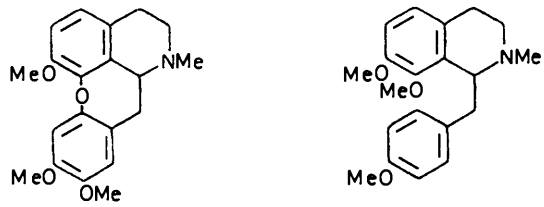
Phenol Oxidation. Part III.[1] Synthesis of the Benzylisoquinoline Alkaloid Cularine

By **Anthony H. Jackson** * and **George W. Stewart**, Department of Chemistry, University College, Cardiff
George A. Charnock and **Joseph A. Martin**, The Robert Robinson Laboratories, The University of Liverpool, Liverpool

(±)-Cularine has been synthesised *via* phenolic coupling of 1,2.3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-7-methoxy-2-methylisoquinolin-8-ol; the latter was prepared by a new variant of the Pomeranz–Fritsch synthesis which leads directly to isoquinolines in good yield, with introduction of the 1-benzyl substituent by the Reissert method. Syntheses of open-chain phenolic bis-(2-phenylethyl)amine derivatives related to cularine are also described; however, none of these could be oxidatively coupled to give cularine derivatives. Other routes to 7,8-dioxygenated isoquinolines were also investigated, but, although moderately successful, additions of 3,4-dialkoxybenzylmagnesium halides to 3,4-dihydroisoquinolines could not be effected owing to formation of dihydrostilbenes from the benzyl halides. The synthesis of a 7,8-dialkoxy-3,4-dihydroquinolone from a bromoindanone is also described.

THE alkaloid cularine (1) is the parent of a small group of benzylisoquinoline alkaloids which are distinguished by the possession of an intramolecular ether linkage between the carbocycle of the isoquinoline nucleus and the 1-benzyl group.[2] The presence of this ether bridge is associated with a relatively unusual 7,8-oxygenation pattern in the isoquinoline system; petaline (2) is another recently discovered simple 1-benzylisoquinoline alkaloid with this oxygenation pattern.[3] Cularine, its *N*-demethyl derivative, and two *O*-demethyl derivatives are found in certain plants of the Dicentra and Corydalis families. The structure of cularine was first elucidated by Manske over twenty years ago.[2]

At the outset of this work two syntheses of cularine had been described, but both involved completion of the nitrogen-containing ring as one of the final stages.[4] In contrast, our interests lay in the possibility of synthesising cularine along 'biogenetic' routes, with the eventual aim of studying the biosynthetic pathway *in vivo* by radiotracer techniques using suitable precursors. In the light of earlier speculations,[5] and related biosynthetic studies of other benzylisoquinoline alkaloids,[6] it seemed likely that cularine might be formed in nature by one of two routes, either by oxidative phenolic coupling of a preformed 1-benzylisoquinoline such as (3a), or by phenolic coupling of a bis-(2-phenylethyl)amine (4a) followed by oxidative closure of the nitrogen-containing ring.[7-9] Variants such as oxidative cyclisation of the isomeric phenolic amines (3b) and (4b) may also be envisaged and these could lead *via* dienone-type intermediates to cularine.[10] The oxidative cyclisation of open-chain intermediates such as (4a) and (4b) also seemed attractive possibilities, as initial formation of the ether bridge would direct the subsequent formation of the nitrogen-containing ring and account for the unusual 7,8-oxygenation pattern of cularine and its congeners.



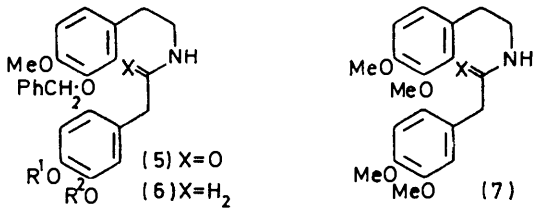
a; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = Me

The corresponding amides (5a) and (5b) were therefore prepared by coupling of the appropriate phenylethylamine and phenylacetyl chlorides. Attempts to reduce these amides with an excess of lithium aluminium hydride in tetrahydrofuran gave complex mixtures, although other workers have reported [11] the reduction of (5a) with a 30-fold excess of reagent by refluxing for 12 days. However, cleavage of the nitrogen–carbon bond is a possible side reaction in the reduction of amides by lithium aluminium hydride.[12] Diborane,[12,13] however,

[1] Part II, A. H. Jackson and J. A. Martin, *J. Chem. Soc.* (*C*), 1966, 2061.
[2] R. H. F. Manske, in 'The Alkaloids,' eds. R. H. F. Manske and H. L. Holmes, vol. IV, Academic Press, New York, 1954, p. 1.
[3] J. McShefferty, P. F. Nelson, J. L. Paterson, J. B. Stenlake, and J. P. Todd, *J. Pharm. Pharmacol.*, 1956, **8**, 1117; N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Letters*, 1964, 3841.
[4] T. Kametani and K. Fukumoto, *J. Chem. Soc.*, 1963, 4289; 1964, 4142.
[5] D. H. R. Barton and T. Cohen, in 'Festschrift A. Stoll,' Birkhauser, Basel, 1957, p. 117.
[6] A. R. Battersby, Tilden Lecture, *Proc. Chem. Soc.*, 1963, 189.
[7] J. A. Martin, Ph.D. Thesis, Liverpool, 1965.
[8] K. W. Bentley, 'The Isoquinoline Alkaloids,' Pergamon, Oxford, 1965, p. 63.
[9] N. S. Bhacca, T. Cymerman-Craig, R. H. F. Manske, S. K. Roy, M. Shamma, and W. A. Slusarchyk, *Tetrahedron*, 1966, **22**, 1467.
[10] R. B. Woodward and T. Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494; R. B. Woodward in 'Perspectives in Organic Chemistry,' ed. A. R. Todd, Academic Press, New York, 1956, p. 178.
[11] J. E. Gervay, F. McCapra, T. Money, G. M. Sharma, and A. I. Scott, *Chem. Comm.*, 1966, 142. Tertiary amides are, however, readily reduced by lithium aluminium hydride [D. H. R. Barton, R. James, G. W. Kirby, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1968, 1529].
[12] H. C. Brown, *J. Amer. Chem. Soc.*, 1964, **86**, 3566.
[13] A. Mondon and M. Ehrhardt, *Tetrahedron Letters*, 1966, 2557.

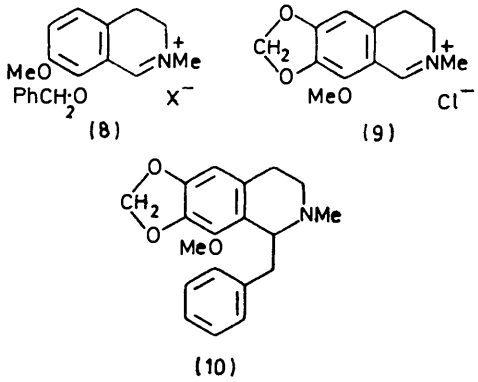
generated *in situ*, rapidly reduced the readily available model compound (7a) to the amine (7b) in over 90% yield. Reduction of (5b) under similar conditions then gave the amine (6b), in excellent yield. *N*-Methylation of the latter (by *N*-formylation followed by treatment with lithium aluminium hydride) and cleavage of the benzyl ether groups with boiling hydrochloric acid afforded the bis-(2-phenylethyl)amine (4b).

The oxidation of the crystalline product with each of the four reagents manganese dioxide, silver oxide, neutral iron(III) chloride, and alkaline potassium ferricyanide was then investigated under a variety of conditions, including two-phase systems for the latter two

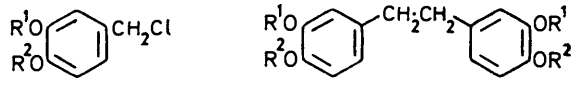


reagents. However, in all the experiments complex products were obtained which appeared to be polymeric in character as judged by their behaviour on t.l.c. and the absence of ketonic products (such as dienones). Similar results were obtained in attempts to oxidise the phenolic amides derived from the benzyl ethers (5a and b). Work on the related series [(5a), (6a), and (4a)] was not pursued, as other workers [11] had by this time shown that Erythrina-type alkaloids were formed on oxidation of (4a).

