The Synthesis of Emetine and Related Compounds. Part IX.† The Use of Wittig-type Reagents in the Synthesis of 2,3-Dehydroemetine

By **Norman Whittaker**, The Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS

The (±)-ketone (I) (3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one) is converted in one operation through the mixture of isomeric 2-ethoxycarbonylmethylene derivatives (IIb) and (IIIb) into ethyl 3-ethyl-1,4,6,7-tetrahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizine-2-acetate (Vb), which gives, in 75% overall yield from (I), the (±)-*N*-(3,4-dimethoxyphenethyl) amide (VI) required for production of racemic 2,3-dehydroemetine (IX). Similarly, the (−)-ketone (I) gives the (−)-amide (VI) corresponding to (−)-2,3-dehydroemetine (IX).

The emetine skeleton has also been synthesised by linking together the benzo[*a*]quinolizine and isoquinoline moieties directly. The novel 3,4-dihydro-6,7-dimethoxyisoquinolin-1-ylmethylenetriphenylphosphorane (XIV) obtained from the chloromethyldihydroisoquinoline hydrochloride (XI) condenses with the ketone (I) to form 2,3-dehydro-*O*-methylpsychotrine (VIII) or its isomer (X), depending on the reaction conditions. Treatment of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-ylmethyltriphenylphosphonium bromide hydrobromide (XVI) with sodium methylsulphinylmethanide produces methylenetriphenylphosphorane as well as the 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-ylmethylenetriphenylphosphorane (XVIII) and the latter reacts with the ketone (I) to give the 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-ylmethylene) derivative (XXI) of (I).

Fusion of 2-(2-acetamidoethyl)-4,5-dimethoxyphenacylidenetriphenylphosphorane (XXVII) with the ketone (I) leads to a variety of fragmentation products.

RACEMIC 2,3-dehydroemetine [1] is an effective amoebicide [2] and the (—)-enantiomer [3] (IX) ‡ has been shown [3,4] to be the biologically active component, comparable in activity to emetine. In the original synthesis [1] of racemic 2,3-dehydroemetine, the condensation product (IV) formed from the ketone (I) and malononitrile,[5] was subjected to acid hydrolysis; concurrent decarboxylation and migration of the ethylenic bond into the ring gave rise to the carboxylic acid (Vc). Cyclisation of the derived *N*-(3,4-dimethoxyphenethyl) amide (VI) gave 2,3-dehydro-*O*-methylpsychotrine (VIII) which was reduced to a mixture of 2,3-dehydroemetine (IX) and its 1′-epimer, 2,3-dehydroisoemetine. It was therefore of interest to see whether that route could be improved by use of intermediates arising out of our synthesis of emetine.[6]

We have shown [6] that the ketone (I) is converted by Wittig-type reagents into the unsaturated ester (III), or into a mixture of *cis*- and *trans*-forms of its C(3)-epimer (II), and that reaction of the ester (IIIa) with 3,4-dimethoxyphenethylamine at 180° is accompanied by migration of the ethylenic bond into the ring to give the amide (VI) directly, although in only 20% overall yield from the ketone (I). When either the *cis*- or the *trans*-ester (IIa) is treated similarly, however, only a trace of the amide (VI) is obtained, and at higher temperatures decomposition occurs and the only isolable product is *NN*′-bis-(3,4-dimethoxyphenethyl)urea. Catalysis of the reaction of the amine with the ester (IIIa) by 2-hydroxypyridine [7] increased the yield of the desired amide (VI), but the product was contaminated with the isomeric αβ-unsaturated amide (VII) which was difficult to remove. The latter, obtained in good yield through the acid chloride, could not be isomerised by heating with 3,4-dimethoxyphenethylamine. Cyclisation of the αβ-unsaturated amide (VII) by phosphoryl chloride was also accompanied by a partial migration of the ethylenic bond and led to a mixture of the desired 2,3-dehydro-*O*-methylpsychotrine (VIII) with a lesser amount of a new base (X).

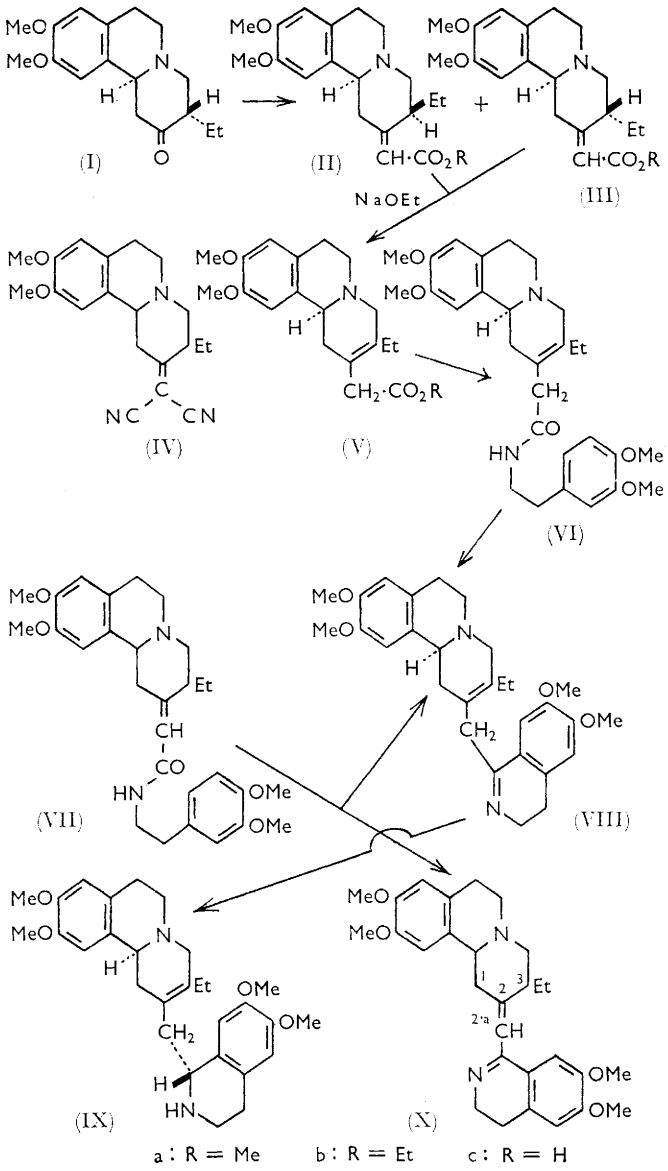
The foregoing observations show that it is the ester (III) rather than the amide (VII) which undergoes double-bond migration in the presence of the amine, and the isomerisation of the ester by other bases was therefore studied. With ethanolic sodium ethoxide under reflux, the esters (III) and (II) (both isomers) were converted almost quantitatively into the 2,3-de-

† Part VIII, H. T. Openshaw and N. Whittaker, preceding paper.

