2), and 7.54 (1 H, s, H-5); *m/e* 255 (M^+), 238, and 208 (base peak).

3-*Hydroxy*-4-*methoxy*-6-*nitrobenzaldehyde Ethylene Acetal* (11).—Aqueous 20% potassium hydroxide (470 ml) was added to the acetal (10) (25 g), dissolved in hot dioxan (75 ml), and the mixture was heated under reflux for 45 h. The clear reddish-brown solution was cooled in an ice-bath and carefully neutralised (to slightly acidic); yellow crystals of the product separated. The *acetal* (11) was collected, washed with water, and dried in a desiccator; yield 20.2 g (85.4%), m.p. 129—130° (from acetone–benzene) (Found; C, 49.65; H, 4.7; N, 5.7. $C_{10}H_{11}NO_6$ requires C, 49.8; H, 4.6; N, 5.8%), $\nu_{max.}$ (Nujol) 3 275, 1 582, and 1 337 cm^{-1}; $\lambda_{max.}$ 246 (9 286), 286 (4 561), and 336 (4 643); $\lambda_{max.}$ (OH^-) 270 (8 349), and 426 nm (12 667); δ[$(CD_3)_2SO$] 3.84 (3 H, s, CH_3O), 3.92 (4 H, s, OCH_2CH_2O), 6.32 (1 H, s, OCHO), 7.13 (1 H, s, H-2), 7.55 (1 H, s, H-5), and 10.45br (1 H, m, OH); *m/e* 241 (M^+), 224, and 194 (base peak).

3-*Hydroxy*-4-*methoxy*-6-*nitrobenzaldehyde* (12).—The acetal (11) (3.4 g) was dissolved in acetone (30 ml) and aqueous 10% hydrochloric acid (20 ml) was added. The stirred solution was warmed on a water-bath (55—60 °C) for 35 min. The acetone was evaporated off; the yellow crystals were collected, washed with water, and dried in a desiccator to give the *aldehyde* (12) (2.55 g, 91.7%). Recrystallisation from acetone–water gave yellow needles, m.p. 186—187° (Found: C, 48.95; H, 3.65; N, 7.1. $C_8H_7NO_5$ requires C, 48.75; H, 3.6; N, 7.11%); $\nu_{max.}$ (Nujol) 3 220, 1 694, 1 615, 1 570, and 1 370 cm^{-1}; $\lambda_{max.}$ 222 (9 980), 261 (11 507), 310 (5 470), and 336 (5 282); $\lambda_{max.}$ (OH^-) 235 (12 215), 293 (9 243), and 438 nm (12 639); δ[$(CD_3)_2SO$] 3.97 (3 H, s, CH_3O), 7.24 (1 H, s, ArH), 7.68 (1 H, s, ArH), and 10.20 (1 H, s, CHO); *m/e* 197 (M^+), 167 (base peak), 150, and 122; *m** 141.57 (197 ⟶ 167).

3-*Hydroxy*-4-*methoxy*-6-*nitro*-trans-*cinnamic Acid* (13).—A mixture of the aldehyde (12) (1.90 g), and malonic acid (1.90 g) in pyridine (4 ml) and piperidine (10 drops) was heated under reflux for 105 min. The pyridine and piperidine were removed *in vacuo* and the crystals which appeared when the solution was concentrated were digested with acetone–water, collected, washed with acetone–water, and dried in a desiccator to give the *cinnamic acid* (13) (2.15 g, 93.3%). Recrystallisation from acetone–water gave yellow crystals, m.p. 256—257.5° (decomp.) (Found: C, 50.05; H, 3.8; N, 6.05. $C_{10}H_9NO_6$ requires C, 50.2; H, 3.8; N, 5.95%); $\nu_{max.}$ (Nujol) 3 600, 3 520, 3 360, 2 500—2 800br, 1 695, 1 635, 1 575, and 1 370 cm^{-1}; $\lambda_{max.}$ 230 (11 121), 273 (20 689), and 345 (6 457); $\lambda_{max.}$ (OH^-) 246 (14 888), 296 (12 317), and 432 nm (12 915); δ[$(CD_3)_2SO$] 3.90 (3 H, s, CH_3O), 6.26 (1 H, d, *J* 15 Hz, *trans* olefinic), 7.12 (1 H, s, H-2), 7.75 (1 H, s, H-5), and 7.95 (1 H, d, *J* 15 Hz, *trans* olefinic).