We next turned to the preparation of a 3,4-dihydroisoquinoline which it was hoped might undergo Grignard addition of benzyl groups.[14] The normal Bischler–Napieralski-type cyclisations of amides of type (5) or (7) lead to isoquinoline derivatives oxygenated in the 5- and 6-positions,[15] and similar reservations apply to the related Pictet–Spengler synthesis.[16] The alternative Pomerantz–Fritzsch synthesis [17] seemed attractive, for although the original procedure gave poor yields, the new modification developed by Bobbitt seemed more suitable.[18] 2-Hydroxy-3-methoxybenzaldehyde was converted into the 7-methoxytetrahydroisoquinolin-8-ol as described previously, and *N*-methylation and *O*-benzylation followed by oxidation with mercuric acetate or iodine [19] then gave the 3,4-dihydroisoquinolinium salt (8). Model experiments involving Grignard additions to the related dihydroisoquinoline, cotarnine chloride (9), were encouraging insofar as a 30% yield of the benzylisoquinoline (10) could be obtained. Brossi *et al.* have also reported [20] the synthesis of petaline (2) and korpaverine by addition of benzyl Grignard reagents to a



3,4-dihydroisoquinoline. However, in attempts to prepare the Grignard derivatives of either of the benzyl halides (11) in tetrahydrofuran reaction apparently proceeded normally, but after treatment of the product with a suspension of the dihydroisoquinoline salt (8) a complex mixture was obtained. T.l.c. showed the presence of starting material and another major component of high R_F value which was isolated by chromatography and shown to be the dihydrostilbene (12a) (60%). It seems likely that the Wurtz-type product (12) is formed either by a radical dimerisation or by reaction of unchanged halide with initially formed Grignard reagent,

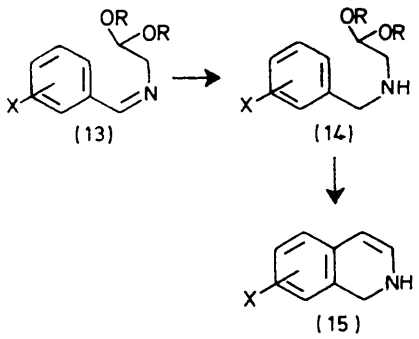


both processes being facilitated by the presence of two electron-releasing groups in the benzyl halide.

In view of these results we returned to the synthesis of isoquinolines by variants of the Pomerantz–Fritzsch process with the aim of alkylating the 1-position by the Reissert method. The original procedure does not usually give good yields of isoquinoline, presumably because under the strongly acidic conditions needed for the cyclisation (*e.g.* hot concentrated sulphuric acid) the Schiff's base of type (13) is protonated on the nitrogen atom; the latter is conjugated with the benzene ring and hence deactivates it towards electrophilic substitution. Bobbitt [18] overcame this effect by reducing the Schiff's base to the corresponding amine (14) and showed that the latter could then be readily cyclised in good yields under more moderately acidic conditions to the dihydroisoquinoline (15). This, however, tends to disproportionate to a mixture of the corresponding isoquinoline and tetrahydroisoquinoline; consequently it is best to reduce the

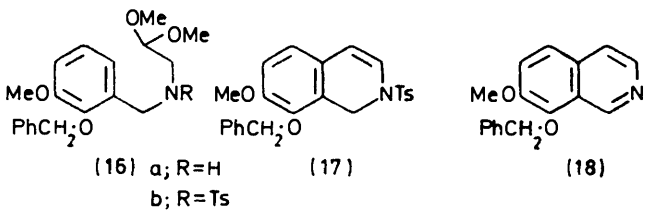
[14] C. Djerassi, F. X. Markley, and R. Ehrlich, *J. Org. Chem.*, 1956, **21**, 975.
[15] W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, 74.
[16] W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, 151.
[17] W. J. Gensler, *Org. Reactions*, 1951, **6**, 191.
[18] J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.
[19] N. J. Leonard and G. W. Leubner, *J. Amer. Chem. Soc.*, 1949, **71**, 3408; S. F. Dyke and D. W. Brown, *Tetrahedron*, 1966, **8**, 2429.
[20] A. Brossi, G. Grethe, and M. Uskokovic, *Tetrahedron Letters*, 1966, 1599; A. Brossi and S. Teitel, *Helv. Chim. Acta*, 1966, **49**, 1757.

crude product *in situ* to give the pure tetrahydroisoquinoline. Dehydrogenation of tetrahydroisoquinolines to give isoquinolines has, however, proved difficult in our experience, for although 3,4-dihydroisoquinolines are



readily produced by chemical oxidation of tetrahydroisoquinolines, removal of the remaining two hydrogen atoms presents considerable problems. Direct dehydrogenation of the tetrahydroisoquinoline over palladium-charcoal in boiling xylene gave only low yields of isoquinolines, and we therefore sought an alternative approach to the solution of this problem, involving *N*-tosyl intermediates.

2-Benzyloxy-3-methoxybenzaldehyde was condensed with aminoacetaldehyde dimethyl acetal and the resulting Schiff's base reduced to the corresponding amine (16a) over platinum. The latter was converted into the corresponding *N*-tosylate (16b) by treatment with toluene-*p*-sulphonyl chloride in pyridine. After a number of preliminary experiments, suitable mild acidic conditions for the cyclisation of this amide were found, and the *N*-tosyl-1,2-dihydroisoquinoline (17) was produced.



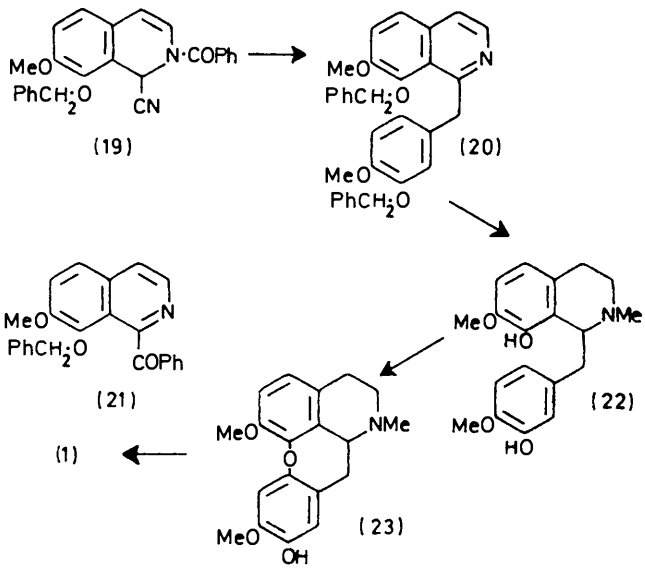
This product proved to be moderately stable, and did not disproportionate (unlike the *N*-substituted analogues described previously) because of the stabilising effect of the tosyl group. Conversion into the corresponding isoquinoline (18) was then effected by taking advantage of the variable valency of sulphur, which allowed the elimination of toluene-*p*-sulphinic acid under strongly basic conditions (potassium t-butoxide in t-butyl alcohol). The overall yield from aldehyde of the isoquinoline (18) was 55%. This new synthesis has since been extended and further developed for a variety of other isoquinolines.[21]

[21] A. J. Birch, A. H. Jackson, P. V. R. Shannon, and P. S. P. Varma, *Tetrahedron Letters*, 1972, 4789.

[22] G. Grethe, H. L. Lee, and M. R. Uskokovic, *Tetrahedron Letters*, 1969, **24**, 1937; G. Grethe, H. L. Lee, M. R. Uskokovic, and A. Brossi, *Helv. Chim. Acta*, 1970, **53**, 874.

Benzoylation of the isoquinoline (18) with benzoyl chloride in the presence of potassium cyanide gave the Reissert compound (19), the sodio-derivative of which was alkylated with 3-benzyloxy-4-methoxybenzyl chloride (11b) in dimethylformamide; after hydrolysis the required 1-benzylisoquinoline (20) was obtained in good yield. In early experiments in which the temperature of the reaction mixture was allowed to rise to 30° the product isolated was the 1-benzoylisoquinoline (21), which must have arisen by a Stevens-type migration from nitrogen. Similar migrations of benzyl groups from the nitrogen atom to the 1-position of isoquinolines are now well known, and although they require more vigorous conditions they form the basis of an alternative [22] to the Reissert method for the synthesis of 1-benzylisoquinolines.

N-Methylation of the isoquinoline (20) followed by borohydride reduction of the heterocyclic ring and acidic

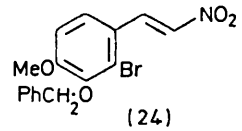


cleavage of the benzyl ether groups then afforded the diphenolic benzylisoquinoline (22). The latter underwent phenolic coupling on oxidation with potassium ferricyanide in a two-phase system (8% ammonium acetate and chloroform). Chromatography of the product afforded *O*-demethylcularine (23), in 7% yield, which could be converted into (±)-cularine (1) by methylation with diazomethane. The structure was confirmed by elemental and spectral analysis, and by the identity of its n.m.r. spectrum with that published for natural (—)-cularine.[23] Other oxidising agents tried for the phenolic coupling (22) included silver carbonate, silver oxide, and manganese dioxide on Celite, as well as iron(III) chloride, but although t.l.c. showed the presence of demethylcularine (13) the yields were much lower than in the ferricyanide oxidations.

[23] N. S. Bhacca, J. Cymerman-Craig, R. H. F. Manske, S. K. Roy, M. Shamma, and W. A. Slusarshyk, *Tetrahedron*, 1966, **22**, 1467.

Several other syntheses of cularine have been described,[24-28] and shortly after our preliminary publication [29] of this work Kametani reported [30] a similar biogenetic-type synthesis of cularine by phenolic coupling; however the requisite benzylisoquinoline was prepared by the Pictet–Spengler method using bromine as a blocking substituent to force cyclisation to occur in the desired fashion.