‡ Where compounds are optically active, the formulae depict their absolute configurations; for racemic compounds, only one enantiomer is represented.

[1] A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Würsch, F. Schneider, and O. Schnider, *Helv. Chim. Acta*, 1959, **42**, 772.
[2] G. Woolfe, *Progr. Drug. Res.*, 1965, **8**, 12.
[3] A. Brossi, M. Baumann, F. Burkhardt, R. Richle, and J. R. Frey, *Helv. Chim. Acta*, 1962, **45**, 2219.
[4] P. Johnson and R. A. Neal, *Ann. Trop. Med. Parasitol.*, in the press.
[5] A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 1953, 2463.
[6] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1963, 1461.
[7] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 89.

hydro-ester (Vb); the stronger base dimsylsodium (sodium methylsulphinylmethanide) [8] effected isomerisation of ester (IIIb) in less than 5 min. at room temperature, but the process was complicated by partial further



reaction of the ester group with the carbanion to give some β-keto-sulphoxide. On the basis of the above results a useful route to the 2,3-dehydroemetine intermediate (VI) became available. The ketone (I) was treated with an alkoxycarbonylmethylphosphonate in an excess of concentrated alcoholic sodium ethoxide,[9] with cooling, and the resulting solution, containing the *cis*–*trans*-esters (IIb) and the ester (IIIb), was then heated under reflux for 2 hr. to bring about the required isomerisation. The single ester (Vb) thus produced was then heated with 3,4-dimethoxyphenethylamine in the presence of 2-hydroxypyridine [7] to give the *N*-(3,4-dimethoxyphenethyl) amide (VI) in an overall yield of *ca.* 75% with respect to the ketone (I).

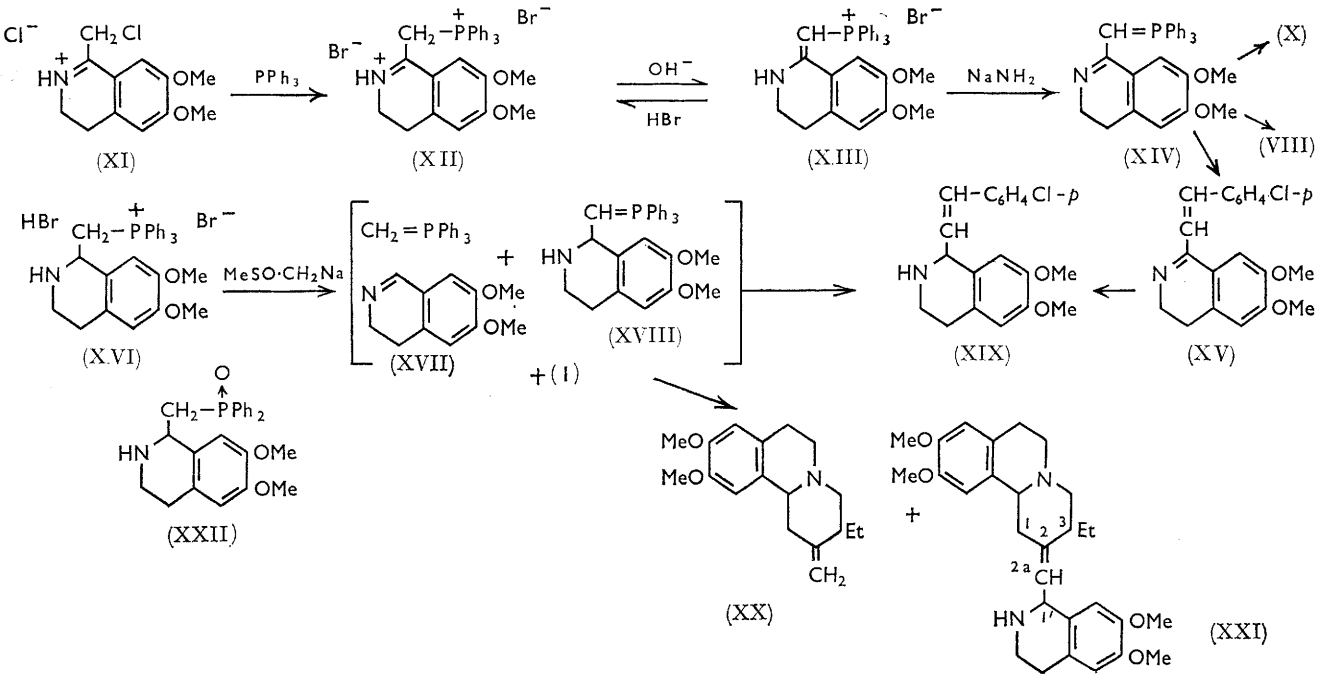
For their synthesis of (—)-2,3-dehydroemetine (IX), Brossi and his co-workers [3] obtained the required (—)-carboxylic acid (Vc) by resolution of the racemic methyl ester, followed by hydrolysis of the (—)-enantiomer (Va). We have found that the (—)-ketone (I) cannot be converted into the (—)-carboxylic acid (Vc) through the condensation product (IV), since racemisation takes place during the condensation with malononitrile. Racemisation did not take place, however, when the (—)-ketone (I) was subjected to the procedure described in the preceding paragraph, and the (—)-ester (Vb) and the (—)-N-(3,4-dimethoxyphenethyl) amide (VI) were produced in high yield. Since the (—)-ketone (I) is obtained by an asymmetric transformation [6] and not by a conventional resolution with attendant loss of material, the above procedure constitutes an efficient route to the (—)-*N*-(3,4-dimethoxyphenethyl) amide (VI) and thus to (—)-2,3-dehydroemetine (IX).