6-*Hydroxy*-7-*methoxy*-3,4-*dihydroquinolin*-2(1H)-*one* (15).—The cinnamic acid (13) (6.0 g) dissolved in hot ethanol (250 ml) was allowed to cool. Concentrated hydrochloric acid (2 drops) and 10% palladium–charcoal (600 mg) were added before hydrogenation (Parr hydrogenator) at 45 °C and 45 lb in^{-2} for 24 h. The mixture was filtered through Celite, and the residue washed with hot methanol. The filtrate was concentrated *in vacuo*; crystals slowly separated. The product was collected and washed with cold ethanol; yield 3.80 g. The combined filtrate was concentrated and a small portion of ether added, and the mixture was kept in a refrigerator; thus more crystals were obtained. The total yield of *lactam* (15) was 4.28 g (88.2%). After recrystallisation from methanol it melted at 211—213° (Found: C, 60.75; H, 6.0; N, 6.95. $C_{10}H_{11}NO_3$,0.25H_2O requires C, 60.75; H, 5.85; N, 7.1%); $\nu_{max.}$ (Nujol) 3 565, 3 200br, 1 652, and 1 630 cm^{-1}; $\lambda_{max.}$ 220 (14 769), 266 (8 876), and 292 nm (5 818); δ(C_5D_5N) 2.72 (4 H, m, CH_2), 3.72 (3 H, s, CH_3O), 6.76 (1 H, s, ArH), and 10.64br (1 H, s, exchanged with D_2O, NH); *m/e* 193 (M^+), 178, 165, and 150; *m** 141.06 (193 ⟶ 165) and 126.40 (178 ⟶ 150).

6-*Benzyloxy*-7-*methoxy*-3,4-*dihydroquinolin*-2(1H)-*one* (16).—A mixture of the quinolone (15) (1.20 g), benzyl chloride (1.20 g; excess), and anhydrous potassium carbonate (800 mg) in dry methanol (10 ml) was heated under reflux for 5 h. The mixture was filtered, the residue washed with hot methanol, and the combined filtrate evaporated. The crude product was redissolved in chloroform; the solution was washed with aqueous potassium carbonate and water, and dried. Evaporation and recrystallisation from methanol gave the *lactam* (16) as crystals (1.70 g, 96.6%), m.p. 169—170.5° (Found: C, 71.4; H, 6.1; N, 5.0. $C_{17}H_{17}NO_3$,0.25H_2O requires C, 70.95; H, 6.1; N, 4.85%), $\nu_{max.}$ 3 410, 3 210br, 1 681, and 1 625 cm^{-1}; $\lambda_{max.}$ 220 (21 315), 265 (10 554), and 292infl nm (6 332); δ 2.58 (2 H, m, CH_2CO), 2.82 (2 H, *ca.* t, *J* 6 Hz, $ArCH_2$), 3.82 (3 H, s, CH_3O), 5.04 (2 H, s, $PhCH_2$), 6.40 (1 H, s, H-8), 6.67 (1 H, s, H-5), 7.36 (5 H, m, Ph), and 9.07br (1 H, s, NH); *m/e* 283 (M^+), 192 (base peak), and 122.

Methylation of the Lactam (16).—A solution of the lactam (16) (28.3 mg) in dry *NN*-dimethylacetamide (2 ml) was added to a suspension of sodium hydride (200 mg of 50% dispersion in oil) in 1 : 1 benzene–dimethylacetamide (5 ml). After warming at 55—60 °C for 20 min the mixture was cooled to 5 °C and methyl iodide (0.6 ml) was added. The mixture was stirred at 20 °C for 2 h, then diluted with benzene. The aqueous layer was separated and extracted with ethyl acetate, and the combined organic extract was washed with water and evaporated to give the *N*-methyl derivative, m.p. 94—96°; *m/e* 297, 220, 206 (base), and 91; $\nu_{max.}$ 1 655 cm^{-1}; $\lambda_{max.}$ 263 and 292 nm; δ 2.68 (4 H, m, 2 × CH_2), 3.32 (3 H, s, NMe), 3.88 (3 H, s, OMe), 5.09 (2 H, s, $PhCH_2O$), 6.58 and 6.72 (each 1 H, s, 2 × ArH), and 7.36 (5 H, m, Ph).