While the earlier part of this work was in progress we also investigated [7,31] other routes to 7,8-dioxygenated isoquinolines, involving for example attempts to synthesise the bromophenyl ethylamine (26a) and phenylacetic acid (25). It was hoped that the corresponding lithio-derivatives (formed by replacement of bromine) could be formylated or carboxylated and then cyclised to the desired isoquinolines. 2-Bromo-3-hydroxy-4-methoxybenzaldehyde was therefore converted into the related nitrostyrene (24) and the acid (25) by standard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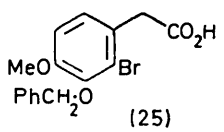
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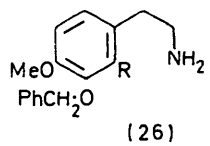
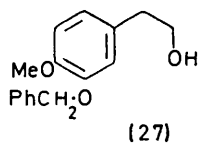
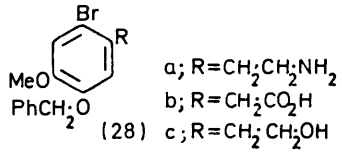

(26)
a; R=Br
b; R=H

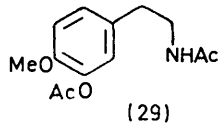

(27)

procedures, but unfortunately treatment of the nitrostyrene with lithium aluminium hydride gave the phenylethylamine (26b) owing to concomitant debromination. Attempts to lithiodebrominate the bromo-acid (25) were unsuccessful because of the insolubility of the lithium salt of the acid, and treatment of either the acid (25) or its methyl ester with lithium aluminium hydride gave the debrominated phenylethanol (27).

Another approach investigated was to block the reactive 6-position in 3-benzyloxy-4-methoxyphenethylamine with bromine, and to attempt to formylate the product (28a) at the 2-position. However, no reaction occurred even with the powerful reagent methyl dichloromethyl ether in the presence of tin(IV) chloride, nor could the corresponding bromophenylacetic acid (28b) or bromophenylethanol (28c) be formylated. In the light of these experiments we did not attempt Bischler–Napieralski-type [15] syntheses with the bromophenylethylamine; however, Kametani and his co-workers have since shown that such intramolecular-type reactions are feasible and the resulting 7,8-dialkoxy-5-bromoisoquinoline derivatives were utilised in their recent synthesis of cularine.[30]

The successful introduction of a 2-formyl group into a phenethylamine derivative was eventually effected as


(28) a; R=$CH_2CH_2NH_2$ b; R=CH_2CO_2H c; R=CH_2CH_2OH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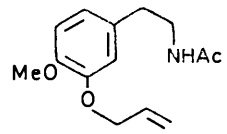
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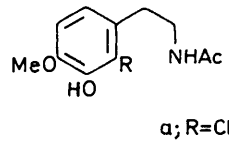

(31) a; R=CH·CH=CH_2 b; R=CH=CHMe

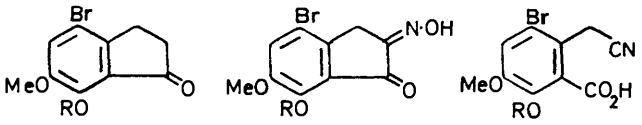
follows. The *NO*-diacetyl derivative (29) was selectively *O*-deacylated, and treated with allyl bromide. The resulting allyl ether (30) readily underwent a Claisen rearrangement to the allylphenol (31a), which was then isomerised to the propenyl derivative (32b) by alkali. The *O*-benzyl derivative of the latter was cleaved with osmium tetraoxide and sodium periodate but gave a complex mixture of products in which the desired aldehyde was shown to be present by t.l.c. The crude aldehyde, isolated chromatographically, was hydrolysed with alkali (to remove the *N*-acetyl group) and the basic product was methylated to give the 3,4-dihydroisoquinoline salt (8) in 5% overall yield from the propenylphenylethylamine (32b). Direct oxidation of the latter with permanganate also proved unsatisfactory; the only product isolated was benzoic acid, presumably derived from the benzyl ether group.

While the foregoing experiments were in progress a different approach to the 7,8-dioxygenated isoquinolines was also being studied. The readily available indanone [31] (33a) was selectively demethylated with boron trichloride in methylene chloride at −70°, and the phenolic product (33b) was benzylated in the usual fashion. An improved synthesis of this indanone is described in the Experimental section. Nitrosation of the resulting benzyl ether with ethyl nitrite afforded the hydroxyimino-ketone (34a), and the derived acetate then underwent fragmentation to give the ring opened cyano-acid (35a) on treatment with alkali. Hydrogenation of the latter over platinum afforded the amino-acid (36), which proved too insoluble in organic solvents for coupling with the usual peptide reagents but was cyclised by thionyl chloride in pyridine to the lactam (37). The results of attempts to convert the latter into the hydroxyimino-

[24] T. Kametani and K. Fukumoto, *Chem. and Ind.*, 1963, 291; *J. Chem. Soc.*, 1963, 4289; 1964, 4142.
[25] T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *Tetrahedron Letters*, 1964, 25; T. Kametani, H. Iida, and C. Kibayashi, *J. Heterocyclic Chem.*, 1970, **7**, 339.
[26] T. Kametani and S. Shibuya, *Tetrahedron Letters*, 1965, 1897.
[27] H. Iida, T. Kikuchi, K. Sakurai, and T. Watanabe, *J. Pharm. Soc. Japan*, 1969, **89**, 645; H. Iida, T. Kikuchi, S. Tanaka, and M. Shinbo, *ibid.*, p. 1169.
[28] S. Ishiwata, T. Fujii, N. Miyaji, Y. Satoh, and K. Itakura, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1850.
[29] A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149.
[30] T. Kametani, K. Fukumoto, and M. Fugihara, *Chem. Comm.*, 1971, 352; *Bio-org. Chem.*, 1972, **1**, 40.
[31] G. A. Charnock, Ph.D. Thesis, Liverpool, 1969.

ketone (34c) were erratic, and fragmentation to the nitriles (35b or c) could not be achieved satisfactorily.

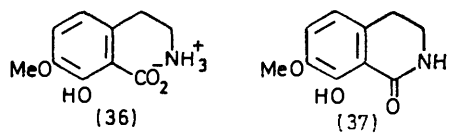
The overall yields of the lactam (37) were unacceptable owing to difficulties at the nitrosation and later stages in



(33) a; R=Me
b; R=H
c; R=CH_2Ph
d; R=Ac

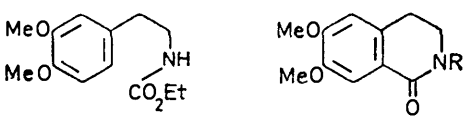
(34) a; R=CH_2Ph
b; R=H
c; R=Ac

(35) a; R=CH_2Ph
b; R=Ac
c; R=H



(36) (37)

particular; moreover the model lactam (39a) proved to be unreactive towards benzylmagnesium bromide. The lactam (39a) (corydaldine) was prepared by polyphosphoric-acid-catalysed cyclisation of the carbamate (38);



(38) (39) a; R=H
b; R=Me

the *N*-methyl derivative (39b) was also prepared by direct methylation of corydaldine.

We therefore decided to abandon the foregoing route to the desired benzylisoquinolines through indanones, especially as the other series of experiments (described above) being carried out simultaneously showed the virtual impossibility of generating the required 3,4-dialkoxybenzyl Grignard reagents.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. spectra were observed with a Unicam SP 800 spectrophotometer and i.r. spectra with a Unicam SP 200G spectrometer. N.m.r. spectra were determined at 60 MHz with a Varian A60 or Perkin-Elmer R10 spectrometer, and at 100 MHz with a Varian HA-100 or Perkin-Elmer R14 spectrometer. Mass spectra were determined with an A.E.I. MS9 spectrometer by direct insertion (inlet at 200°; ionising voltage 70 eV; current 50 μA). T.l.c. was carried out on Merck (Kiesel GF_{254}) silica or Merck neutral alumina and the chromatograms were developed with iodine vapour, unless otherwise stated. Column chromatography was conducted with Grace silica or Merck neutral alumina with the addition of water to give the activity as specified.

N-(*4-Benzyloxy-3-methoxyphenethyl*)-(*3-benzyloxy-4-methoxyphenethyl*)*amine* (6b).—Finely ground sodium borohydride (3·45 g, 0·094 mol) was suspended in a solution of 4-benzyloxy-*N*-(3-benzyloxy-4-methoxyphenyl)-3-methoxyphenylacetamide (10·2 g, 0·02 mol) in dry tetrahydrofuran (250 ml). The mixture was cooled in ice–salt and a solution of freshly distilled boron trifluoride–ether complex (13·9 g, 0·1 mol) in dry tetrahydrofuran (150 ml) was added, with stirring, during 45 min. (Addition was slow and a dilute solution was used in order to avoid any build-up of boron trifluoride which would have resulted in removal of the benzyl groups.) Cooling was maintained for 6 h and finally the mixture was allowed to reach room temperature and stirred for 12 h. Methanol was cautiously added, and vigorous effervescence occurred as unchanged diborane decomposed. Saturated aqueous sodium carbonate was then added gradually until precipitation of sodium borate was complete and the supernatant liquors were clear and colourless. The inorganic material was filtered off and washed with fresh solvent. The combined filtrate and washings were evaporated to remove the organic solvents; an oil separated and was extracted into chloroform (3 × 50 ml). The combined extracts were washed with water (3 × 20 ml), dried ($MgSO_4$), and evaporated to yield an oil. This was treated with saturated ethanolic hydrogen chloride to yield a solution from which the *hydrochloride* (9·8 g, 92%) crystallised as needles, m.p. 162·5—163·5° (Found: C, 72·0; H, 6·8; N, 2·5. $C_{32}H_{36}ClNO_4$ requires C, 72·0; H, 6·75; N, 2·6%), τ ($CDCl_3$) 6·75 (8H, $CH_2{\cdot}CH_2$), 6·23 (OMe), 4·96 and 2·77 (OCH_2Ph), and 3·28br (ArH).