An attractive alternative method of constructing the emetine skeleton would be the linking together of the pre-formed benzo[*a*]quinolizine and isoquinoline components; this has now been accomplished by subjecting the ketone (I) to a Wittig reaction with the novel phosphorane (XIV). Owing to competing self-condensation, the readily available 1-chloromethyl-3,4-dihydro-6,7-dimethoxyisoquinoline [10] did not react smoothly as the free base with triphenylphosphine but the more stable hydrochloride (XI) did react satisfactorily, to give a phosphonium salt (80%) which was isolated as a hydrogen bromide adduct of the bromide hydrobromide (XII). This on treatment with an excess of aqueous ammonia gave the phosphonium bromide (XIII) which is formulated as a 1-(substituted methylene)tetrahydroisoquinoline [11] rather than as a 1-(substituted methyl)dihydroisoquinoline in view of its i.r. and u.v. absorption. In the presence of acid, protonation takes place on the exocyclic carbon atom to regenerate the dihydroisoquinolinium ion. Treatment of the salt (XIII) with sodamide or dimsylsodium gave the desired phosphorane (XIV) which was unstable in water with hydrolysis to 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline and triphenylphosphine oxide. It gave the known *p*-chlorostyryldihydroisoquinoline (XV) [12] on treatment with *p*-chlorobenzaldehyde. Reaction of the phosphorane (XIV) with the ketone (I) in anisole at *ca.* 150° gave a small yield of the 2,2a-dehydro-base (X) already mentioned, whereas in the absence of solvent the Wittig reaction was followed by migration of the ethylenic bond into the ring, to give 2,3-dehydro-*O*-methylpsychotrine (VIII) (48%).

[8] R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 1963, **28**, 1128; G. G. Price and M. C. Whiting, *Chem. and Ind.*, 1963, 775.
[9] *Cf.* ref. 6.
[10] R. Child and F. L. Pyman, *J. Chem. Soc.*, 1931, 41.
[11] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1961, 4939.
[12] A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schnider, *Helv. Chim. Acta*, 1960, **43**, 1459.

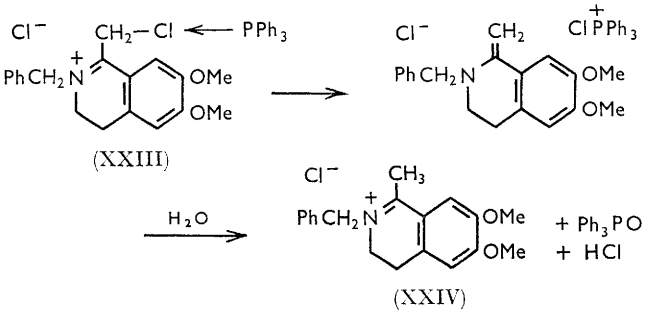
Whether the base-catalysed isomerisation was brought about by the phosphorane or by traces of sodamide is not known.

Catalytic hydrogenation of the phosphonium salt (XII) produced almost quantitatively the tetrahydroisoquinolylmethylphosphonium salt (XVI) from which hydroxide ion displaced one phenyl group, as expected [13] of a phenethyltriphenylphosphonium salt, yielding the diphenylphosphine oxide (XXII). With dimsylsodium



in dimethyl sulphoxide, the phosphonium salt gave the novel, very reactive phosphorane (XVIII) as shown by the formation of the *p*-chlorostyryltetrahydroisoquinoline derivative (XIX) in moderate yield on treatment with *p*-chlorobenzaldehyde. When the solution containing the phosphorane was treated with the ketone (I) at room temperature it gave the 2,2a-dehydro-compound (XXI), the structure of which was confirmed by high resolution mass spectroscopy and n.m.r., but the major product was the methylenebenzo[*a*]quinolizine (XX). The latter could have resulted from base-catalysed fission of the product (XXI) first formed but it seems more probable that it arose through direct reaction of the ketone (I) with methylenetriphenylphosphorane produced, together with the dihydroisoquinoline (XVII), as a result of initial abstraction by the dimsylsodium of the N–H proton of the phosphonium salt (XVI). Some triphenylphosphine was also isolated from the above reaction mixtures, arising from a Hofmann-type β-elimination.

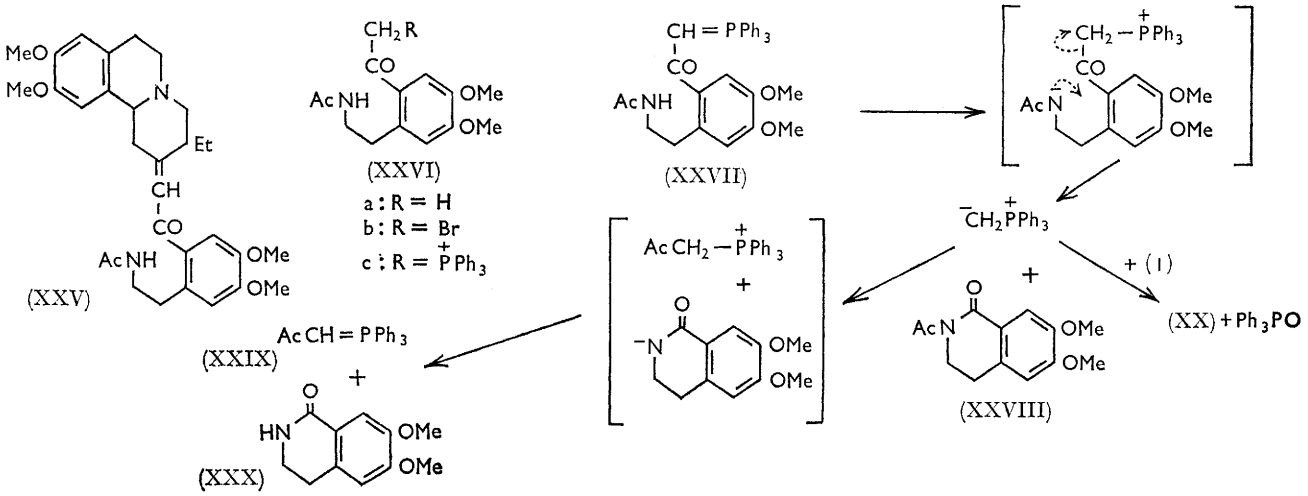
In view of the foregoing results, we attempted to obtain the *N*-benzyl derivative of the phosphonium salt (XVI) which could not undergo the undesirable base-catalysed fission when treated with base. Cyclisation of *N*-chloroacetyl-*N*-benzyl-3,4-dimethoxyphenethylamine with phosphoryl chloride gave the required 1-chloromethyldihydroisoquinolinium salt (XXIII), which reacted exothermically with triphenylphosphine in nitromethane or acetonitrile, but the product was the unexpected 1-methyldihydroisoquinolinium salt (XXIV). The latter is unlikely to have arisen through hydrolysis of an intermediate phosphonium salt, for the related salt (XII) had survived similar treatment, and we suggest that the reaction with triphenylphosphine followed the course indicated in the formulae.



