Synthesis of C-Homoerysodienone and its Conversion into B-Homoerysodienone *via* a Dibenz[*d,f*]azecine; Potential Precursors of the Homoerythrina Alkaloids

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C-Homoerysodienone (12) was synthesised by the unambiguous route (26) ⟶ (27) ⟶ (28) ⟶ (30) ⟶ (32) ⟶ (12) with a high-yielding oxidative phenolic coupling as the key step. The intermediate (27) was also converted *via* a reductive fragmentation into the dibenzazecine (9), oxidation of which gave a dienone different from (12), clearly having the 5;7-fused structure (10). A report of the synthesis of (10) by a different route is thus confirmed, and efficient routes are available to the phenols (9) and (10), likely biosynthetic precursors of the *Schelhammera* alkaloids.

An alternative cycloaddition approach to the dienone (12) was abandoned when (19) and (25) failed to give Diels–Alder adducts with the oxygenated dienones (20) and (21).

THE biosynthesis of the *Erythrina* alkaloids has been investigated in detail. Barton and Widdowson have shown that they are built up [1] from 2 molecules of tyrosine (1) *via* the 1-benzylisoquinoline norprotosinomenine (2) as outlined in the Scheme. The key precursor erysodienone (5) is later modified in a variety of ways to generate the wide range of *Erythrina* alkaloids, *e.g.* erythraline (6) and erythroidine (7).

More recently a series of B-homoerythrina alkaloids [*e.g.* schelhammeridine (8)] has been found in *Schelhammera* and *Cephalotaxus* plants, and it seems likely that these alkaloids are biosynthesised by an analogous pathway [2] *via* the intermediates (9) and (10). Furthermore the dibenz[*d,f*]azecine (9) might also serve as a precursor of the more unusual *Cephalotaxus* alkaloids [*e.g.* cephalotaxine (11)]. No C-homoerythrina alkaloids have yet been reported, though these might reasonably be expected from the dibenzazecine (9) *via* the 6;6-fused dienone (12).

Kametani found that oxidation of the amine (13) by ferricyanide gave in 4% yield a dienone presumably formed *via* (9). He initially suggested [3] the 6;6-fused structure (12) for this compound but later [4] changed the assignment in favour of the 5;7-fused structure (10) because oxidation of the amine (14) under similar conditions gave (15) (0.7%) rather than (16). In the latter case the distinction could be made readily from the ^{1}H n.m.r. spectrum of the product. Accordingly we chose the missing 6;6-fused dienone (12) as our initial target for unambiguous total synthesis. We reasoned that, by analogy with earlier work [5] in the *Erythrina* series, reductive cleavage of (12) should afford (9), and if Kametani's conclusions were correct, oxidation of (9) should give the isomeric 5;7-fused dienone (10).

The Diels–Alder Approach to the 6;6-*Fused Dienone* (12).—Although many dienone alkaloids have been prepared *in vitro via* oxidative phenolic coupling,[6] the coupling reaction itself often proceeds in poor yield. We decided to investigate an entirely new approach to naturally occurring dienones *via* a Diels–Alder reaction. The saturated ketone (18) was prepared in 89% yield by heating the hydrochloride of the dihydroisoquinoline [7] (17) in neat methyl vinyl ketone; [8] and oxidation by

[1] D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1213; see also D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *J.C.S. Perkin I*, 1974, 2278, and references cited therein.

[2] See A. R. Battersby, E. McDonald, J. A. Milner, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Tetrahedron Letters*, 1975, 3419, and references cited therein.

[3] T. Kametani and K. Fukumoto, *Chem. Comm.*, 1968, 26.

[4] T. Kametani and K. Fukumoto, *J. Chem. Soc.* (*C*), 1968, 2156.

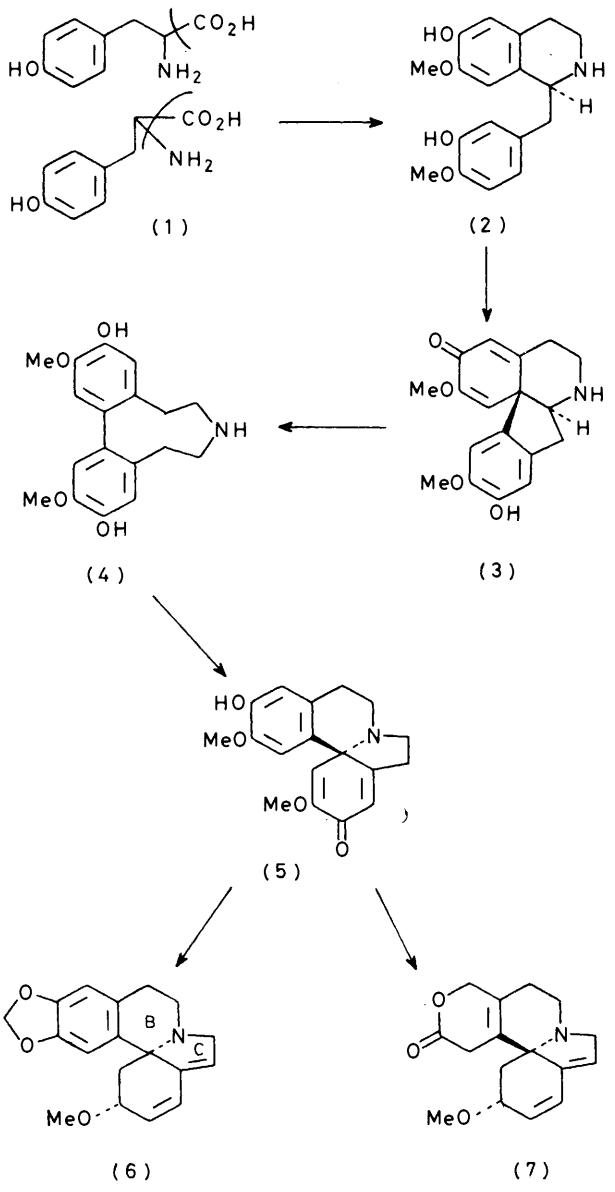
[5] D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1968, 1529.

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

[7] A. R. Battersby, D. J. Le Count, S. Garatt, and R. I. Thrift, *Tetrahedron*, 1961, **14**, 46; an improved preparation of this dihydroisoquinoline is given in the Experimental section.