N-(*4-Benzyloxy-3-methoxyphenethyl*)-N-(*3-benzyloxy-4-methoxyphenethyl*)*formamide*.—The foregoing amine hydrochloride (7·5 g, 0·014 mol) was heated with formamide (25 ml) at 140°, under a nitrogen, for 1 h. The resulting solution was quenched with water (250 ml) and extracted with benzene (3 × 50 ml). The combined extracts were washed with water (3 × 30 ml), dried ($MgSO_4$), and evaporated to yield an oil, which could not be crystallised. Chromatography on neutral alumina (activity II) again yielded an oil, which was shown by t.l.c. to be homogenous. On trituration in petroleum the oil gradually solidified, and recrystallisation from this solvent gave the *N-formyl compound* (6·9 g, 93%) as pale yellow cubes, m.p. 82—83° (Found: C, 75·4; H, 6·7; N, 2·7. $C_{33}H_{35}NO_5$ requires C, 75·6; H, 7·0; N, 2·7%), τ ($CDCl_3$) 6·4—7·6 (8H, m, $CH_2{\cdot}CH_2$), 6·21 (6H, OMe), 4·95 and 2·70 (OCH_2Ph), 3·1—3·5 (m, ArH), and 2·33 (CHO).

N-(*4-Benzyloxy-3-methoxyphenethyl*)-N-*methyl*-(*3-benzyloxy-4-methoxyphenethyl*)*amine*.—The foregoing *N*-formyl compound (6·5 g, 0·012 mol) was reduced with lithium aluminium hydride in dry tetrahydrofuran as described above. The free base was obtained as an oil (5·2 g, 82%) which was shown by t.l.c. to be homogenous and slowly crystallised. Attempts to prepare the hydrochloride gave oils, which could not be crystallised. The picrate was prepared, which was also an oil, and percolated in chloroform through a column of alumina. Removal of the solvent gave the crystalline *free base*, m.p. 68—69°, which was analysed directly (Found: C, 77·6; H, 7·0; N, 2·75. $C_{33}H_{37}NO_4$ requires C, 77·5; H, 7·3; N, 2·7%), τ ($CDCl_3$) 7·67 (NMe), 6·35br ($CH_2{\cdot}CH_2$), 6·18 and 6·16 (OMe), 4·91, 4·89, 2·65, and 2·62 (OCH_2Ph), and 3·25br (ArH).

N-(*4-Hydroxy-3-methoxyphenethyl*)-N-*methyl*-(*3-hydroxy-4-methoxyphenethyl*)*amine* (4b).—A solution of the foregoing amine (5·0 g, 0·01 mol) in benzene (50 ml) was stirred with an equal volume of concentrated hydrochloric acid, under nitrogen, at room temperature for 15 h. The organic layer was separated and extracted with more acid (10 ml), and the combined aqueous phases were basified with ammonium carbonate. At this stage the product had separated out as a gum, and a large volume of chloroform was used to ensure

the collection of all the material. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to yield an oil which was shown by t.l.c. to be homogenous, and slowly crystallised. The *phenolic amine* (3·0 g, 90%) formed pale yellow cubes, m.p. 96—98° (from ethanol) (Found: C, 68·5; H, 7·4. $C_{19}H_{25}NO_4$ requires C, 68·9; H, 7·6%), τ ($CDCl_3$) 7·57 (NMe), 7·27 (CH_2·CH_2), 6·15 (OMe), 4·2br (ArOH), and 3·3 (m, ArH).

1-*Benzyl*-1,2,3,4-*tetrahydro*-8-*methoxy*-2-*methyl*-6,7-*methylenedioxyisoquinoline* (10).—Magnesium turnings (0·2 g, 0·084 mol), which had been washed with ether and dried, were placed in a flask fitted with a reflux condenser, dropping funnel, and stirrer, and covered with dry ether (15 ml). Then a small crystal of iodine was added, and the system was flushed with dry nitrogen. Freshly distilled benzyl chloride (0·8 g, 0·0063 mol) in ether (10 ml) was added dropwise, with vigorous stirring, until effervescence commenced, accompanied by the rapid discharge of the iodine colour and a rise in temperature which caused the solvent to reflux. The halide solution was diluted with more ether (10 ml) and added at such a rate as to maintain refluxing. When addition was complete the solution was heated under reflux for 30 min.

To the resulting solution was added solid cotarnine chloride (3,4-dihydro-8-methoxy-2-methyl-6,7-methylenedioxyisoquinolinium chloride) (0·77 g, 0·003 mol), and the suspension was stirred vigorously for 48 h. T.l.c. showed the gradual formation of a major new component. Aqueous ammonium chloride (50 ml; 10%) was added and two layers separated out. The mixture was basified with 2M-sodium hydroxide and the organic layer separated. The aqueous phase was extracted with fresh solvent (3 × 30 ml) and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to yield a buff-coloured oil, which was shown by t.l.c. to contain one major component and material running at the solvent front.

Attempts to prepare the hydrochloride resulted in the formation of oils which could not be crystallised. The product was finally characterised as the *picrate* (380 mg, 31%), m.p. 162—164° (Found: C, 55·7; H, 4·7; N, 10·5. $C_{25}H_{24}N_4O_{10}$ requires C, 55·6; H, 4·45; N, 10·4%), τ ($CDCl_3$) 7·07 (NMe), 6·3—7·0 (6H, m, CH_2), 6·21 (OMe), 5·1 (m, 1-H), 4·06 ($O{\cdot}CH_2{\cdot}O$), 3·6 (NH), and 2·85 (Ph).

Attempted Synthesis of 8-*Benzyloxy*-1-(4-*benzyloxy*-3-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline*.—Conditions were similar to those used in the foregoing model reaction of cotarnine. A solution of 4-benzyloxy-3-methoxybenzyl chloride (3·86 g, 0·015 mol) in dry 1 : 1 diethyl ether–tetrahydrofuran (20 ml) was added slowly, under oxygen-free nitrogen, with stirring to magnesium turnings (0·5 g, 0·016 mol) covered with the same solvent to which a small crystal of iodine had been added. The magnesium had previously been washed with diethyl ether and dried. In contrast to the model reaction, discharge of the iodine colouration did not take place readily and the mixture was refluxed briefly. When the iodine colouration was destroyed, addition of the halide solution was continued. On completion of addition the solution was refluxed for 10 min and 8-benzyloxy-3,4-dihydro-7-methoxy-2-methylisoquinolinium iodide (2 g, 0·005 mol) was added. The resulting suspension was stirred overnight, under nitrogen, but t.l.c. showed the absence of a benzyl isoquinoline and the mixture was then heated under reflux for 2 h before work-up as before. T.l.c. of the solid product showed it to be a complex mixture, with a major component running near the solvent front, but no 1-benzylisoquinoline. Chromatography, on alumina (activity II) gave a compound (4·0 g, 60% based on starting chloride) which was shown by elemental analysis and n.m.r. and mass spectrometry to be 1,2-*bis*-(4-*benzyloxy*-3-*methoxyphenyl*)*ethane* (12a), m.p. 129—131° (Found: C, 79·45; H, 6·55. $C_{30}H_{30}O_4$ requires C, 79·2; H, 6·6%), τ ($CDCl_3$) 7·30 (CH_2), 6·25 (OMe), 4·99 (OCH_2), 3·3 (d, ArH), and 2·7 (m, Ph). The starting isoquinoline (61%) could also be recovered from the crude product, by conversion into the perchlorate.

2-*Benzyloxy*-3-*methoxybenzylideneaminoacetaldehyde Dimethyl Acetal*.—2-Benzyloxy-3-methoxybenzaldehyde (242 g) and redistilled aminoacetaldehyde dimethyl acetal (105 g) in sodium-dried benzene (500 ml) were heated under a Dean–Stark separator for 18 h [water (16 ml) (theory 18 ml) was collected]. Evaporation of a sample of the solution gave material showing no aldehyde peak in the i.r. spectrum at 1690 cm^{-1} and imine absorption at 1650 cm^{-1}. Removal of the benzene from the reaction mixture gave the imine in quantitative yield as an oil which was used without further purification. The product could, however, be distilled; b.p. 174—178° at 0·06 mmHg (Found: C, 68·9; H, 7·3; N, 4·1. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·05; N, 4·25%), τ ($CDCl_3$) 1·54 (CH=N), 2·36—3·11 (m, ArH), 5·00 ($ArCH_2O$), 6·42 (d), 5·46 (t), and 6·71 [$(MeO)_2CH{\cdot}CH_2$], and 6·19 (OMe). Attempts to cyclise this imine to the isoquinoline under mild conditions with (*a*) trifluoroacetic anhydride at 20°, (*b*) toluene-*p*-sulphonic acid in benzene at 80°, or (*c*) phosphoryl chloride in polyphosphoric acid at 20° were unsuccessful.