A further approach to the emetine skeleton consisted in the attempted conversion of the ketone (I) by a Wittig reaction with the phosphorane (XXVII) into the phenacylidene derivative (XXV), which would be expected [12] to give the dehydro-*O*-methylpsychotrine (X), or its isomer (VIII), on acid hydrolysis. To obtain the desired phosphorane (XXVII), the bromo-ketone (XXVIb) derived from the readily available acetophenone derivative (XXVIa) [12] was treated with triphenylphosphine in nitromethane and the resulting phosphonium salt (XXVIc) was then extracted into

[13] J. Meisenheimer, J. Casper, M. Höring, W. Lauter, L. Lichtenstadt, and W. Samuel, *Annalen*, 1926, **449**, 213; G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 1929, 2342.

water and treated with base. The yield of phosphorane derived in this way was only about 20% because of competing enol-phosphonium salt formation [14] but, surprisingly, it exceeded 80% when the reaction between the bromo-ketone and triphenylphosphine was conducted in nitromethane–water. The phosphorane reacted rather slowly with, for example, benzaldehyde in boiling benzene and did not react in the desired manner with the ketone (I) at an elevated temperature in the absence of solvent, but gave, instead, a complex mixture of products. These were separated and identified as



N-acetylcorydaldine (XXVIII), corydaldine (XXX), triphenylphosphine oxide, acetonylidenetriphenylphosphorane (XXIX), and the methylenebenzo[*a*]quinolizine (XX). We suggest that the phosphorane (XXVII) underwent initial fragmentation through an intermediate phosphonium betaine to *N*-acetylcorydaldine and methylenetriphenylphosphorane, and that the latter reacted concurrently with the *N*-acetylcorydaldine and with the ketone (I). The first reaction could yield a mixture of acetonylidenetriphenylphosphorane with corydaldine, whereas the second would produce the methylenebenzo[*a*]quinolizine and triphenylphosphine oxide.

EXPERIMENTAL

Infrared spectra were measured for potassium chloride dispersions. The ^{1}H n.m.r. spectra were determined for solutions in deuteriochloroform, with tetramethylsilane as internal reference, by use of a Varian HA 100 spectrometer.

2-(3,4-*Dimethoxyphenethylcarbamoylmethylene*)-3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2H-*benzo*[a]-*quinolizine* (VII).—The anhydrous carboxylic acid (IIIc) hydrochloride [6] (7·5 g.) and thionyl chloride (15 ml.) were set aside at room temperature for 2½ hr., the excess of thionyl chloride was evaporated off *in vacuo* and a cooled (−10°) solution of the residual gum in dry chloroform (25 ml.) was treated with 3,4-dimethoxyphenethylamine (15 g.). The mixture was set aside at room temperature for 1 hr. and, after addition of 0·5N-aqueous potassium hydroxide (200 ml.), the chloroform was evaporated off *in vacuo* and the resulting gum was extracted into benzene (200 ml.). The benzene solution was washed several times with water to remove traces of 3,4-dimethoxyphenethylamine, dried (Na_2SO_4), and evaporated, and the residual crude amide (VII) was converted in ethanol (75 ml.) into the hydrogen oxalate (10·9 g.), m.p. 166—172° (efferv.). The base recovered from this salt was digested with ether (100 ml.) to give colourless needles (8·6 g.), m.p. 117—119°, of the *amide* (VII) (Found: C, 70·15; H, 7·35; N, 5·65. $C_{29}H_{38}N_2O_5$ requires C, 70·4; H, 7·75; N, 5·65%), δ 5·48 p.p.m. (1H, =CH–CO–). Heating the amide (VII) with 3,4-dimethoxyphenethylamine (1·5 mol.) at 180° (bath) for 2 hr., under nitrogen, did not give the isomer (VI) but a small quantity of *NN'*-bis(3,4-dimethoxyphenethyl)urea, m.p. 150—151° (from ethyl acetate), was isolated (Found: C, 64·75; H, 7·3; N, 7·25. Calc. for $C_{21}H_{28}N_2O_5$: C, 64·95; H, 7·25; N, 7·2%).

Cyclisation of the αβ-Unsaturated Amide (VII).—The amide (3·4 g.), dry benzene (70 ml.), and phosphoryl chloride (2 ml.) were heated under reflux together for 1 hr. and cooled, and the benzene was decanted from the resulting gum. A solution of the gum in dilute methanolic hydrogen chloride (12 ml.) was treated with ether to turbidity and set aside for 1 day, to give crystals (0·74 g.), m.p. 177—178° (efferv.) (from methanol), of 2,3-dehydro-*O*-methylpsychotrine (VIII) dihydrochloride. The methanol–ether liquors were evaporated and the residue, dissolved in a few ml. of methanol, was treated with concentrated aqueous hydrogen bromide (1 ml.) and with ether, to give crystals (0·45 g.)., m.p. 225° (efferv.), of 2-(3,4-*dihydro*-6,7-*dimethoxyisoquinolin*-1-*ylmethylene*)-3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2H-*benzo*[a]*quinolizine* (X) *dihydrobromide* (Found: C, 52·15; H, 5·8; Br, 24·5; N, 3·9; loss on drying, 4·2. $C_{29}H_{38}Br_2N_2O_4,1{\cdot}5H_2O$ requires C, 52·35; H, 6·2; Br, 24·05; N, 4·2; H_2O, 4·05%). A stirred solution of the dihydrobromide (0·23 g.) in water (15 ml.) was treated with ether (3 ml.) and basified with concentrated aqueous ammonia; nitrogen was passed through the resulting suspension of crystals to remove the ether and the crystals were collected and washed with water to yield the 2,2a-*dehydro-base* (X) (0·16 g.), m.p. 137—139° (Found: C, 72·8; H, 7·65; N, 5·75. $C_{29}H_{36}N_2O_4$ requires

[14] F. Hampson and S. Trippett, *J. Chem. Soc.*, 1965, 5129, and references cited therein.