[8] *Cf.* D. Beke and Ds. Szantay, *Chem. Ber.*, 1962, **95**, 2132.

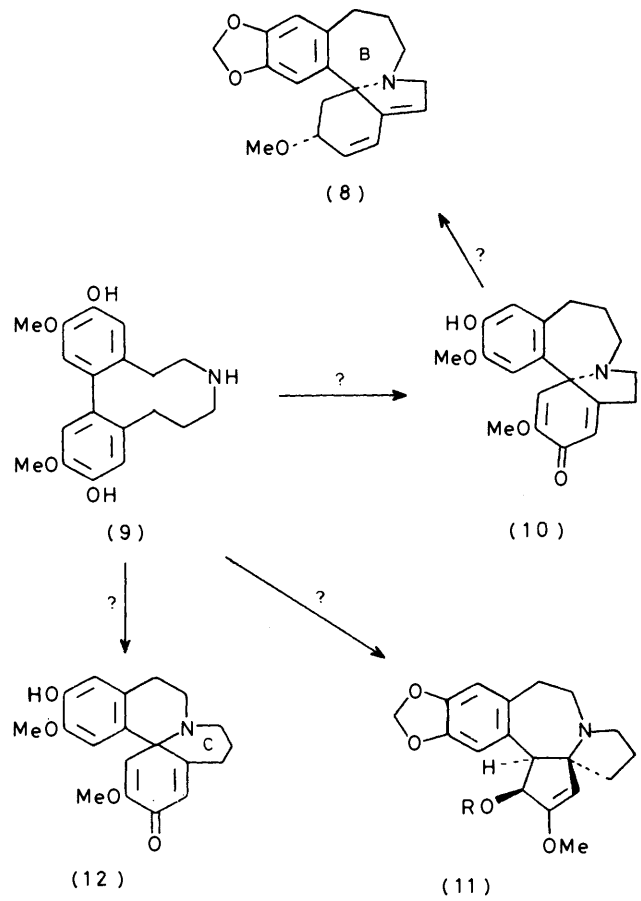
mercury(II) acetate then served to introduce the 1,11b double bond affording (19) in 81% yield. The Diels–Alder adducts (22) from 3,4-dimethoxybuta-1,3-diene [9] (20) or 3,4-dimethoxyfuran [10] (21) and the potential dienophile (19) have appropriate substitution patterns for further elaboration to the dienone (12), but neither adduct was



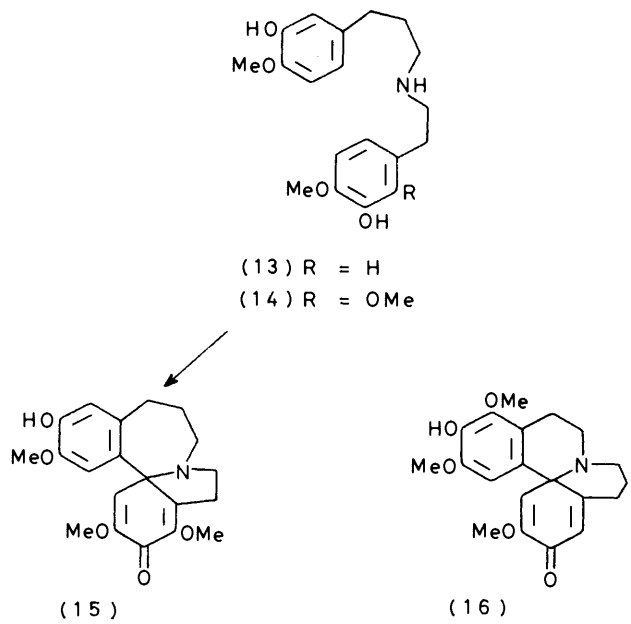
SCHEME

obtained despite many attempts using a wide variety of reaction conditions.

An alternative dienophile (25) was prepared from the amide (23) as outlined in Scheme 2, but once again no adduct was obtained with either of the dienes (20) and (21). In related research [11] we have subsequently



found that the dienes (20) and (21), although apparently electron-rich, are insufficiently reactive to form adducts with most substituted styrenes.

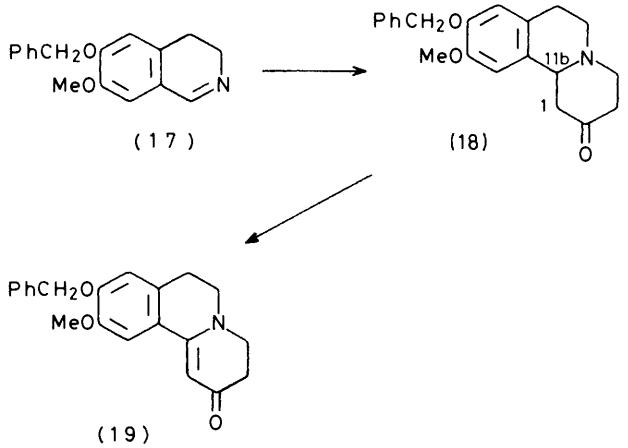


[9] J. R. Johnson, W. H. Jobling, and G. W. Bodamer, *J. Amer. Chem. Soc.*, 1941, **63**, 131; we will describe an improved preparation of this diene in a later paper.[11]

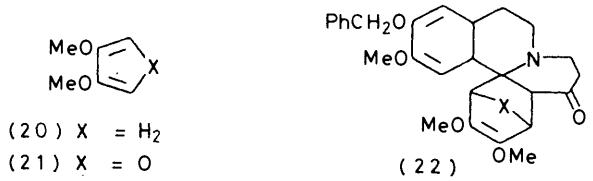
[10] W. M. Hoehn, *Iowa State College J. Sci.*, 1936, **11**, 66, (*Chem. Abs.*, 1937, **31**, 1800).

[11] E. McDonald, A. Suksamrarn, and R. D. Wylie, in preparation.