Hydrogenation of the Foregoing Imino-acetal.—(a) *At atmospheric pressure*. The acetal (7·4 g) in absolute ethanol (50 ml) was treated with platinum oxide (200 mg) and hydrogenated at atmospheric pressure [uptake 480 ml in 4 h (theoretical 506 ml)]. Filtration and removal of the solvent gave the corresponding *benzylamino-acetal* (6·4 g) as an oil, showing no imine absorption in the i.r. at 1640 cm^{-1}, which was used without further purification. A sample distilled for analysis had b.p. 164—168° at 0·06 mmHg (Found: C, 68·9; H, 7·9; N, 4·0. $C_{19}H_{25}NO_4$ requires C, 68·9; H, 7·6; N, 4·2%), τ ($CDCl_3$) 2·5—2·8 (5H, m, ArH), 3·0—3·15 (ArH), 4·96 ($ArCH_2O$), 6·28 ($ArCH_2N$), 6·28 (NCH_2N), 7·35 (d), 5·60 (t), and 6·71 [$(MeO)_2CH{\cdot}CH_2$], 6·14 (OMe), and 8·07 (NH).

(b) *At 50 atm pressure*. The imino-acetal (345 g) was dissolved in absolute ethanol (1 l), treated with platinum oxide (500 mg) and hydrogenated at 50 atm and 20°. After 24 h a sample showed no imine absorption at 1640 cm^{-1}; the solution was filtered and evaporated giving a quantitative yield of the benzylamino-acetal (16a) as an oil.

Attempts were made to cyclise the acetal (16a) under acidic conditions; among the reagents investigated were (*a*) Jones chromic acid; (*b*) 6N-sulphuric acid followed by Jones chromic acid, (*c*) toluene-*p*-sulphonic acid, (*d*) trichloroacetic acid, and (*e*) phosphoryl chloride in polyphosphoric acid. However none of these was successful, in contrast to the conditions used by Bobbitt.[5]

N-*Tosyl*-2-*benzyloxy*-3-*methoxybenzylaminoacetaldehyde Dimethyl Acetal* (16b).—Tosyl chloride (140 g) in dry pyridine (200 ml) was added to a solution of the amino-acetal (16a) (237 g) in dry pyridine (300 ml). The solution immediately became warm and was left at 20° overnight. Pyridine hydrochloride was then filtered off and washed with methylene chloride (150 ml). The solutions were combined and the solvent was removed under vacuum leaving

an oil which was redissolved in methylene chloride (500 ml). The solution was washed with water (300 ml), 2N-hydrochloric acid (500 ml), and water again (300 ml), dried ($MgSO_4$), filtered, and evaporated, leaving an oil (326·7 g, 94%). Silica t.l.c. in 10% ether–benzene showed only minor traces of impurity and the oil was used without further purification. A *sample* was purified for analysis by column chromatography on neutral alumina (elution with benzene) (Found: C, 64·4; H, 6·5; N, 2·7. $C_{26}H_{31}NO_6S$ requires C, 64·35; H, 6·4; N, 2·4%), τ ($CDCl_3$) 2·30—3·20 (m, ArH), 5·01 ($ArCH_2O$), 5·62 ($ArCH_2N$), 6·8 (m), 5·69, and 6·88 [$(MeO)_2CH{\cdot}CH_2$], 7·60 (ArMe), and 6·13 (OMe).

8-Benzyloxy-1,2-dihydro-7-methoxy-2-tosylisoquinoline (17).—The foregoing tosylate (48·5 g) was dissolved in dioxan (100 ml) (which had been freed of peroxide by passage down a column of Spence type H alumina) and heated under reflux with 6N-hydrochloric acid for 1 h. The vessel was wrapped in aluminium foil as the product, when impure, appeared to turn dark brown when exposed to sunlight. After 1 h silica t.l.c. in 10% ether–benzene showed that all the starting tosylate had reacted, so the solvent was removed giving an oil which appeared (t.l.c.) to contain only a trace of impurity. It was therefore used without further purification.

Chromatography of this material on alumina (grade III) in benzene (in a dark room in order to stop photochemical decomposition) gave the *isoquinoline* (17) as yellow-brown crystals, which were extracted with ether. Recrystallisation first from ether–petroleum and then from ether alone gave almost colourless needles (40 g, 80%), m.p. 99·5—100·5° (Found: C, 68·3; H, 5·4; N, 3·1. $C_{24}H_{23}NO_4S$ requires C, 68·4; H, 5·5; N, 3·3%), τ ($CDCl_3$) 2·37—2·93 (9H, ArH), 3·29—3·60 (3H, ArH), 4·39 (d, *J* 8 Hz, 3-H), 5·10 ($ArCH_2O$), 5·63 ($ArCH_2N$), 6·24 (OMe), and 7·71 (ArMe).

8-Benzyloxy-7-methoxyisoquinoline (18).—Potassium (16 g) was added with stirring to t-butyl alcohol (350 ml) heated under reflux in nitrogen. When all the potassium had dissolved (*ca.* 1 h) the tosylate (17) (42·1 g of oil) in dry benzene (100 ml) was added during 15 min. After stirring and heating under reflux for 2 h, silica t.l.c. in 10% ether–benzene showed that all the tosylate had reacted, so the alcohol was removed, leaving an oil. This was dissolved in ether (750 ml) and washed with water (2 × 500 ml). The basic material was then extracted into N-hydrochloric acid (2 × 700 ml) and the aqueous phase was basified with dilute aqueous sodium hydroxide. The product was extracted into ether (2 × 500 ml). The ether layer was dried ($MgSO_4$), filtered, and evaporated giving an oil which slowly crystallised. Silica t.l.c. in 10% ether–benzene showed that the brown crystalline product (19·7 g, 74%), m.p. 55—60°, contained only traces of impurity, and the material was therefore used without further purification. It was possible, with some difficulty, to recrystallise the product from benzene–petroleum, but a good analysis was not obtained. *7-Methoxy-8-benzyloxyisoquinoline* was characterised as the *picrate*, m.p. 172—175° (Found: C, 55·65; H, 3·65; N, 11·2. $C_{23}H_{18}N_4O_9$ requires C, 55·9; H, 3·7; N, 11·2%), τ ($CDCl_3$) 0·50 (1-H), 1·62 (d, *J* 6 Hz, 3-H), 2·4—2·85 (8H, ArH), 4·81 ($ArCH_2O$), and 6·12 (OMe).

2-Benzoyl-8-benzyloxy-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile (19).—8-Benzyloxy-7-methoxyisoquinoline (17 g) was dissolved in methylene chloride (180 ml) and potassium cyanide (30 g) in water (72 ml) was added. The mixture was stirred at room temperature under nitrogen and benzoyl chloride (30 g) was added dropwise during 30 min. After stirring for a further 2½ h, silica t.l.c. in 10% ether–benzene showed that the Reissert compound had been formed, but that about 50% of the 8-benzyloxy-7-methoxyisoquinoline remained. More potassium cyanide (15 g) in water (15 ml) was added and the solution stirred for a further 1 h; t.l.c. then showed the reaction to be complete. The methylene chloride layer was separated and washed with water (3 × 100 ml), 2N-hydrochloric acid (100 ml), dilute sodium hydroxide solution (100 ml), and water again (2 × 100 ml). Drying ($MgSO_4$), filtration, and evaporation gave the Reissert derivative as a brown crystalline solid (22·0 g, 86%) which on silica t.l.c. in 10% ether–benzene showed only minor impurities. This was recrystallised from methanol (or benzene–di-isopropyl ether) to give pale yellow sugary *crystals* (15·9 g, 62·5%), m.p. 132—133° (Found: C, 75·3; H, 5·25; N, 7·2. $C_{25}H_{20}N_2O_3$ requires C, 75·7; H, 5·1; N, 7·1%), τ ($CDCl_3$) 2·3—2·7 (10H, m), 3·00 (2H), 3·19 (1H), and 3·74 (2H, ABq, *J* 8 Hz) (ArH), 4·73 ($ArCH_2O$), and 6·06 (OMe).