C, 73·1; H, 7·6; N, 5·9%), δ 5·90 p.p.m. (1H, =CH–). Treatment of the base with methanolic hydrogen chloride and ether gave colourless prisms of the dihydrochloride, m.p. 222° (efferv.), $\lambda_{max.}$ (0·1N-aq. hydrochloric acid) 238, 289, 310, and 359 mμ (ε 15,900, 6350, 6930, and 7550).

Isomerisation of the 2-*Alkoxycarbonylmethylene*-3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2H-*benzo*[a]*quinolizines* (II) *and* (III).—(a) *With* N-*benzyldimethylamine*. The (+)-ester (IIIb) [6] was heated with *N*-benzyldimethylamine (2 mol.) at 180° (bath) for 4 hr.; the cooled product, dissolved in ethanol, had $[\alpha]_D^{25}$ −37·5° (*c* 2 in EtOH), corresponding to 28% isomerisation to the (−)-ester (Vb).

(b) *With sodium ethoxide*. A solution of the (+)-ester (IIIb) (2 g.) in anhydrous alcoholic sodium ethoxide [prepared by heating a solution of sodium (0·8 g.) in ethanol (16 ml.) under reflux with ethyl phthalate (2 g.) for 15 min.] was heated under reflux, under nitrogen, for 1¼ hr. The resulting (−)ester (Vb) was isolated [as described for the preparation of the amide (VI), see below] as a pale yellow gum (1·84 g.), $[\alpha]_D^{25}$ −218° (*c* 2 in EtOH) and was characterised as its (−)-*N*-(3,4-dimethoxyphenethyl) amide (VI). Similarly the *cis–trans*-esters (IIa) were each converted into the racemic ester (Vb).

(c) *With dimsylsodium*. The (+)-ester (IIIb) (1 g.) was added to a solution of dimsylsodium [prepared [8] from sodium hydride (0·17 g.) and dimethyl sulphoxide (6·5 ml.)] with cooling and, after 5 min. at room temperature, the mixture was shaken with ice-cold water (40 ml.) and ether (40 ml.). The filtered ethereal solution was washed with water, dried (Na_2SO_4), and evaporated, to yield the (−)-ester (Vb) (0·49 g.), $[\alpha]_D^{24}$ −227° (*c* 1·9 in EtOH), $\nu_{max.}$ 1738 cm.$^{-1}$ (C=O, non-conjugated).

(−)-2-(3,4-*Dimethoxyphenethylcarbamoylmethyl*)-3-*ethyl*-1,4,6,7-*tetrahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]-*quinolizine* (VI).—Anhydrous alcoholic sodium ethoxide [from sodium (4·75 g.), ethanol (76 ml.), and ethyl phthalate (9·5 g.)] was stirred at 0° during the successive addition of diethyl methoxycarbonylmethylphosphonate (14·4 g.) and the (−)-ketone (I) [6] (15·8 g.). Reaction was exothermic and occasional cooling was necessary to keep the temperature below 25°. After 3 hr. at room temperature, the solution was heated under reflux under nitrogen for 2 hr., cooled, and evaporated *in vacuo*. The residue was shaken with ice–water (350 ml.) and benzene (350 ml.), the benzene solution was extracted with 0·2N-hydrochloric acid (500 ml.), and the extract was washed with benzene and basified with aqueous potassium hydroxide. The liberated base was extracted into ether (2 × 300 ml.) and the ethereal solution was washed with water, dried (Na_2SO_4), and evaporated, to give the crude (−)-ester (Vb) (19·4 g.). The latter was heated with 3,4-dimethoxyphenethylamine (23·5 g.) and 2-hydroxypyridine (3·9 g.) at 164° for 5 hr. under nitrogen, and the mixture was cooled to *ca.* 120° and stirred into water (350 ml.). The resulting suspension of almost colourless needles was stirred with ether (80 ml.) and ethyl acetate (10 ml.) and filtered, to yield the (−)-*N*-(3,4-dimethoxyphenethyl) amide (VI) (20·3 g., 75%), m.p. 157—159°, $[\alpha]_D^{24}$ −184° (*c* 1 in MeOH). A recrystallised (ethyl acetate) sample had m.p. 159—160°, $[\alpha]_D^{24}$ −191° (*c* 1 in MeOH) (lit.,[3] m.p. 156—157°, $[\alpha]_D$ −189°) (Found: C, 70·15; H, 7·9; N, 5·65. Calc. for $C_{29}H_{38}N_2O_5$: C, 70·4; H, 7·75; N, 5·65%).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxyisoquinolin*-1-*ylidenemethyltriphenylphosphonium Bromide* (XIII).—A mixture of 1-chloromethyl-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride [10] (30 g.), triphenylphosphine (57 g., 2 mol.), and nitromethane (90 ml.) was set aside, with occasional shaking, at room temperature for 8 days. Suspended triphenylphosphine was dissolved by addition of acetone (1800 ml.) and the solution was treated with hydrogen bromide–acetic acid (50% w/v; 75 ml.), to yield yellow crystals (61·3 g., 80%), m.p. 218—220° (efferv.), of a hydrated hydrogen bromide *adduct* of the salt (XII) (Found: Br, 29·95; N, 1·75; P, 3·8. $C_{30}H_{30}Br_2NO_2P,HBr,5·5H_2O$ requires Br, 29·75; N, 1·75; P, 3·85%). The water of crystallisation and hydrogen bromide (1 mol.) were removed when the adduct was heated at 100° *in vacuo* (weight loss, 22·8. Calc. 22·3%). The adduct (69 g.) was heated with water (1050 ml.) and concentrated aqueous ammonia (17 ml.) and the solution obtained was cooled to 50°, treated with more concentrated aqueous ammonia (17 ml.), seeded, and stirred with benzene (525 ml.). After several hr. at room temperature, the resulting colourless crystals (50 g.), m.p. 220—222° (decomp.) of the *phosphonium bromide* (XIII) monohydrate were collected (Found: C, 64·05; H, 5·65; Br, 14·25; N, 2·6; P, 5·3; loss on drying, 3·5. $C_{30}H_{29}BrNO_2P,H_2O$ requires C, 63·9; H, 5·5; Br, 14·2; N, 2·5; P, 5·5; H_2O, 3·2%), $\nu_{max.}$ 3427 cm.$^{-1}$ (ε 48) (N–H), $\lambda_{max.}$ (EtOH) 227, 275—276, and 331 mμ (ε 40,800, 10,360, and 22,400), $\lambda_{max.}$ 0·01N-(HCl–EtOH) 207, 223, 256, 327, and 389 mμ (ε 45,800, 34,500, 11,300, 12,600, and 6060). The phosphonium bromide was hydrolysed by potassium hydroxide at room temperature, or by dilute hydrochloric acid at *ca.* 50°, to triphenylphosphine oxide and 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline.