Synthesis of the Dienone (12) via *Oxidative Phenolic Coupling*.—Since the dienone (12) could not be prepared

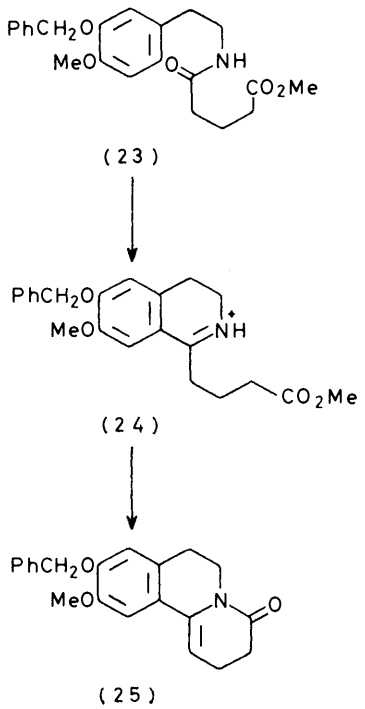


(17) (18) (19)



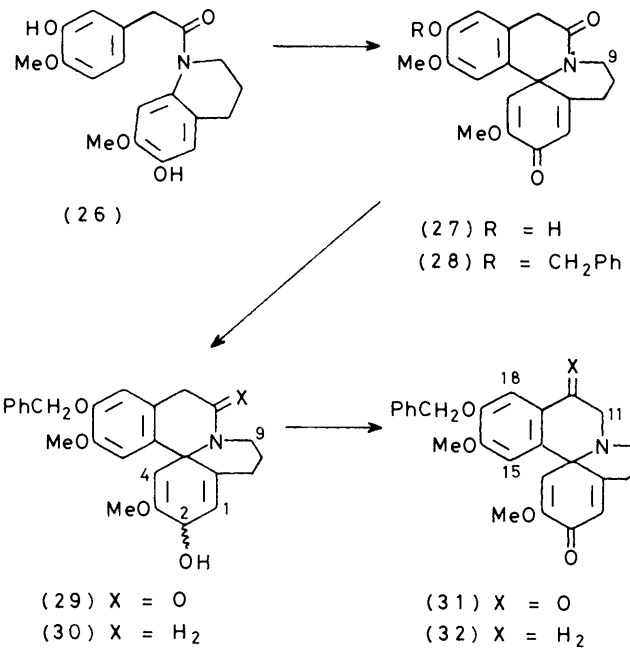
(20) X = H_2
(21) X = O (22)

via the Diels–Alder reaction, the oxidative phenolic coupling approach was carefully reassessed, and in



(23) (24) (25)

consequence the lactam dienone (27) was prepared [12] in excellent yield by oxidation of the *N*-acyltetrahydroquinoline (26) with ferricyanide (see the following paper [12]). Reduction of the lactam carbonyl group of (26) would be expected to afford the required c-homoerythrina dienone (12), but this could not be achieved directly in the presence of interfering functional groups. Consequently the lactam (27) was protected by benzylation, and reduction of the product (28) with borohydride gave a mixture of epimeric lactam dienols (29) in 70% overall yield. Further reduction of (29) with $LiAlH_4$ afforded the corresponding free bases * (30) and several reagents were tried in the search for a suitable oxidant for the preparation of (12). Short treatment of



(26) (27) R = H (28) R = CH_2Ph

(29) X = O (31) X = O
(30) X = H_2 (32) X = H_2

the dienol mixture (30) with CrO_3–pyridine in dichloromethane at 0—5 °C gave the unexpected oxo-dienone (31) in 46% yield. The gross structure assigned to this diketone was fully supported by all the spectral and analytical data, and the location of the carbonyl group was revealed by the ^1H n.m.r. spectrum, with a low-field singlet at δ 7.6 (H-18) and an AB quartet at δ 3.44 and 4.40 (*J* 19 Hz) for the protons at C-11. This benzylic oxidation product (31) was also formed in oxidations with CrO_3–3,5-dimethylpyrazole [13] and with MnO_2, and attempts to avoid its formation by using milder conditions and short reaction times were unsuccessful. Eventually the required dienone (32) was prepared (in 11% yield) by careful Jones oxidation (0—5 °C; 45 s) of the dienol mixture (30), along with the oxo-dienone (31). Hydrogenolysis was clearly unsuitable for removal of the protecting benzyl group of (31) and so solvolysis in neat CF_3CO_2H [14] was attempted. Trial experiments on

* The epimeric mixture of free bases (30) could also be prepared in a single step by reduction ($LiAlH_4$) of the dienone lactam (28), but the yield was better in the two-step procedure.

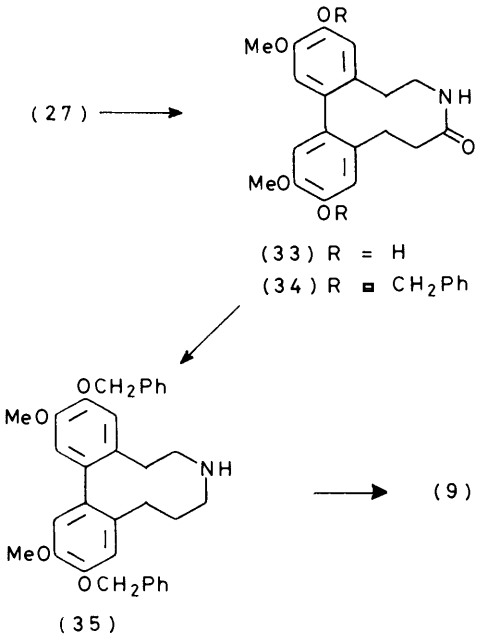
[12] E. McDonald and A. Suksamrarn, following paper; preliminary communications, E. McDonald and A. Suksamrarn, *Tetrahedron Letters*, 1975, 4421, 4425.

[13] E. J. Corey and G. W. J. Fleet, *Tetrahedron Letters*, 1973, 4499.

[14] *Cf.* J. P. Marsh, jun. and L. Goodman, *J. Org. Chem.*, 1965, **30**, 2491.

the lactam dienone (28) showed that the phenolic dienone (27) was formed very slowly under these conditions, but the reaction was faster in the presence of water. Accordingly (32) was treated with wet CF_3CO_2H (25 °C; 48 h) and was cleanly converted into the required phenolic 6;6-fused dienone (12) in virtually quantitative yield.

Conversion of 6;6-*Fused Dienone Lactam* (27) *into the* 5;7-*Fused Dienone* (10) via *the Dibenzazecine* (9).—Reductive cleavage of the dienone lactam (27) with $CrCl_2$–Me_2CO–aq. HCl gave the fragmentation product (33) in 87% yield. (For a similar reductive fragmentation in the *Erythrina* series see ref. 5). Protection of (33) by benzylation gave the lactam (34), which was reduced to the corresponding amine (35) by $LiAlH_4$.