8-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-7-methoxyisoquinoline (20).—A 50% dispersion in oil of sodium hydride (0·53 g) was washed free of the oil with petroleum (2 × 10 ml), and dimethylformamide (25 ml) (dried over Linde type 4A molecular sieves) was added. The resulting slurry was stirred under dry, oxygen-free nitrogen and cooled in ice–salt to −6°. The Reissert compound (19) (3·96 g) in dimethylformamide (15 ml) was added over 10 min and the solution was stirred for a further 5 min. 3-Benzyl-4-methoxybenzyl chloride (2·9 g) in dimethylformamide (15 ml) was then added dropwise over 30 min, and the red colouration slowly faded. The mixture was stirred for a further 2 h at 0° and left to warm slowly to room temperature (*ca.* 1 h). Ethanol (3 ml) was added to destroy any unchanged sodium hydride and the dimethylformamide was then removed under vacuum. The product was extracted into benzene (250 ml) and washed with water (2 × 150 ml). Removal of the benzene left an oil (7·1 g); silica t.l.c. in 10% ether–benzene showed a major component with the same R_F value as the starting Reissert compound, but an n.m.r. spectrum of this crude intermediate clearly showed the incorporation of the benzyl group. The oil (7·1 g) was dissolved in ethanol (150 ml), sodium hydroxide (50 g) in water (50 ml) was added, and the mixture was heated under reflux (under nitrogen) for 2½ h. On cooling, the aqueous phase separated from the organic layer, which was decanted and collected. Water (200 ml) was added to the alkaline phase, and this was extracted with benzene (250 ml). The organic extracts were combined and evaporated. The resulting oil was redissolved in benzene (400 ml) and washed with water (2 × 300 ml). Removal of the solvent left the *1-benzylisoquinoline* (20) (4·5 g, 92%) as an oil which on silica t.l.c. in 10% ether–benzene showed minor impurities. This oil crystallised from benzene–petroleum giving pale cream crystals (3·7 g, 75%) and a sample was recrystallised from benzene–di-isopropyl ether; m.p. 120° (Found: C, 78·5; H, 6·1; N, 3·2. $C_{32}H_{29}NO_4$ requires C, 78·2; H, 5·95; N, 2·85%), τ ($CDCl_3$), 1·62 (1H, d, *J* 6 Hz), 2·4—2·8 (13H, m), and 3·2—3·4 (3H, m) (ArH), 5·09, 5·18, and 5·21 ($ArCH_2$), and 6·09 and 6·26 (OMe).

8-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-7-methoxy-N-methylisoquinolinium Fluorosulphonate.—The foregoing 1-benzylisoquinoline (2 g) was dissolved in AnalaR carbon tetrachloride (100 ml), and methyl fluorosulphonate (1 ml; stored over anhydrous potassium carbonate for 5 min prior to use) was added. The solution was shaken at room

temperature for 1 h; the fluorosulphonate salt formed as a bright yellow precipitate. This was collected and dried in a vacuum desiccator, giving an almost quantitative yield (2·4 g) of the *N*-methyl fluorosulphonate. It was possible to recrystallise this salt from benzene–ethyl acetate, but a good elemental analysis was not achieved. The product, which showed only a base-line component on silica t.l.c. in methanol, was used without purification.

8-*Benzyloxy*-1-(3-*benzyloxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxy*-N-*methylisoquinoline*.—The foregoing *N*-methyl fluorosulphonate (2 g) in methanol (120 ml) and water (2 ml) was heated under reflux, and sodium borohydride (2 g) was added in portions over 1½ h. The solvent was then removed under vacuum, crushed ice was added to decompose the boron complex, and the reduction product was extracted into benzene (2 × 100 ml). Removal of the solvent gave the tetrahydroisoquinoline (1·5 g, 90%) as an oil which did not crystallise. An attempt to purify a sample by sublimation resulted in decomposition. The n.m.r. spectrum showed τ ($CDCl_3$) 2·4—2·8 (10H, m) and 3·15—3·30 (5H, m) (ArH), 4·90 (2H, ABq, *J* 11 Hz, 8-OCH_2), 5·04 (3′-OCH_2), 6·14 and 6·18 (OMe), 6·7—7·6 (6H, CH_2), and 7·87 (NMe).

1,2,3,4-*Tetrahydro*-1-(3-*hydroxy*-4-*methoxybenzyl*)-7-*methoxy*-N-*methylisoquinolin*-8-*ol* (22).—The foregoing bisbenzyloxytetrahydroisoquinoline (600 mg) was heated under reflux in ethanol (15 ml) with concentrated hydrochloric acid (15 ml) (under nitrogen) for 1 h. The solution was then diluted with water (100 ml) and the aqueous phase was washed with ether (2 × 60 ml), neutralised with sodium hydrogen carbonate, and extracted with chloroform (3 × 80 ml). Removal of the solvent gave the *diphenolic tetrahydroisoquinoline* in quantitative yield. Recrystallisation from ether–petroleum gave needles (320 mg, 82%), m.p. 61—63° (Found: C, 69·25; H, 6·9; N, 4·2. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·0; N, 4·25%), τ ($CDCl_3$) 3·05—3·50 (5H, m, ArH), 4·00 (2H, OH), 5·7—5·95 (1H, m, ArC*H*N), 6·19 and 6·24 (OMe), and 6·5—7·55 (6H, CH_2).

(±)-*Cularine* (1).—The foregoing diphenolic tetrahydroisoquinoline (250 mg) in chloroform (250 ml) was stirred gently at 20° with a solution of potassium ferricyanide (1·3 g) in 8% ammonium acetate (250 ml) for 12 h. The chloroform layer was separated and the aqueous phase basified with ammonium hydroxide solution and re-extracted with chloroform (250 ml). The chloroform extracts were combined and evaporated giving a red-brown semi-solid, which was dissolved in methanol (10 ml) and treated with an excess of diazomethane. After 15 min the unchanged diazomethane was blown out of solution in a stream of nitrogen and the solvent was removed under vacuum giving an oil. Silica t.l.c. in 2% methanol–chloroform showed a component with the same R_F value as cularine and a component running just in front of this band. The mixture was chromatographed on alumina (grade IV) in benzene in order to remove the base-line components and then on silica thick-layer plates in 2% methanol–chloroform. The lower band afforded an oil (13 mg, 5%) which crystallised from ether–light petroleum giving cularine (1) (10 mg, 4%), m.p. 119° (lit.,[4] 113—114°) (Found: C, 70·3; H, 6·75; N, 4·0. Calc. for $C_{20}H_{23}NO_4$: C, 70·35; H, 6·8; N, 4·1%), τ ($CDCl_3$) 3·22 (2H, ABq, *J* 8·5 Hz), 3·20 (1H), and 3·54 (1H), (ArH), 5·50 (1H, d, *J* 4 Hz) and 5·62 (1H, d, *J* 4 Hz) (ArCH_2), 6·15 and 6·24 (OMe), 6·75—7·3 (6H, CH_2), and 7·42 (NMe), in excellent agreement with the n.m.r. spectrum quoted [9] for (−)-cularine. The i.r. spectrum in chloroform and the u.v. spectrum in ethanol were also identical with those of natural cularine. The mass spectrum showed a parent ion at *m/e* 341·163 ± 0·002 (calc. 341·163) and a fragmentation pattern in agreement with the literature data for cularine.[9]

The component of higher R_F afforded an oil (5 mg, 2%), τ ($CDCl_3$) 3·19 (2H, ABq, *J* 8 Hz) and 3·43 (1H) (ArH), 5·4—5·65 (1H, m, ArCHN), 6·13 and 6·14 (OMe), 6·5—7·3 (6H, m, CH_2), and 7·42 (NMe), identified as the coupled phenol arising from incomplete methylation. A mass spectrum showed the parent ion at *m/e* 327·147 ± 0·002 (calc. 327·146). This coupled phenol was also isolated from a phenolic oxidation experiment prior to methylation. The red-brown semi-solid oil from the oxidation wa schromatographed on alumina grade (IV) in benzene and 10-O-*demethylcularine* (23) (17 mg, 7%) was isolated as crystals, m.p. 126—127° (Found: C, 69·6; H, 6·4; N, 4·25. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5; N, 4·3%).

Thermal Rearrangement of the Reissert Anion (19).—Sodium hydride (50% oil dispersion; 140 mg) was washed free of oil with petroleum and suspended in dry dimethylformamide (15 ml). The suspension was stirred under pure, dry nitrogen at 16° and the Reissert compound (19) (1 g) in dimethylformamide (15 ml) was added dropwise over 10 min. The mixture was then allowed to warm to room temperature over 1 h and stirred for a further 1 h. Any unchanged hydride was destroyed with ethanol (2—3 ml) and the solvent was removed, leaving an oil. This was dissolved in benzene–petroleum, giving 1-*benzoyl*-8-*benzyloxy*-7-*methoxyisoquinoline* (21) (500 mg, 54%) as crystals, m.p. 138—140° (Found: C, 78·2; H, 5·3; N, 3·9. $C_{24}H_{19}NO_3$ requires C, 78·0; H, 5·2; N, 3·8%), τ ($CDCl_3$) 1·52 (1H, *J* 6 Hz) and 2·2—2·9 (13H, m) (ArH), 5·00 (2H, $ArCH_2O$) and 6·10 (OMe), $\nu_{max.}$ (Nujol) 1681 cm^{-1} (CO).

3-*Benzyloxy*-2-*bromo*-4-*methoxy*-β-*nitrostyrene* (24).—3-Benzyloxy-2-bromo-4-methoxybenzaldehyde (4 g) was converted into the nitrostyrene by boiling with nitromethane (1·2 g) in glacial acetic acid (10 ml) containing ammonium acetate (1 g). The *product* was isolated by dilution with water and recrystallised from ethanol to afford yellow needles (3·4 g, 75%), m.p. 107° (Found: C, 53·1; H, 3·9; N, 3·6. $C_{16}H_{14}BrNO_4$ requires C, 52·8; H, 3·9; N, 3·8%).

Reduction of the nitrostyrene with lithium aluminium hydride in ether did not afford the expected 2-bromophenethylamine, but reduction and debromination were effected to give 3-benzyloxy-4-methoxyphenethylamine (26b), identical (m.p. and mixed m.p. of the hydrochlorides; i.r. spectrum) with authentic material.