Reactions of 3,4-*Dihydro*-6,7-*dimethoxyisoquinolin*-1-*ylmethylenetriphenylphosphorane* (XIV).—(a) *With* p-*chlorobenzaldehyde*. A solution of the anhydrous phosphonium bromide (XIII) (5·8 g.) in dry dimethyl sulphoxide (22 ml.) was stirred into a solution of dimsylsodium [from sodium hydride (0·27 g.) and dimethyl sulphoxide [8] (6·5 ml.)], with cooling, and the mixture was set aside at room temperature for 10 min. The resulting phosphorane (XIV) reacted exothermically with *p*-chlorobenzaldehyde (3 g.) to give a red solution which was shaken with water (100 ml.) and chloroform (100 ml.). The filtered (Hyflo) chloroform solution was washed with water, dried (Na_2SO_4), and evaporated, and the residue was freed from traces of chloroform by distillation with acetone. A solution of the residue in acetone (65 ml.) was acidified with ethanolic hydrogen chloride and the resulting suspension of orange crystals was diluted with ether (20 ml.) and filtered, to yield the hydrate *p*-chlorostyryldihydroisoquinoline (XV) hydrochloride (2·37 g.), m.p. 196° (efferv.). Recrystallisation from water gave yellow prisms, m.p. 200—201° (efferv.) (lit.,[12] 196—198°) (Found: C, 60·85; H, 5·2; Cl, 18·75; N, 3·7; loss on drying, 2·2. Calc. for $C_{19}H_{19}Cl_2NO_2,0·5H_2O$: C, 61·1; H, 5·4; Cl, 19·05; N, 3·75; H_2O 2·4%), $\lambda_{max.}$ (0·01N-HCl–EtOH) 221, 254, 313, and 329infl. mμ (ε 22,300, 61,300, 9280, and 6620).

(b) *With* 3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizin*-2-*one* (I). (i) The anhydrous phosphonium bromide (XIII) (2·9 g.) and dry anisole (20 ml.) were added to a stirred solution of sodamide [from sodium (0·51 g.) and liquid ammonia (50 ml.)] and the ammonia was evaporated off. The residual anisole suspension was heated to 80° in a current of nitrogen and cooled, and the filtered solution of phosphorane was heated at 150° (bath) with the ketone (I) (0·79 g.), under nitrogen, for 4 hr. The cooled, red solution was stirred with water (30 ml.)

for 2 hr. and the mixture was then acidified with N-hydrochloric acid and shaken with 1 : 1 benzene–light petroleum (b.p. 60—80°) (20 ml.). The aqueous solution was washed with benzene and basified with aqueous potassium hydroxide, and the liberated base was extracted into ether; the base recovered from the ethereal solution was dissolved in methanol, acidified (Congo Red) with 50% hydrogen bromide–acetic acid, and treated with ether to turbidity. The resulting crystals (0·15 g.) m.p. 229° (efferv.), were identical spectroscopically with those of the dihydrobromide of the 2,2a-dehydro-base (X) obtained by cyclisation of the amide (VII) as described above.

(ii) An anisole solution of the phosphorane (XIV), obtained as described under (i), was evaporated *in vacuo* and the residual phosphorane was heated with the ketone (I) (0·79 g.) under nitrogen at 145° (bath) for 3 hr. From the mixture, 2,3-dehydro-*O*-methylpsychotrine (VIII) was isolated as the dihydrobromide (1·04 g.), m.p. 192—194° (efferv.); it gave a crystalline base (VIII) and dihydrochloride which were identical (m.p., i.r. spectrum) with authentic specimens.[1]

1,2,3,4-*Tetrahydro*-6,7-*dimethoxyisoquinolin*-1-*ylmethyltriphenylphosphonium Bromide Hydrobromide* (XVI).—The phosphonium bromide (XIII) monohydrate (10 g.), in methanol (125 ml.), was treated with hydrogen bromide–acetic acid (50% w/v) to give pH *ca.* 2 and shaken with platinum oxide (0·5 g.) under hydrogen [uptake 577 ml. (21°/762 mm.) in 30 min.]. The filtered (Hyflo) solution was evaporated *in vacuo*, the residual gum was warmed with acetone (75 ml.), and the resulting suspension of colourless crystals was diluted with acetone (300 ml.) and filtered, to yield the hydrate *phosphonium bromide hydrobromide* (XVI) (11·22 g.), m.p. 191—192° (efferv.) (Found: C, 55·25; H, 5·05; Br, 24·35; N, 2·2; P, 4·6. $C_{30}H_{32}Br_2NO_2P,1·5H_2O$ requires C, 54·9; H, 5·35; Br, 24·4; N, 2·15; P, 4·7%), $\lambda_{max.}$ (0·01N-HCl–EtOH) 206, 225, 270, and 276 mμ (ε 63,000, 30,000, 4760, and 4980).

Reactions of the Tetrahydroisoquinolylmethylphosphonium Salt (XVI).—(a) *With hydroxide ion.* A solution of the phosphonium salt (XVI) (1 g.) in de-gassed methanol (10 ml.) was poured through a column of Deacidite FF (OH^- form), the eluate was evaporated, and the residue was treated with ether (25 ml.). The resulting colourless crystals (0·35 g.), m.p. 121—130°, were purified by evaporation of a filtered solution in cold benzene (3 ml.) and heating the residue with ether, to give 1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinolin*-1-*ylmethyldiphenylphosphine P*-oxide (XXII), m.p. 136—138° (Found: C, 70·3; H, 6·45; N, 3·4; P, 7·4. $C_{24}H_{26}NO_3P$ requires C, 70·8; H, 6·4; N, 3·45; P, 7·6%), $\lambda_{max.}$ (EtOH) 260, 265, 272, 283, and 286 mμ (ε 2270, 2790, 3270, 3600, and 3600). Its *hydrochloride* gave colourless plates, m.p. *ca.* 90° (with loss of solvent) and then 258—260° (efferv.) (from ethanol) (Found, on dried material: Cl, 8·1; N, 3·1; P, 7·1. $C_{24}H_{27}ClNO_3P$ requires Cl, 8·0; N, 3·15; P, 7·0%).