Deprotection of (35) by hydrogenolysis then afforded the diphenolic dibenz[*d*,*f*]azecine (9), a likely biosynthetic precursor of the *Schelhammera* alkaloids [50% overall yield from (33)]. Oxidation of the diphenol (9) by $K_3Fe(CN)_6$ in the two-phase system $CHCl_3$–aq. 5% $NaHCO_3$ gave in 61% yield a dienone whose spectral properties and m.p. agree with those quoted for the dienone prepared [3,4] by Kametani (see introductory paragraphs). This compound was clearly different from the 6;6-fused dienone (12) (m.p., t.l.c., n.m.r.) which was prepared by an unambiguous route, and it must therefore have the 7;5-fused structure (10). Kametani's revised assignment [4] is thus confirmed.

Although a trace of a second product was noticed during oxidation of the diphenol (9), insufficient was available for further characterisation. The oxidative cyclisation to (10) therefore appears to be efficient and highly regiospecific, affording a practical synthetic entry to alkaloids of the *Schelhammera* type.

Shortly after the appearance of our preliminary communication [12] Marino and Samanen reported [15] the synthesis of the dibenzazecine (9) by a different approach; they obtained a 3 : 1 mixture of (10) and (12) (total yield 60%) from oxidation of (9) by $Fe(CN)_6^{3-}$ in CH_2Cl_2–aq. $NaHCO_3$.

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were determined for solutions in $CHCl_3$ (Perkin-Elmer 257), u.v. spectra for solutions in MeOH (Unicam SP 800), and n.m.r. spectra for solutions in $CDCl_3$ (Varian HA 100).

6-*Benzyloxy*-7-*methoxy*-3,4-*dihydroisoquinoline* (17).—To a solution of *N*-(3-benzyloxy-4-methoxyphenethyl)formamide [7] (20 g) in acetonitrile (300 ml) was added $POCl_3$ (22 ml), and the mixture was kept at room temperature for 3 h. The solvent was evaporated off, the residue redissolved in benzene (150 ml), and the benzene solution shaken with four portions of N-hydrochloric acid (2 × 100 and 2 × 150 ml). The combined aqueous layer was washed with benzene (100 ml) before basification with saturated aqueous sodium carbonate and extraction with three portions of chloroform. The chloroform layer was washed with water, dried, and evaporated to give the dihydroisoquinoline (15.2 g, 80%), m.p. 102—103° (from sublimation) (lit.,[7] 105°); $\nu_{max.}$ 1 630 cm^{-1}; $\lambda_{max.}$ 232, 279, and 311 nm; $\lambda_{max.}$ (H^+) 248, 310, and 363 nm; δ 2.60 (2 H, m, $ArCH_2$), 3.80 (2 H, m, $NH{\cdot}CH_2$), 3.86 (3 H, s, CH_3O), 5.16 (2 H, s, $PhCH_2O$), 6.70 and 6.82 (each 1 H, s, ArH), and 7.40 (6 H, m, ArH and olefinic); *m/e* 267 (M^+), 176, and 91 (base peak).

The *hydrochloride salt* softened at 183—184°, and melted at 193—194°; $\lambda_{max.}$ 248, 310, and 363 nm (Found: C, 66.35; H, 5.95; Cl, 11.0; N, 4.5. $C_{17}H_{18}ClNO_2H_2O$ requires C, 66.25; H, 6.0; Cl, 11.5; N, 4.55%).

Note. This procedure in MeCN is a distinct improvement on the literature method [7] which employs toluene as solvent.

9-*Benzyloxy*-10-*methoxy*-1,3,4,6,7,11b-*hexahydrobenzo*[a]-*quinolizin*-2-*one* (18).—A mixture of 6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline hydrochloride (4.53 g) and an excess of methyl vinyl ketone (20 ml) was heated under nitrogen at reflux temperature for 5 h. The solid (which began to appear after 2 h) was collected by filtration and washed with ether to give the product as the hydrochloride salt (4.20 g). The combined filtrate was concentrated; more methyl vinyl ketone (5 ml) was added and the mixture heated under reflux for 3 h to obtain more product (0.50 g; total 4.70 g, 89%). The free base was obtained by basifying the hydrochloride with aqueous sodium carbonate and extracting into chloroform. The chloroform layer was washed with water, dried, and evaporated. The residue was redissolved in methanol and ether was slowly added until the solution became cloudy. The mixture was then warmed to give a clear solution and set aside to give *crystals*, m.p. 124° (from methanol) (Found: C, 74.75; H, 6.95; N, 3.95. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.8; N, 4.25%); *methiodide*, m.p. 180—181° (from methanol); $\nu_{max.}$ 1 710 cm^{-1}; $\lambda_{max.}$ 233 and 285 nm; δ 2.33—3.75 (11 H, m, aliphatic), 3.81 (3 H, s, CH_3O), 5.10 (2 H, s, $PhCH_2O$), 6.57 and 6.64 (each 1 H, s, ArH), and 7.15—7.50 (5 H, m, Ph), *m/e* (337 (M^+), 246, 188, and 91 (base peak); *m** 179.57 (338 ⟶ 246) and 143.67 (246 ⟶ 188).

[15] J. P. Marino and J. H. Samanen, *J. Org. Chem.*, 1976, **41**, 179.

The reaction of the free base and methyl vinyl ketone was slower and less clean, and gave a lower yield (60—65%).

9-Benzyloxy-10-methoxy-3,4,6,7-tetrahydrobenzo[a]quinolizin-2-one (19).—The hexahydrobenzo[*a*]quinolizinone (18) (167.5 mg, 0.5 mmol) was dissolved in glacial acetic acid (1.5 ml) and an excess of aqueous mercury(II) acetate (1.593 g or 10 × 0.5 mmol in 5.5 ml) added. The mixture was heated, with stirring, at 78—80 °C for 2 h, then filtered and the residue washed with aqueous *ca.* 30% acetic acid. The combined filtrate was saturated with hydrogen sulphide and filtered; the residual sulphide was washed thoroughly with aqueous acetic acid and the combined filtrate re-saturated with hydrogen sulphide. The filtered solution was carefully basified with aqueous 5% sodium hydroxide or saturated sodium carbonate. The product was extracted into chloroform; the chloroform layer was washed with water, dried, and evaporated to give the *tetrahydrobenzo[a]quinolizinone* (135 mg, 81%), m.p. 123—124° (from methanol) (Found: C, 75.15; H, 6.3; N, 4.15. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.25; N, 4.2%); $\nu_{max.}$ 1 613 cm^{-1}; $\lambda_{max.}$ 240, 286, and 363 nm; $\lambda_{max.}$ (H^+) 253 and 344 nm; δ 2.45—3.03 (4 H, m, aliphatic), 3.75—3.85 (4 H, m, aliphatic), 3.87 (3 H, s, CH_3O), 5.18 (2 H, s, PhCH_2O), 5.68 (1 H, s, olefinic), 6.69 (1 H, s, ArH), 7.19 (1 H, s, ArH), and 7.27—7.51 (5 H, m, Ph); *m/e* 335 (M^+), 244, and 91 (base peak); *m** 177.7 (335 ⟶ 244).