Attempted Alkylation of the Lactam (16).—Alkylation was attempted exactly as described above but with the phenethyl mesylate (17) (33 mg) in place of methyl iodide. The major product (13 mg) was isolated by preparative t.l.c. on silica (elution with 1% methanol–chloroform) and identified by its spectra as the styrene (18); *m/e* 240, 149, 121, and 91 (base); $\nu_{max.}$ 1 628 cm^{-1}; $\lambda_{max.}$ 261 and 293sh nm; δ 3.88 (3 H, s, OMe), 5.16 (2 H, s, $PhCH_2O$), 5.09 (1 H, d, *J* 10 Hz), 5.52 (1 H, d, *J* 17 Hz), and 6.60 (1 H, dd, *J* 10 and 17 Hz) (H_A,H_B,H_C respectively of $ArH_CC{:}CH_AH_B$ with H_B and H_C *trans*), *ca.* 6.9 (3 H, s, 3 ArH), and 7.4 (5 H, s, Ph).

3-*Benzyloxy*-4-*methoxyphenethyl Mesylate* (17).—Methane-

sulphonyl chloride (0.5 ml) was added to a solution of 3-benzyloxy-4-methoxyphenethyl alcohol [13] (45 mg) in dry pyridine (0.5 ml). After stirring for 2 h at 20 °C the mixture was partitioned between water and 2 : 1 ethyl acetate–ether, and the organic phase was washed with N-HCl and water, dried, and evaporated to give the *mesylate* (17) (51 mg, 89%), m.p. 106—107° (from dichloromethane–hexane) (Found: C, 60.75; H, 6.15. $C_{17}H_{20}O_5S$ requires C, 60.7; H, 5.95%); *m/e* 336, 245, and 91 (base); $\nu_{max.}$ 1 360 cm^{-1}; $\lambda_{max.}$ 231 and 280 nm; δ 2.76 (3 H, s, $MeSO_2$), 2.93 and 4.32 (each 2 H, t, *J* 6 Hz, $ArCH_2CH_2SO_2$), 3.85 (3 H, s, OMe), 5.14 (2 H, s, $PhCH_2O$), 6.80 (3 H, m, 3 ArH), and 7.38 (5 H, m, Ph).

6-*Benzyloxy*-7-*methoxy*-1,2,3,4-*tetrahydroquinoline* (19).—To a suspension of an excess of lithium aluminium hydride (350 mg) in dry tetrahydrofuran (5 ml) was added dropwise the quinolone (16) (900 mg) in tetrahydrofuran (20 ml) over 15 min. The mixture was stirred at room temperature for another 1 h and the excess of hydride was destroyed by careful addition of cold saturated aqueous Rochelle salt. The mixture was filtered, the residue washed thoroughly with hot chloroform, and the combined filtrate evaporated. The residual syrup was redissolved in chloroform, washed with water, and dried. Evaporation and crystallisation from dichloromethane–ether gave two crops of the *tetrahydroquinoline* (19) (745 mg, 87.1%) as crystals, m.p. 105—106° (Found: C, 75.5; H, 7.3; N, 5.0. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%); $\nu_{max.}$ 3 400br,w, 2 930, 2 840, and 1 620 cm^{-1}; $\lambda_{max.}$ 220 (21 315), 265 (10 554), and 292infl nm (6 332); δ 1.90 (2 H, m, CH_2), 2.62 (2 H, t, *J* 6.5 Hz, $ArCH_2$), 3.22 (2 H, t, *J* 6.5 Hz, CH_2N), 3.37br (1 H, NH), 3.75 (3 H, s, CH_3O), 4.97 (2 H, s, $PhCH_2$), 6.08 (1 H, s, H-8), 6.54 (1 H, s, H-5), and 7.32 (5 H, m, Ph); *m/e* 269 (M^+), 178 (base peak), 150, 122, and 91; *m** 126.40 (178 ⟶ 150) and 83.62 (178 ⟶ 122).