3-*Hydroxy*-N-(3-*hydroxy*-4-*methoxyphenethyl*)-4-*methoxyphenylacetamide*.—3-Benzyloxy-*N*-(3-benzyloxy-4-methoxyphenethyl)-4-methoxyphenylacetamide (5a) (1 g) was debenzylated by hydrogenation at 1 atm in methanol (100 ml) containing hydrochloric acid (1 ml) over 5% palladium–charcoal (0·1 g). The *hydroxy-amide* afforded small prisms, m.p. 117° (from chloroform–ether) (Found: C, 65·1; H, 6·6; N, 4·2. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4; N, 4·2%).

4-*Hydroxy*-N-(3-*hydroxy*-4-*methoxyphenethyl*)-3-*methoxyphenylacetamide*.—Prepared as for the foregoing isomer from the corresponding dibenzyl ether (5b), the phenolic amide was obtained as a foam, but attempts to crystallise it from a variety of solvents were unsuccessful, and it was characterised by spectrometry.

N-(3-*Acetoxy*-4-*methoxyphenethyl*)*acetamide* (29).—3-Benzyloxy-4-methoxyphenethylamine (3 g) was debenzylated by boiling with ethanolic 6M-hydrochloric acid for 1 h. Evaporation to dryness left a residue which was acetylated

with acetic anhydride (5 ml) and pyridine (5 ml) for 14 h at 20°. Evaporation of the mixture and recrystallisation of the residue from benzene afforded the *acetoxy-derivative* (2·1 g, 84%) as white needles, m.p. 105° (Found: C, 66·1; H, 7·0; N, 5·1. $C_{16}H_{21}NO_4$ requires C, 65·9; H, 7·3; N, 4·8%), τ (CDCl$_3$) 8·10 (NAc), 7·71, (OAc), 7·28 (t) and 6·63 (t) (ArCH$_2$·CH$_2$·N), 6·20 (OMe), 3·8br (NH), and 2·9—3·2 (m, ArH).

N-(3-*Allyloxy*-4-*methoxyphenethyl*)*acetamide* (30).—The foregoing amide (1·3 g) was dissolved in aqueous sodium hydroxide (0·9 g in 20 ml) and left overnight at 20°. Unchanged starting material was removed by extraction with chloroform; acidification and extraction with chloroform then afforded an oil (0·98 g) after evaporation. The latter was dissolved in acetone (20 ml) and heated under reflux for 9 h with potassium carbonate (1·0 g) and allyl bromide (0·8 ml). Filtration, evaporation, and recrystallisation of the residue from benzene afforded the *allyloxy-derivative* (0·8 g, 60%) as white needles, m.p. 85° (Found: C, 67·3; H, 7·5; N, 5·6. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%), τ (CDCl$_3$) 8·06 (NAc), 7·25 (t) and 6·57 (t) (ArCH$_2$·CH$_2$·N), 6·15 (OMe), *ca.* 5·4 (OCH$_2$), *ca.* 4·6 and *ca.* 3·9 (CH$_2$=CH), and 3·2 (m, ArH).

N-(3-*Acetoxy*-2-*allyl*-4-*methoxyphenethyl*)*acetamide*.— The foregoing allyl ether (0·5 g) was heated for 1 h at 210° under nitrogen. The phenolic product was extracted into 2M-sodium hydroxide (10 ml) and after acidification the product was extracted into chloroform and afforded an oil on evaporation. The product (31a) failed to crystallise but its structure was confirmed by n.m.r.: τ (CDCl$_3$) 8·04 (NAc), 7·22 (t) and *ca.* 6·5 (m) (ArCH$_2$·CH$_2$·N), 6·13 (OMe), *ca.* 5·0 and *ca.* 4·0 (CH$_2$=CH), and 3·28 (ArH). Acetylation afforded the *acetate* (0·45 g, 78%) as needles, m.p. 105° (from benzene) (Found: C, 66·1; H, 7·0; N, 5·1. $C_{16}H_{21}NO_4$ requires C, 65·9; H, 7·3; N, 4·8%), τ (CDCl$_3$) 8·07 (NAc), 7·69 (OAc), 7·23 (t) and 6·65 (m) (ArCH$_2$·CH$_2$·N), *ca.* 5·0 and *ca.* 4·0 (CH$_2$=CH), and 3·03 (ABq, *J* 8·5 Hz, ArH).

Methyl 3-*Benzyloxy*-4-*methoxyphenylacetate*.— 3-Benzyloxy-4-methoxyphenylacetic acid (5 g) was dissolved in anhydrous methanol (100 ml) containing concentrated sulphuric acid (1 ml) and heated under reflux for 14 h. Concentration to 10 ml and scratching gave the required *ester* (5·0 g, 95%) as needles, m.p. 85° (Found: C, 71·3; H, 6·4. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). Reduction with lithium aluminium hydride afforded 2-(3-benzyloxy-4-methoxyphenyl)ethanol (27), m.p. 80°.

Methyl 5-*Benzyloxy*-2-*bromo*-4-*methoxyphenylacetate*.—5-Benzyloxy-2-bromo-4-methoxyphenylacetic acid (28b) (5 g) was converted into the *methyl ester* (4·9 g, 91%) in the same way as the foregoing acid; it formed needles, m.p. 109° (from methanol) (Found: C, 55·8; H, 4·7; Br, 21·8. $C_{17}H_{17}BrO_4$ requires C, 55·9; H, 4·7; Br, 21·9%). Reduction of this bromo-ester or of the unbrominated analogue with lithium aluminium hydride in ether in the usual way afforded 2-(3-*benzyloxy*-4-*methoxyphenyl*)*ethanol* (27) (90%) as white cubes, m.p. 80° (from di-isopropyl ether) (Found: C, 74·1; H, 6·7. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

2-(5-*Benzyloxy*-2-*bromo*-4-*methoxyphenyl*)*ethanol* (28c).—The foregoing alcohol (2·6 g) in glacial acetic acid (40 ml) buffered with sodium acetate (2 g) was brominated with bromine (1·7 g). After 10 min, water (100 ml) was added and the product extracted with ether (100 ml). The organic layer was washed with 2M-sodium hydroxide (50 ml), dried (Na$_2$SO$_4$), and evaporated. The residue afforded the *alcohol* (3·1 g, 89%) as white needles, m.p. 80° (from di-isopropyl ether) (Found: C, 57·2; H, 5·0; Br, 23·9. $C_{16}H_{17}BrO_3$ requires C, 57·0; H, 5·1; Br, 23·7%).

2-(2-*Bromo*-5-*hydroxy*-4-*methoxyphenyl*)*ethanol*.—The foregoing alcohol (1·0 g) was debenzylated with ethanolic hydrochloric acid in the usual way. Recrystallisation from benzene gave slightly purple needles of the *phenolic alcohol* (0·61 g, 85%), m.p. 132° (Found: C, 43·9; H, 4·4; Br, 32·4. $C_9H_{11}BrO_3$ requires C, 43·7; H, 4·5; Br, 32·3%).

3-(5-*Benzyloxy*-2-*bromo*-4-*methoxyphenyl*)*propionic Acid*.—3-(5-Benzyloxy-4-methoxyphenyl)propionic acid [32] (21 g) was dissolved in glacial acetic acid (200 ml) containing anhydrous sodium acetate (10 g), and bromine (12·0 g) was added. After 10 min the product began to crystallise, and water was then added to complete precipitation. The *bromo-acid* (24·1 g, 90%) was collected and recrystallised from aqueous ethanol to give needles, m.p. 112° (Found: C, 56·0; H, 4·7. $C_{17}H_{17}BrO_4$ requires C, 55·9; H, 4·7%).

3-(2-*Bromo*-5-*hydroxy*-4-*methoxyphenyl*)*propionic Acid*.—The above acid (21·0 g) was dissolved in glacial acetic acid (300 ml) and concentrated hydrochloric acid (50 ml) and heated at 70° for 45 min. The solution was then evaporated to dryness under vacuum to afford a white residue which gave the *phenolic acid* (15·2 g, 94%) as needles, m.p. 139° (from benzene) (Found: C, 43·9; H, 4·3. $C_{10}H_{11}BrO_4$ requires C, 43·7; H, 4·0%).

4-*Bromo*-7-*hydroxy*-6-*methoxyindan*-1-*one* (33b).—The foregoing acid (5 g) was dissolved in concentrated sulphuric acid (25 ml) preheated to 75°, and was heated at 75° for 5 min. The yellow solution was poured onto crushed ice (500 g) and extracted with chloroform (2 × 100 ml). The extracts were washed with aqueous sodium hydrogen carbonate, dried (Na$_2$SO$_4$), and evaporated to afford a pale green solid. Recrystallisation from ethanol afforded the *indanone* (3·3 g, 70%) as long needles, m.p. 130° (Found: C, 46·5; H, 3·4. $C_{10}H_9BrO_3$ requires C, 46·7; H, 3·5%), τ (CDCl$_3$) 7·15 (m, CH$_2$·CH$_2$), 6·11 (OMe), and 2·80 (ArH). The same product was obtained in 50% yield from 4-bromo-6,7-dimethoxyindanone [33] (33a) by selective demethylation with boron trichloride in methylene chloride at −70°.