Methyl N-(3-Benzyloxy-4-methoxyphenethyl)glutaramate (23).—A mixture of 3-benzyloxy-4-methoxyphenethylamine (447 mg) and glutaric anhydride (228 mg, 2 mmol) in chloroform was heated under reflux for 1 h. The solution was evaporated, the residue redissolved in ethyl acetate, and benzene (*ca.* 1 : 1 ratio) added. After being kept in a refrigerator, the product (556 mg, 88%), m.p. 128—129° (from ethanol–ethyl acetate), crystallised; $\nu_{max.}$ (Nujol) 3 300—2 500 and 1 700—1 650 cm^{-1}; $\lambda_{max.}$ 213 and 279 nm; δ(C_5D_5N) 2.10—3.30 (10 H, m, aliphatic), 3.72 (3 H, s, CH_3O), 5.12 (2 H, s, PhCH_2O), 6.88 (2 H, *ca.* s, ArH), and 7.05—7.35 (6 H, m, ArH and Ph).

The foregoing acid (550 mg), absolute methanol (3 ml), and concentrated sulphuric acid (4 drops) were heated under reflux for 1 h. The excess of methanol was evaporated off and the residue redissolved in chloroform; the solution was washed with aqueous sodium carbonate and water, dried, and evaporated to give the *product* (545 mg, 96%), m.p. 83—84° (from benzene–ether) (Found: C, 68.45; H, 6.9; N, 3.6. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.05; N, 3.65%); $\nu_{max.}$ 3 420, 1 720, and 1 662 cm^{-1}; $\lambda_{max.}$ 230 and 279 nm; δ 1.75 (8 H, m, aliphatic), 3.40 (2 H, m, NCH_2), 3.63 (3 H, s, CH_3CO_2), 3.83 (3 H, s, CH_3O), 5.10 (2 H, s, PhCH_2O), 5.47br (1 H, m, NH), 6.65—6.90 (3 H, m, ArH), and 7.35 (5 H, m, Ph); *m/e* 385 (M^+), 354, 240, and 91 (base peak); *m** 149.61 (385 ⟶ 240).

Methyl 6-Benzyloxy-7-methoxy-3,4-dihydroisoquinoline-1-butyrate (24).—A solution of the amide ester (23) (135 mg) in dry benzene (2 ml) was treated with phosphoryl chloride–benzene [1 ml; prepared from $POCl_3$ (1 ml) diluted with dry benzene to 20 ml] and the mixture heated under reflux for 45 min. The solvent was evaporated off and the residue redissolved in dichloromethane. The solution was vigorously shaken with aqueous 20% sodium carbonate, washed with three portions of water, dried, and partially evaporated, and the concentrate was dried by blowing the warm solution with nitrogen to give the pure *product* (113 mg, 88%), m.p. 91—93° (from sublimation); $\nu_{max.}$ 1 725 and 1 625 cm^{-1}; $\lambda_{max.}$ 229, 272, and 309 nm; $\lambda_{max.}$ (H^+) 245, 306, and 356 nm; δ 2.02 (2 H, m, CH_2), 2.34—2.80 (8 H, m, aliphatic), 3.55 (partially superimposed with CH_3CO_2, 2 H, NCH_2), 3.62 (3 H, s, CH_3CO_2), 3.88 (3 H, s, CH_3O), 5.13 (2 H, s, PhCH_2O), 6.17 (1 H, s, ArH), 7.09 (1 H, s, ArH), and 7.32 (5 H, m, Ph); *m/e* 367(M^+) 336, 281, and 91 (base peak); *hydrochloride*, m.p. 126—128° (from methanol–ether) (Found: C, 64.65; H, 6.7; N, 3.65. $C_{22}H_{26}NO_4Cl,\frac{1}{2}H_2O$ requires C, 64.0; H, 6.6; N, 3.4%).

9-Benzyloxy-10-methoxy-2,3,6,7-tetrahydrobenzo[a]quinolizin-4-one (25).—The dihydroisoquinoline (24) (251.5 mg) in pyridine (30 ml) was heated under nitrogen at reflux temperature for 26—27 h. The solvent was evaporated off, aqueous 5% hydrochloric acid (10 ml) was added, and the residual oil was stirred vigorously to make a thorough contact with the aqueous acid. The pale yellow solid was collected by filtration, washed again with dilute aqueous acid and water, and dried in a desiccator to give the product (170 mg, 74%), which softened at 91—93 °C and melted at 110—113 °C. Recrystallisation from pyridine–water gave very pale greenish-grey crystals, m.p. 123—125° (Found: C, 75.2; H, 6.75; N, 4.2. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.2%); $\nu_{max.}$ 1 655 cm^{-1}; $\lambda_{max.}$ 250, 279, and 310 nm; δ 2.30—3.00 (6 H, m, aliphatic), 3.82 (m, partially superimposed with CH_3O, 2H, CH_2NCO), 3.85 (3 H, s, CH_3O), 5.10 (2 H, s, PhCH_2O), 5.65 (1 H, m, olefinic), 6.62 (1 H, s, ArH), 7.03 (1 H, s, ArH), and 7.35 (5 H, m, Ph); *m/e* 335(M^+), 244, 216, and 91 (base peak); *m** 191.21 (244 ⟶ 216) and 177.72 (335 ⟶ 244).