6-*Benzyloxy*-1-(3-*Benzyloxy*-4-*methoxyphenylacetyl*)-7-*methoxy*-1,2,3,4-*tetrahydroquinoline* (21).—To a stirred solution of the amine (19) (1.35 g) and the acid [13] (20) (1.60 g) in dry dichloromethane (25 ml), cooled in an ice-bath, was added *NN'*-dicyclohexylcarbodi-imide (DCC) (1.09 g) in dry dichloromethane (3 ml), and the mixture was stirred for ½ h, then at room temperature overnight. The crystals of dicyclohexylurea were filtered off (1.17 g); the filtrate was diluted with more dichloromethane, washed with aqueous potassium carbonate to get rid of the excess of starting acid, back-washed with water, and dried. The solution was concentrated to *ca.* 6—7 ml and kept in an ice-bath; more urea (6—7 mg) separated. The filtered solution was diluted with hexane and kept in a refrigerator; crystals (2.39 g, 91%) separated. Recrystallisation from dichloromethane–ether gave needles of the *amide* (21), m.p. 112.5—113.5° (Found: C, 75.4; H, 6.2; N, 2.5. $C_{33}H_{33}NO_5$ requires C, 75.7; H, 6.35; N, 2.7%); $\nu_{max.}$ 1 639 cm^{-1}; $\lambda_{max.}$ 250 infl (12 785) and 286 nm (7 935); δ 1.80 (2 H, m, CH_2), 2.48 (2 H, t, *J* 6.5 Hz, $ArCH_2CH_2$), 3.76 (2 H, partially superimposed with signals at 3.77—3.84, CH_2N), 3.74 and 3.77 (2 H + 3 H, each s, $ArCH_2CON$ and CH_3O), 3.84 (3 H, s, CH_3O), 5.10 (2 × 2 H, s, 2 × $PhCH_2O$), 6.72 (5 H, m, ArH and Ar'H), and 7.36 (2 × 5 H, m, 2 × Ph); *m/e* 523 (M^+), 432, 228, 227, and 91 (base peak); *m** 356.83 (523 ⟶ 432).

6-*Hydroxy*-1-(3-*Hydroxy*-4-*methoxyphenylacetyl*)-7-*methoxy*-1,2,3,4-*tetrahydroquinoline* (8).—The benzyloxy-amide (21) (1.20 g) was dissolved in chloroform (3 ml) in a long-neck flask (50 ml), and methanol (16 ml), hydrogen chloride–methanol (½ ml), and 10% palladium–charcoal (200 mg) were added. The compound was hydrogenated at atmospheric pressure and at room temperature until the theoretical volume of hydrogen was consumed (1—1½ h). The mixture was filtered through Celite and the residue washed with methanol. Evaporation gave the *phenolic amide* (8) as a semisolid (0.786 g), m.p. 64—67° (Found: C, 64.7; H, 6.2; N, 4.05. $C_{19}H_{21}NO_5,\frac{1}{2}H_2O$ requires C, 64.75; H, 6.25; N, 4.0%); $\nu_{max.}$ 3 540, 3 300br, 1 639, and 1 595 cm^{-1}; $\lambda_{max.}$ 253 (9 331) and 287 nm (7 498); δ 1.85 (2 H, m, CH_2), 2.55 (2 H, t, *J* 6.5 Hz, $ArCH_2CH_2$), 3.75 (2 H, partially superimposed with signals at 3.71, CH_2N), 3.71br (2 H + 3 H, s, $ArCH_2CON$ and CH_3O), 3.80 (3 H, s, CH_3O), 5.69br (20 H, m, exchanged with D_2O), and 6.71 (5 H, m, ArH and Ar'H); *m/e* 343 (M^+), 207, 179 (base peak), and 137.

Phenolic Oxidation of the Diphenolic Amide (8).—A degassed solution of the diphenolic amide (8) (450 mg) in chloroform (20 ml) was injected through a serum cap into degassed, two-phase chloroform–aq. 5% sodium hydrogen carbonate (150 : 150 ml) containing potassium ferricyanide (1.08 g), and the mixture was shaken at room temperature under nitrogen for 2½ h (during which time samples of the chloroform layer were withdrawn for t.l.c.). More ferricyanide (432 mg) in water (3 ml) was added and the mixture shaken for another 1 h. Water (150 ml) was added, and the chloroform layer was separated. The aqueous layer was extracted twice with chloroform (2 × 100 ml) and the combined extracts were washed with water and dried. The solution was concentrated *in vacuo* and the syrup chromatographed on silica gel (14 g; 50% dichloromethane–hexane changing to chloroform) to give, after recrystallisation from dichloromethane–ether the *dienone* (23) as dichloromethane solvate (303 mg, 67.7%), m.p. 135—137° (Found: C, 63.05; H, 5.35; Cl, 6.0; N, 3.95. $C_{19}H_{19}NO_5,\frac{1}{2}CH_2Cl_2$ requires C, 62.8; H, 5.3; Cl, 6.4; N, 3.8%) (after prolonged drying at 72—80°, m.p. 229—231°); $\nu_{max.}$ 3 530, 1 680, 1 645, and 1 621 cm^{-1}; $\lambda_{max.}$ 239 (19 931) and 282 nm (3 927); δ 1.80—2.60br (5 H, m, $[CH_2]_2CH_\alpha N$), 3.55 and 3.72 (2 × 3 H, each s, 2 × CH_3O, 3.66br (2 H, s, $ArCH_2O$), 4.60 (dd, *J* 13 and 6.5 Hz, H-9β), 5.72 (1 H, s), 6.44 (2 H, s,) and 6.72 (1 H, s) (2 × dienone-H and 2 × ArH), and 6.06 (1 H, s, exchanged with D_2O, OH); *m/e* 341 (M^+, base peak), 313, 298, 282, and 270; *m** 287.29 (341 ⟶ 313) and 244.63 (298 ⟶ 270). *Note.* When 6 and 4 mol. equiv. of ferricyanide were employed, the reaction went to completion in 25—35 min, but yields were only 35—40%.