(b) *With dimsylsodium and* p-*chlorobenzaldehyde.* A solution of the anhydrous phosphonium salt (XVI) (5·75 g.) in dry dimethyl sulphoxide (22 ml.) was stirred into a solution of dimsylsodium [from sodium hydride (0·44 g.) and dimethyl sulphoxide [8] (10·5 ml.)], with cooling, and the mixture was set aside at room temperature for 10 min. Addition of *p*-chlorobenzaldehyde (2·57 g., 2 mol.) to the resulting phosphorane solution caused an exothermic reaction. The solution was shaken with water (100 ml.) and chloroform (100 ml.) and the filtered (Hyflo) chloroform solution was washed with water, dried (Na_2SO_4), and evaporated. The residual base was freed from traces of chloroform by distillation with benzene *in vacuo* and converted, in acetone (60 ml.), into a hydrochloride which gave colourless fine needles (1·38 g.) (from ethanol), m.p. 263° (efferv.) (lit.,[12] m.p. 243—245°), of the *p*-chlorostyryltetrahydroisoquinoline (XIX) hydrochloride (Found: C, 61·55; H, 5·85; Cl, 19·25; N, 3·9; loss on drying, 1·3. Calc. for $C_{19}H_{21}Cl_2NO_2,0·25H_2O$: C, 61·55; H, 5·8; Cl, 19·15; N, 3·8; H_2O, 1·2%), $\lambda_{max.}$ (0·01N-HCl–EtOH) 204, 218infl., 261, 287infl., and 298infl. mμ (ε 56,800, 22,300, 27,700, 9150, and 3750). An identical compound was obtained from the product of reduction of the *p*-chlorostyryldihydroisoquinoline (XV) with sodium borohydride in methanol at room temperature.

(c) *With dimsylsodium and the ketone* (I). A phosphorane solution, prepared as described under (b), was treated with the ketone (I) (1·98 g.) and set aside, under dry nitrogen, at room temperature for several days. The mixture was separated by conventional means into a basic and a neutral fraction; the latter yielded triphenylphosphine oxide, m.p. 154—155°, and a trace of triphenylphosphine, m.p. 78—80°. The basic fraction consisted of petroleum-soluble base (A) and petroleum-insoluble base (B) which were examined as follows. Base (A) was purified by chromatography (Al_2O_3) in benzene and treated, in ether, with ethanolic hydrogen chloride, to yield 3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2-*methylene*-2H-*benzo*[a]*quinolizine* (XX) *hydrochloride* (0·53 g.), m.p. 230—231° (efferv.) (Found: C, 66·35; H, 8·15; Cl, 11·4; N, 4·3. $C_{18}H_{26}ClNO_2$ requires C, 66·8; H, 8·05; Cl, 11·0; N, 4·35%). Treatment of an aqueous solution of this salt with aqueous ammonia gave the free *base* (XX), m.p. 80—81·5° (Found: C, 75·55; H, 8·85; N, 5·05. $C_{18}H_{25}NO_2$ requires C, 75·2; H, 8·75; N, 4·85%), δ 4·89 and 4·72 p.p.m. (=CH_2, quartets resulting from long-range coupling with the C-1- and C-3-protons). Base (B) was a complex mixture of compounds which was chromatographed (Al_2O_3); benzene–chloroform (2 : 1) eluted 3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2-2-(1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinolin*-1-*ylmethylene*)-2H-*benzo*[a]*quinolizine* (XXI), which gave a *dihydrochloride* (150 mg.) as colourless needles (from ethanol–ether); this formed a red glass at *ca.* 220° (efferv. from 230°) (Found, on dried material: C, 62·85; H, 7·25; N, 5·0. $C_{29}H_{40}Cl_2N_2O_4$ requires C, 63·15; H, 7·3; N, 5·1%). Mass spectral analysis of the derived amorphous base (XXI) confirmed the empirical formula $C_{29}H_{38}N_2O_4$ [M^+ 478·2820 (calc. 478·28314), M^{++} 239·14280] and showed prominent peaks at *m/e* 286 and 192 from fragmentation of the molecule at the 2a,1′- bond (see formula). The ^1H n.m.r. spectrum of the base showed one-proton doublets with centres at δ 5·40 and 4·95 p.p.m. (2a- and 1′-hydrogens) (*J* 8 c./sec.); the coupling was confirmed by double resonance.

2-*Benzyl*-1-*chloromethyl*-3,4-*dihydro*-6,7-*dimethoxyisoquinolinium Chloride* (XXIII).—A solution of *N*-benzyl-3,4-dimethoxyphenethylamine [15] (10 g.) in dry benzene (10 ml.) was added during 5 min. to a cooled solution of chloroacetyl chloride (2·1 g.) in dry benzene (20 ml.). After 1 hr., the mixture was stirred with water (250 ml.) and benzene (150 ml.), and the benzene solution was washed with dilute hydrochloric acid and with water, dried (Na_2SO_4), and evaporated, to leave crude *N*-benzyl-*N*-chloroacetyl-3,4-dimethoxyphenethylamine (6·8 g.). The

[15] J. S. Buck, *J. Amer. Chem. Soc.*, 1931, **53**, 2192.

crude product (4·3 g.) was heated with phosphoryl chloride (5 ml.) under reflux for 1 hr., the resulting red-brown solution was evaporated *in vacuo*, and the residue was dissolved in water (50 ml.) and washed with benzene (50 ml.). The aqueous solution was extracted with chloroform (3 × 75 ml.), the combined extract was dried (Na_2SO_4) and evaporated, and the residual gum was freed from traces of chloroform by distillation with acetone. A solution of the gum in acetone (35 ml.) was set aside and yielded deep yellow crystals (2·93 g.), m.p. 156° (efferv.), of the *isoquinolinium salt* (XXIII) (Found: C, 60·45; H, 6·0; Cl, 18·95; N, 3·65; loss on drying, 3·1. $C_{19}H_{21}Cl_2NO_2,0·67H_2O$ requires C, 60·35; H, 5·95; Cl, 18·8; N, 3·7; H_2O, 3·2%), $\lambda_{max.}$ (EtOH) 255, 326—327, and 393 mμ (ε 12,500, 9350, and 9740).