The mother liquor was chromatographed on alumina (grade III; ether–CH_2Cl_2, CH_2Cl_2, then Me_2CO) and *6-benzyloxy-7-methoxyisoquinolin-1(2H)-one* was obtained (17—18 mg) as plates, m.p. 182—183° (from acetone) (Found: C, 71.7; H, 6.15; N, 5.05. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.95%); $\nu_{max.}$ 3 420 and 1 660 cm^{-1}; $\lambda_{max.}$ 260 and 299 nm; δ 2.86 (1 H, t, *J* 6.5 Hz, H-4), 3.52 (1 H, dt, *J* 6.5 and 2.5 Hz, H-3), 3.94 (3 H, s, CH_3O), 5.18 (2 H, s, PhCH_2O), 6.50 (1 H, m, exchanged with D_2O, NH), 6.70 (1 H, s, H-5), 7.40 (5 H, m, Ph), and 7.60 (1 H, s, H-8) [on irradiation at δ 2.86 the dt at 3.52 changed to a (complex) d; on irradiation at 3.52, the t at 2.86 collapsed to s; on irradiation at 6.50, the dt at 3.52 collapsed to t]; *m/e* 283(M^+), 192, 163, 125, and 91 (base peak).

Diels–Alder reactions of (19) and (25) with 2,3-dimethoxybuta-1,3-diene [9] (20) and 3,4-dimethoxyfuran [10] (21) were attempted in *p*-xylene solution (*a*) under reflux, 24 h, (*b*) at 165 °C (sealed tube), 19 h, (*c*) under reflux with $AlCl_3$, 13 h. A similar set of experiments was carried out in the absence of solvent. The reactions were followed by t.l.c. and u.v. but only decomposition and polymerisation of the diene was observed. No encouraging result was obtained using NaOMe–MeOH or $KOBu^t$–Bu^tOH, conditions designed to trap any adduct which might be formed transiently in a reversible cycloaddition.

Benzylation of the Dienone (27).—The dienone [12] (27) (200 mg) was dissolved in dry methanol (10 ml), and anhydrous potassium carbonate (400 mg) and benzyl chloride (redistilled 400 mg) were added. The mixture was heated under reflux for 5½ h and the solvent was evaporated off. The residue was redissolved in chloroform, washed with aqueous potassium carbonate and water, and dried. The solvent and excess of benzyl chloride were evaporated off (rotary evaporator; oil pump) and the crude product was recrystallised from dichloromethane–ether–pentane to give the *O-benzyl-C-homo-oxoerysodienone* (28) as needles (221 mg, 87.4%), m.p. 198—199° (Found: C, 72.1; H, 6.0; N,

3.35. $C_{26}H_{25}NO_5$ requires C, 72.35; H, 5.85; N, 3.25); $\nu_{max.}$ 3 400br,w, 1 677, 1 642, and 1 620 cm^{-1}; $\lambda_{max.}$ 240 (19 046) and 282 (4 094) nm; δ 1.8—2.7 (5 H, m, $[CH_2]_2CH_\alpha N$), 3.56 (3 H, s, CH_3O), 3.74 (2 H, only d seen, $ArCH_2CO$), 3.72 (3 H, s, CH_3O), 4.61 (1 H, ddd, *J* 13, 6, and 1 Hz, H-9β), 5.10 (2 H, s, $PhCH_2O$), 5.70 6.46, 6.49, and 6.68 (4 × 1 H, each s, 2 × dienone H and 2 × ArH), and 7.36 (5 H, m, Ph); *m/e* 431 (M^+), 340, 312, and 91 (base peak).

Reduction of the Dienone (28) *with Sodium Borohydride*.—The dienone (28) (200 mg) was dissolved in warm methanol (15 ml) and the solution allowed to cool to room temperature. Sodium borohydride (excess; 400 mg) was added in portions to the stirred solution while the reaction temperature was kept lower than 25 °C. The mixture was stirred at room temperature for 1½ h, and the methanol was evaporated off. Chipped ice and cold water were added; the white solid which precipitated was collected, washed with cold water, and dried in a drying pistol to give a mixture (162 mg, 80.6%) of the epimeric two O-*benzyl*-c-*homo-oxoerysodienols* (29), m.p. 185—189° (Found: C, 70.95; H, 6.25; N, 3.1. $C_{26}H_{27}NO_5,\frac{1}{2}H_2O$ requires C, 70.57; H, 6.4; N, 3.15%); $\nu_{max.}$ (Nujol) 3 350 and 1 627 cm^{-1}; $\lambda_{max.}$ 239 and 285 nm; δ(CD_3OD) major isomer: 1.8—3.1 (5 H, m, $[CH_2]_2CH_\alpha N$), 3.63 (5 H, superimposed, $ArCH_2CO$ and CH_3O), 3.74 (3 H, s, CH_3O), 4.40 (1 H, dd, *J* 13 and 5 Hz, H-9β), 4.60 (1 H, d, *J* 5 Hz, H-1), 6.58 and 6.86 (2 × 1 H, each s, 2 × ArH), and 7.38 (5 H, m, Ph); minor isomer: 1.8—3.1 (m, 5 H, $[CH_2]_2CH_\alpha N$), 3.63 (5 H, superimposed, $ArCH_2CO$ and CH_3O), 3.78 (3 H, s, CH_3O), 4.40 (1 H, dd, *J* 13 and 6 Hz, H-9β), 4.60 (1 H, d, *J* 5 Hz, H-2), 5.00 (1 H, s, H-4), 5.08 (2 H, s, $PhCH_2O$), 6.07 (1 H, d, *J* 5 Hz, H-1), 6.82 and 7.05 (2 × 1 H, each s, 2 × ArH), and 7.38 (5 H, m, Ph); *m/e* 433(M^+), 416, 402, 342, and 91 (base peak).

Reduction of the Epimeric Dienols (29).—To a suspension of lithium aluminium hydride (800 mg) in dry tetrahydrofuran (35 ml) were added dropwise the epimeric dienols (29) (125 mg) in dry tetrahydrofuran (15 ml) during 15 min. The mixture was stirred at room temperature for 40 min. and heated at 70—80 °C for 3½ h. The excess of hydride was destroyed by adding ethyl acetate and the mixture filtered. The residue was washed thoroughly with methanol and chloroform. The combined filtrates were evaporated and the residue redissolved in chloroform; the solution was washed with water, dried over anhydrous potassium carbonate–sodium sulphate, and evaporated to leave the crude epimeric *O*-benzyl-c-homoerysodienols (30) (86 mg). The alcohols were used directly for oxidation reaction.