7-*Benzyloxy*-4-*bromo*-6-*methoxyindan*-1-*one* (33c).—The above indanone (2·5 g) was dissolved in dimethylformamide (100 ml), and benzyl chloride (1·3 ml) was added, followed by anhydrous potassium carbonate (5 g). The mixture was heated at 100° for 2 h with stirring. On cooling and pouring into water (1 l) the benzylated product was precipitated. Recrystallisation from light petroleum gave *needles* (2·1 g, 50%), m.p. 84° (Found: C, 58·9; H, 4·3. $C_{17}H_{15}BrO_3$ requires C, 58·7; H, 4·3%), τ (CDCl$_3$) 7·2 (m, CH$_2$·CH$_2$), 6·18 (OMe), 4·80 (OCH$_2$), and 2·3—2·8 (m, ArH).

7-*Benzyloxy*-4-*bromo*-2-*hydroxyimino*-6-*methoxyindan*-1-*one* (34a).—The foregoing indanone (3·6 g) was dissolved in ethanol (100 ml) containing concentrated hydrochloric acid (5 ml) and then saturated with ethyl nitrite. The precipitated *isonitroso-derivative* (3·1 g, 81%) had m.p. 210° (Found: C, 53·9; H, 3·8. $C_{17}H_{14}BrNO_4$ requires C, 54·2; H, 3·7%).

6-*Benzyloxy*-3-*bromo*-2-*cyanomethyl*-5-*methoxybenzoic Acid* (35a).—The foregoing isonitroso-derivative (1 g) was dissolved in pyridine (5 ml) and acetic anhydride (5 nil) was added. After 5 min the product began to separate, and water (50 ml) was added to complete precipitation. The *acetoxy-derivative* (1·0 g) was recrystallised from ethanol to

[32] R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 1931, 3169.
[33] R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 1927, 550.

give long, yellow (light-sensitive) needles, m.p. 169° (Found: C, 54·5; H, 4·1. $C_{19}H_{16}BrNO_5$ requires C, 54·6; H, 3·9%).

This product (418 mg) was dissolved in dimethylformamide (5 ml), and sodium hydroxide (45 mg) in water (3 ml) was added. Almost immediately the solution was decolourised and then darkened. Water was added (100 ml) and the solution was acidified and then extracted with chloroform (2 × 30 ml). The extracts were then extracted with sodium hydrogen carbonate solution (2 × 20 ml), and acidification followed by re-extraction with chloroform, drying ($MgSO_4$), and evaporation afforded a white solid. Recrystallisation from benzene gave the *nitrile acid* (241 mg, 64%) as needles, m.p. 159° (Found: C, 54·5; H, 3·8; N, 3·7. $C_{17}H_{14}BrNO_4$ requires C, 54·3; H, 3·8; N, 3·7%), τ (NaOD) 6·37 (CH_2), 6·40 (OMe), *ca.* 5·0 and 2·55 (OCH_2Ph), and 2·90 (ArH).

7-*Acetoxy*-4-*bromo*-6-*methoxyindan*-1-*one* (33d).—The phenolic indanone (33b) was treated with acetic anhydride, in the presence of pyridine, to yield the corresponding *acetate*, which afforded yellow plates, m.p. 136° (from ethanol) (Found: C, 48·0; H, 3·95. $C_{12}H_{11}BrO_4$ requires C, 48·15; H, 3·8%), τ ($CDCl_3$) 7·60 (OAc), *ca.* 7·15 (m, $CH_2{\cdot}CH_2$), 6·11 (OMe), and 2·59 (ArH).

7-*Acetoxy*-4-*bromo*-2-*hydroxyimino*-6-*methoxyindan*-1-*one* (34c).—The foregoing acetate (5 g) was dissolved in absolute ethanol (150 ml) containing concentrated hydrochloric acid (10 ml) and treated with ethyl nitrite [prepared by the addition of a solution of concentrated sulphuric acid (5·1 ml) and absolute ethanol (5·3 ml) in water (40 ml) to a solution of sodium nitrite (12·4 g) and absolute ethanol (5·3 ml) in the same volume of water] for 1 h. The resulting solution was evaporated to yield gum which was shown by t.l.c. to be a mixture of products. Attempts to crystallise out the product were not successful, and the crude mixture was treated directly with acetic anhydride–pyridine. After heating for 10 min the solution was added to water (250 ml) and extracted with chloroform (3 × 100 ml). The combined extracts were washed with hydrochloric acid, then aqueous sodium carbonate, and then water, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue from ethanol yielded yellow plates (3·2 g, 52%) of the *acetoxyoxime*, m.p. 177—179° (Found: C, 45·65; H, 3·3; N, 3·5. $C_{14}H_{12}BrNO_6$ requires C, 45·4; H, 3·25; N, 3·8%), τ ($CDCl_3$) 7·63 (OAc), 7·57 (NAc), 6·2 (ArMe), 6·08 (OMe), and 2·53 (ArH).

6-(2-*Aminoethyl*)-2-*hydroxy*-3-*methoxybenzoic Acid* (36).—The nitrile acid (35a) (370 mg) was dissolved in methanol (10 ml) containing hydrochloric acid (1 ml) and hydrogenated over Adams catalyst (100 mg) for 24 h. The resulting amino-acid hydrochloride was dissolved in hot water and pyridine (0·5 ml) was added. On cooling, the free *amino-acid* (260 mg, 89%) was obtained as needles, m.p. 225°. A good analysis could not be obtained but the identity of the product was confirmed by i.r., n.m.r., and mass spectral data (Found: C, 55·8, 55·9, 56·1; H, 6·5, 6·3, 6·3; N, 6·4. $C_{10}H_{13}NO_4$ requires C, 56·85; H, 6·2; N, 6·6%), τ (NaOD) *ca.* 7·3 (m, $ArCH_2{\cdot}CH_2{\cdot}N$), 6·27 (OMe), and 3·69 (d) and 3·24 (d) (*J* 8·5 Hz, ArH).

Ethyl N-(3,4-*Dimethoxyphenethyl*)*carbamate* (38).—To a stirred mixture of 3,4-dimethoxyphenethylamine (30·2 g) and water (65 ml) was added ethyl chloroformate (7 g), with cooling to maintain a temperature of 30°. At this stage the pH of the solution was 7·0 and the addition of potassium hydroxide in water (25%) was commenced. When alkalinity had been restored further ethyl chloroformate was added and the alternate addition of these reagents was continued, during 70 min, with the temperature maintained at 30°, until 23·3 g of ethyl chloroformate and 75 ml of potassium hydroxide solution had been added. The temperature of the mixture was then lowered to 20°, and stirring was continued for a further 30 min. A buff-coloured oil had then separated out, which gradually solidified to give the *carbamate* (30·4 g, 72%) as yellow needles, m.p. 64—66° (from diethyl ether) (Found: C, 61·4; H, 7·6; N, 5·6. $C_{13}H_{19}NO_4$ requires C, 61·65; H, 7·55; N, 5·55%).

3,4-*Dihydro*-6,7-*dimethoxyisoquinolin*-1(2H)-*one* (*Corydaldine*) (39a).—The carbamate (38) (25·0 g) was added, with stirring, to polyphosphoric acid (225 g) which had been preheated to 110—111°. The temperature was raised to 120—121° and the mixture stirred for 45 min; foaming was observed. The resultant mixture was poured onto ice (380 g), neutralised with sodium hydroxide solution (50%), keeping the temperature at 10—15° by gradual addition of ice, and extracted with a large volume of methylene chloride. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to yield a yellow solid. Recrystallisation from methyl ethyl ketone gave needles (9·2 g, 45%) of the lactam, m.p. 174—175° (lit.,[34] 173°), τ ($CDCl_3$) 7·1 (t) and 6·4 (m) ($ArCH_2{\cdot}CH_2{\cdot}N$), 6·05 (OMe), 3·28 (5-H), 2·38 (8-H), and 2·3br (NH).

N-*Methylcorydaldine* (39b).—Sodamide (4·25 g) was prepared, as a suspension in liquid ammonia, by the gradual addition of fresh sodium (2·5 g) in the presence of a trace of iron(III) nitrate. To this suspension was added a solution of corydaldine (5 g) and methyl iodide (35 g) in dry tetrahydrofuran. The mixture was stirred for 12 h and ammonium chloride solution (200 ml; 10%) was added. The mixture was extracted with chloroform (3 × 100 ml), and the combined extracts were washed, dried, ($MgSO_4$), and evaporated to yield a pale yellow oil, which was shown by t.l.c. to be homogenous, and crystallised spontaneously. Recrystallisation from benzene–light petroleum (b.p. 60—80°) gave the N-*methyl-lactam* (5·1 g, 94%) as pale yellow rods (Found: C, 65·2; H, 6·8: N, 6·55. $C_{12}H_{15}NO_3$ requires C, 65·1; H, 6·8; N, 6·3%), τ ($CDCl_3$) 7·1 (t) and 6·45 (t) ($ArCH_2{\cdot}CH_2{\cdot}N$), 6·85 (NMe), 6·08 (OMe), 3·33 (5-H), and 2·35 (8-H).

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[34] E. Spath and A. Dobrowsky, *Ber.*, 1925, **58**, 1274; L. M. Mohunta and J. N. Ray, *J. Chem. Soc.*, 1934, 1263.