6-*Benzyloxy*-1-(3-*benzyloxy*-4-*methoxyphenethyl*)-7-*methoxy*-1,2,3,4-*tetrahydroquinoline* (22).—To a stirred suspension of lithium aluminium hydride (300 mg) in dry tetrahydrofuran (10 ml) was added dropwise a solution of the dibenzyloxy-amide (21) (700 mg) in dry tetrahydrofuran (15 ml) over 15 min. The mixture was stirred at room temperature for another 1 h and the excess of hydride destroyed by addition of cold saturated aqueous Rochelle salt. The mixture was filtered, the residue was washed thoroughly with hot chloroform, and the combined filtrates were evaporated. The residual syrup was redissolved in chloroform, washed with water, and dried. Evaporation and recrystallisation from dichloromethane–ether gave *dibenzyloxy-amine* (22) as crystals (505 mg, 74.1%), m.p. 100—102° (Found: C, 77.65; H, 6.8; N, 2.75. $C_{33}H_{35}NO_4$ requires C, 77.75; H, 6.9; N, 2.75%); $\nu_{max.}$ 1 615 and 1 586 cm^{-1}; $\lambda_{max.}$ 264 and 315 nm; δ 1.85 (2 H, m, CH_2), 2.64 (2 H, t, *J* 6 Hz, $ArCH_2[CH_2]_2N$), 2.76 (2 H, t, *J* 7 Hz,

Ar'CH_2CH$_2$N), 3.12 (2 H, t, J 6 Hz, Ar[CH$_2$]$_2$CH_2N), 3.41 (2 H, t, J 7 Hz, Ar'CH$_2$CH_2N), 3.76 (3 H, s, CH$_3$O), 3.82 (3 H, s, CH$_3$O), 4.98 (2 H, s, PhCH_2O), 5.06 (2 H, s, PhCH_2O), 6.17 (1 H, s, ArH), 6.56 (1 H, s, ArH), 6.76 (3 H, m, ArH), and 7.36 (2 × 5 H, m, 2 × Ph) (on irradiation at 1.85, the t at 2.64 and t at 3.12 each collapsed to s; on irradiation at 3.12, the m at 1.85 and t at 2.64 and 3.12 each collapsed to s; on irradiation at 3.12, the m at 1.85 changed to t; on irradiation at 2.76, the t at 3.41 collapsed to s; on irradiation at 3.41, the t at 2.76 collapsed to s); *m/e* 509 (M^+), 418, and 91 (base peak).

6-*Hydroxy*-1-(3-*hydroxy*-4-*methoxyphenethyl*)-7-*methoxy*-1,2,3,4-*tetrahydroquinoline* (5).—The dibenzyloxy-amine (22) (200 mg) was dissolved in dichloromethane (0.5 ml), and methanol (3 ml), hydrogen chloride-saturated methanol (0.5 ml), and 10% palladium–charcoal (50 mg) were added. The mixture was hydrogenated at 1 atm and room temperature until the theoretical volume of hydrogen was consumed, then filtered through Celite into methanolic hydrogen chloride (0.3 ml). Evaporation gave the diphenolic amine (5) as the hydrochloride salt (98 mg, 75.8% crude yield). After recrystallisation from methanol–ether the *amine hydrochloride* melted at 179—182°; $\nu_{max.}$ 3 320br, 2 540br, 1 625, and 1 592 cm^{-1}; $\lambda_{max.}$ 228 and 293 nm; δ[(CD$_3$)$_2$SO] 1.9—3.7 (10 H, m, CH$_2$), 3.73br (2 × 3 H, s, 2 × CH$_3$O), and 6.6—7.0 (5 H, m, ArH and Ar'H); *m/e* 329 (M^+) and 192 (base peak); *m** 112.05 (329 ⟶ 192). *Note.* The free amine (5) is unstable; attempted oxidation as described above for the corresponding amide (8) gave only complex mixtures of coloured materials which were not further examined.

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