Oxidation of the Epimeric Dienols (30).—(a) *With chromium trioxide–pyridine complex*. To the crude dienols (30) (86 mg) in dry dichloromethane (1.5 ml) cooled in an ice-bath, was added cold chromium trioxide–pyridine complex (60 mg CrO_3 and 96 mg pyridine) in dry dichloromethane (3 ml), and the mixture was stirred at 0—5 °C for 20 min. Water and aqueous sodium hydrogen carbonate were added and the mixture was quickly extracted with chloroform; the extract was washed with water and dried. Evaporation gave the crude oxo-dienone (31) (72 mg), which was purified by preparative t.l.c. (silica; 4% methanol–chloroform) to give the *oxo-dienone* (31) (41 mg, 46.3%), m.p. 196—198° (Found: C, 70.3; H, 5.75; N, 3.0. $C_{26}H_{25}O_5,\frac{1}{2}H_2O$ requires C, 70.9; H, 5.95; N, 3.2%); $\nu_{max.}$ 1 677, 1 650, 1 620, and 1 592 cm^{-1}; $\lambda_{max.}$ 242 (35 811), 282 (10 830), and 317 (8 173) nm; δ 1.6—3.1 (6 H, m, CH_2), 3.44 (1 H, d, *J* 19 Hz, one of H-11), 3.60 (3 H, s, CH_3O), 3.80 (3 H, s, CH_3O), 4.40 (1 H, d, *J* 19 Hz, another H-11), 5.14 (2 H, s, $PhCH_2O$), 6.17, 6.28, and 6.46 (3 × 1 H, each s, 2 × dienone H and H-15), 7.36 (5 H, m, Ph), and 7.62 (1 H, s, H-18); *m/e* 431(M^+), 400, 340, and 91.

(b) *With chromium trioxide–aqueous sulphuric acid* (*Jones reagent*). The crude dienol mixture (30) (40 mg) dissolved in redistilled acetone (2 ml) was cooled in an ice-bath and 3 drops of cold Jones reagent (from 1 g CrO_3 in 7 ml water and 0.9 ml reagent grade conc. H_2SO_4) were added. The solution was stirred for 45 s, and cold ammonium hydroxide (*ca.* 15%; 20 drops) was then added, followed by chloroform and water. The organic layer was separated, washed with aqueous sodium hydrogen carbonate, water, and saturated brine, and dried. Evaporation, followed by preparative t.l.c. of the residue (thin silica t.l.c. plate; 5% methanol–chloroform) afforded O-*benzyl*-c-*homoerysodienone* (32) (45 mg, 11.3%) (Found: M^+, 417.190 5. $C_{26}H_{27}NO_4$ requires *M*, 417.194 0); $\nu_{max.}$ 1 675, 1 645, and 1 620 cm^{-1}; $\lambda_{max.}$ 238 and 283 nm; δ 1.60—3.60 (10 H, m, aliphatic H), 3.61 (3 H, s, CH_3O), 3.71 (3 H, s, CH_3O), 5.11 (2 H, s, $PhCH_2O$), 6.15, 6.28, 6.37, and 6.66 (4 × 1 H, each s, 2 × dienone H and 2 × ArH), and 7.38 (5 H, m, Ph); *m/e* 417 (M^+), 386, 326, 298, and 91. The oxo-dienone (31) (*ca.* 3 mg) was also isolated from the t.l.c. plate.

c-*Homoerysodienone* (12).—The benzyloxydienone (32) (3 mg) was dissolved in trifluoroacetic acid (1 ml) and water (0.3 ml) was added. The solution was stirred at room temperature for 48 h, and the CF_3CO_2H was then removed (rotovap). The product was extracted into chloroform, and the extract was washed with aq. $NaHCO_3$, then water. The extract was evaporated to dryness and the residue dried *in vacuo* to give the phenolic *dienone* (12) (*ca.* 2.4 mg, essentially quantitative), homogeneous by t.l.c. (silica; 9 : 1 $CHCl_3$–MeOH) (Found M^+, 327.146 6. $C_{19}H_{21}NO_4$ requires *M*, 327.147 0); $\nu_{max.}$ 3 530, 1 672, 1 643, and 1 617 cm^{-1}; $\lambda_{max.}$ 239 and 284 nm; *m/e* 327(M^+) 296 and 284, δ 3.61 and 3.72 (each 3 H, s, 2 × OMe), 6.16, 6.22, 6.36, and 6.68 (each 1 H, s, 2 ArH, 2 olefinic H) (aliphatic proton signals appear as complex multiplets spread over the range *ca.* 1.8—3.8). The hydrochloride of (12) showed δ 3.70 and 3.79 (each 3 H, s, 2 × OMe), and 5.89, 6.27, 6.60, and 6.83.

3,12-*Dihydroxy*-2,13-*dimethoxy*-6,7,9,10-*tetrahydrodibenz*-[d,f]*azecin*-8(5H)-*one* (33).—Chromium dichloride (6.0 g) was dissolved in aq. 3% hydrochloric acid (60 ml) and the residue was filtered off under nitrogen. The solution was placed in a three-neck flask (250 ml) equipped with stirrer, nitrogen inlet, and serum cap. A solution of the dienone (27) (455 mg) in acetone (30 ml) was injected through the serum cap and the mixture was stirred at room temperature for 2 h. The white solid which separated was collected and washed with cold water. The product was dissolved in hot methanol; the solution was warmed with a small portion of charcoal, filtered, and evaporated to give the pure *dibenzazecinone* (33) (408 mg, 89.2%), m.p. 244—245.5° (from methanol or by sublimation) (Found: C, 64.2; H, 6.0; N, 4.3. $C_{19}H_{21}NO_5,\frac{1}{2}H_2O$ requires C, 64.75; H, 6.3; N, 3.95%); $\nu_{max.}$ (Nujol) 3 470, 3 300, 1 637, and 1 600 cm^{-1}; $\lambda_{max.}$ 227 and 285 nm; δ[$(CD_3)_2SO$] 1.6—3.1br (8 H, m, aliphatic H), 3.74 and 3.76 (2 × 3 H, each s, 2 × CH_3O), 6.51, 6.56, 6.74, and 7.28 (4 × 1 H, each s, ArH and Ar'H), 7.10 (1 H, m, exchanged with D_2O, NH), and 8.93br (2 H, s, exchanged with D_2O, OH); *m/e* 343 (M^+, base peak), 326, and 171.5 (M^{2+}).

3,12-*Dibenzyloxy*-2,13-*dimethoxy*-6,7,9,10-*tetrahydro*-*dibenz*[d,f]*azecin*-8(5H)-*one* (34).—To a solution of the

dibenzazecinone (33) (103 mg) in hot dry methanol (30 ml) were added anhydrous potassium carbonate (1 g) and benzyl chloride (1 g), and the mixture was heated under reflux for 9 h. It was then filtered; the residue was washed with hot methanol and the combined filtrates were evaporated. The residue was redissolved in chloroform and the solution washed with water and dried. The solvent and excess of benzyl chloride were removed *in vacuo*. The crude product was recrystallised from dichloromethane–ether–pentane to give crystals of the *dibenzyloxydibenzacinone lactam* (34) (135 mg, 86.0%), m.p. 176.5—177.5° (Found: C, 75.45; H, 6.3; N, 2.45. $C_{33}H_{33}NO_5$ requires C, 75.7; H, 6.35; N, 2.7%); $\nu_{max.}$ 3 400, 1 650, and 1 605 cm^{-1}; $\lambda_{max.}$ 236 (28 392) and 284 nm (26 566); δ 1.70 (2 H, m, CH_2), 2.40 (2 H, m, Ar'CH_2CH_2), 3.02 (2 H, m, CH_2N), 3.40 (2 H, d, or ABq, *J* 15 Hz, $ArCH_2CO$), 3.81 (3 H, s, CH_3O), 3.85 (3 H, s, CH_3O), 5.20 (2 × 2 H, s, 2 × PhCH_2O), 5.69 (1 H, m, exchanged with D_2O, NH), 6.58, 6.67, 6.76, and 7.57 (4 × 1 H, each s, ArH and Ar'H), and 7.40 (2 × 5 H, m, 2 × Ph); *m/e* 523 (M^+) 432.

3,12-*Dibenzyloxy*-2,13-*dimethoxy*-5,6,7,8,9,10-*hexahydrodibenz*[d,f]*azecine* (35).—To a suspension of lithium aluminium hydride (200 mg) in dry tetrahydrofuran (4 ml) was added dropwise a solution of the dibenzyloxydibenzazecinone (34) (95 mg) in dry tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 3 h, then at 40—50 °C for 1 h. The excess of hydride was destroyed by careful addition of saturated aqueous Rochelle salt; the mixture was filtered and the residue washed thoroughly with hot chloroform. The combined filtrates were evaporated and the residue was redissolved in chloroform; the solution was washed with water and saturated brine, dried, and evaporated to give the *dibenzyloxydibenzazecine* (35) (69 mg, 74.7%), m.p. 229—231° (from dichloromethane–hexane) (Found: M^+, 509.258 2. $C_{33}H_{35}NO_4$ requires *M*, 509.256 4); $\nu_{max.}$ 3 350br,w, and 1 601 cm^{-1}; $\lambda_{max.}$ 223 and 288 nm; δ 1.56 (2 H, m, CH_2), 2.20—2.80 (8 H, m, CH_2), 3.81 (2 × 3 H, s, 2 × CH_3O), 5.16 (2 × 2 H, s, 2 × PhCH_2O), 6.57, 6.61, 6.75, and 6.79 (ArH and Ar'H), and 7.35 (2 × 5 H, m, 2 × Ph); *m/e* 509 (M^+), 419, 418, 328, and 91 (base peak).

2,13-*Dimethoxy*-5,6,7,8,9,10-*hexahydrodibenz*[d,f]*azecine*-3,12-*diol* (*Homoerybidine*) (9).—The dibenzyloxydibenzazecine (35) (69 mg) was dissolved in dichloromethane (0.5 ml) and transferred to a 10 ml hydrogenation flask. Methanol (3 ml) and hydrogen chloride-saturated methanol (0.2 ml) and 10% palladium–charcoal (30 mg) were added and the mixture was hydrogenated at 1 atm and room temperature for 3 h. The solution was filtered through Celite and evaporated to give as a white solid the *dibenzazecine* (9) *hydrochloride* (37 mg, 83%), m.p. 251—253°.* The hydrochloride was passed down a short alumina column to liberate the *free base*, m.p. (sealed tube) 300—302° (decomp.) (from methanol–chloroform–ether) (Found: M^+, 329.162 9. $C_{19}H_{23}NO_4$ requires *M*, 329.162 7); $\lambda_{max.}$ 288 (shifting to 246 and 302 nm on adding NaOH); δ(CD_3OD) 1.7—3.1 (10 H, m, aliphatic CH_2), 3.78 (6 H, s, 2 × OMe), and 6.56, 6.60, 6.74, and 6.86 (each 1 H, s, 4 × ArH); *m/e* 329 (M^+), 297, and 164.5 (M^{2+}).

Phenolic Oxidation of the Dibenzazecine (9).—A degassed solution of potassium ferricyanide (63 mg) in 5% aqueous sodium hydrogen carbonate (3 ml) was injected through a serum cap into degassed two-phase chloroform–aq. 5% $NaHCO_3$ (10 : 7 ml) containing 24 mg of the hydrochloride of (9). The mixture was shaken under nitrogen for 15 min. The chloroform layer was separated and the aqueous phase extracted repeatedly with more chloroform. The combined extracts were washed with water, dried, and evaporated to give the crude B-homoerysodienone (10) (24 mg). Preparative t.l.c. on silica gave pure dienone (10) (13 mg, 60.7%), m.p. 134—135.5° (lit.,[4] m.p. 135—137° from ether; ref. 15 quotes 166—167° *); $\nu_{max.}$ 3 530, 1 668, 1 655, and 1 619 cm^{-1}; $\lambda_{max.}$ 239 and 282 nm; δ 1.4—3.5 (10 H, m, CH_2), 3.64 and 3.70 (each 3 H, s, 2 × OMe), 6.27 (1 H, t, *J* 1.5 Hz, H-4), and 6.40, 6.58, and 6.70 (each 1 H, s, 2 ArH and 1 olefinic H); *m/e* 327 (M^+), 296 (base peak), and 163.5 (M^{2+}).

N.b. A trace of another product was observed on t.l.c. of the crude product but insufficient was available for characterisation.

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* Professor Marino informs us that the hydrochloride of his sample [15] of (9) has m.p. 251—253°, though he reports m.p. 211—212° for the free base (9). He also finds that the m.p. of the dienone (10) depends on the recrystallisation solvent (personal communication).