Reaction of the Isoquinolinium Salt (XXIII) *with Triphenylphosphine*.—When the isoquinolinium salt (XXIII) (1 g.) and triphenylphosphine (1·43 g.) were mixed in dry acetonitrile (3 ml.), an exothermic reaction occurred with liberation of hydrogen chloride. After 1½ hr. the mixture was treated with ethanol (20 ml.), concentrated aqueous perchloric acid (2 ml.), and ether (7 ml.), to give pale yellow crystals (0·94 g.), m.p. 179—180°, of *2-benzyl-3,4-dihydro-6,7-dimethoxy-1-methylisoquinolinium perchlorate* (Found: C, 57·95; H, 5·85; Cl, 8·8; N, 3·7. $C_{19}H_{22}ClNO_6$ requires C, 57·7; H, 5·6; Cl, 9·0; N, 3·55%), $\lambda_{max.}$ (EtOH) 249, 312, and 366 mμ (ε 18,000, 10,700, and 11,200). Its structure followed from its identity with the product of cyclisation of *N*-acetyl-*N*-benzyl-3,4-dimethoxyphenethylamine with phosphoryl chloride.

2-(2-Acetamidoethyl)-4,5-dimethoxyphenacylidenetriphenylphosphorane (XXVII).—The ketone (XXVIa) [12] (10 g.), in dry chloroform (60 ml.), was heated to *ca.* 55° and treated during 20 min. with a solution of bromine (1·9 ml.) in dry chloroform (15 ml.). The cooled solution was stirred with aqueous sodium hydrogen carbonate until effervescence ceased, the mixture was treated with light petroleum (b.p. 60—80°) (150 ml.), and the resulting crystals gave *2-(2′-acetamidoethyl)-2-bromo-4′,5′-dimethoxyacetophenone* (XXVIb) (4 g.), m.p. 132—134° (from ethanol) (Found: C, 49·2; H, 5·3; Br, 23·2; N, 3·9. $C_{14}H_{18}BrNO_4$ requires C, 48·85; H, 5·25; Br, 23·25; N, 4·05%). A stirred suspension of the bromoketone (3·08 g.) and triphenylphosphine (3·52 g., 1·5 mol.) in water (300 ml.) was treated with nitromethane (70 ml.) at room temperature and, after 1½ hr., the mixture was shaken with benzene (350 ml.), water (150 ml.), and ammonium chloride (*ca.* 2 g.). The aqueous solution was washed with benzene, stirred with ether (100 ml.) and light petroleum (b.p. 60—80°) (10 ml.), and basified with concentrated aqueous ammonia, to give crystals (3·88 g., 82%), m.p. 197—199°, of the *phosphorane* (XXVII) (Found: C, 72·9; H, 6·35; N, 2·55; P, 5·75. $C_{32}H_{32}NO_4P$ requires C, 73·15; H, 6·1; N, 2·65; P, 5·9%), $\lambda_{max.}$ (0·01N-NaOH–EtOH–H_2O) 214, 267, 275, and 292 mμ (ε 48,600, 11,100, 11,000, and 11,700).

Reaction of the Phosphorane (XXVII) *with the Ketone* (I).—A mixture of the phosphorane (5·04 g.) and the ketone (I) (1·85 g.) was heated under nitrogen at 185° (bath) for 4 hr. The cooled product was treated with ethyl acetate (25 ml.), to give unchanged phosphorane (2·3 g.), the ethyl acetate liquors were evaporated, and the residue was dissolved in benzene (100 ml.) and extracted with 0·05N-hydrochloric acid (200 ml.) [extract, solution (A)]. Evaporation of the benzene solution and treatment of the residue with ether gave mixed crystals (1·2 g.) which gave *N*-acetylcorydaldine (XXVIII) (0·33 g.), m.p. 132—133° (from methanol) (lit.,[16] 131°) (Found: C, 62·65; H, 5·85; N, 5·55. Calc. for $C_{13}H_{15}NO_4$: C, 62·65; H, 6·05; N, 5·6%). Its identity was established by comparison with an authentic sample prepared by acetylation (as described [17] for the des-methoxy-derivative) of corydaldine [18] (XXX) with acetic anhydride. Triphenylphosphine oxide (0·48 g.), m.p. 152—154°, was obtained by evaporation of the above methanolic liquors and crystallisation of the residue from light petroleum (b.p. 80—100°). Solution (A) was basified with aqueous potassium hydroxide and extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed (Al_2O_3; 60 g.), with, as eluant (i) benzene, (ii) ether–chloroform (1 : 1), and (iii) chloroform. Eluent (i) gave the 2-methylenebenzo[*a*]quinolizine (XX), characterised as the hydrochloride (0·27 g.), and unchanged ketone (I) (0·55 g.); eluent (ii) afforded a little acetonylidenetriphenylphosphorane (XXIX) as prisms (from ethyl acetate), m.p. and mixed m.p. with authentic material [19] 205—207° (Found: C, 79·25; H, 5·5; N, nil. Calc. for $C_{21}H_{19}OP$: C, 79·3; H, 6·0%); eluant (iii) yielded corydaldine (XXX) (60 mg.) as prisms (from ethanol), m.p. and mixed m.p. with authentic material [18] 172—173° (Found: C, 64·25; H, 6·05; N, 6·75. Calc. for $C_{11}H_{13}NO_3$: C, 63·75; H, 6·3; N, 6·75%).

The author thanks Dr. A. J. Everett and Mr. A. Ferrige for measuring and interpreting the n.m.r. spectra, Dr. S. M. Aftalion (Strathclyde) for the mass spectrum, and Dr. H. T. Openshaw for his interest and encouragement.

[8/1038 *Received, July 22nd,* 1968]

[16] A. Brossi, J. Würsch, and O. Schnider, *Chimia* (*Switz.*), 1958, **12**, 114.
[17] E. Bamberger and W. Dieckmann, *Ber.*, 1893, **26**, 1205.
[18] E. Späth and A. Dobrowsky, *Ber.*, 1925, **58**, 1274; E. L. Anderson, J. W. Wilson, and G. E. Ullyot, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1952, **41**, 643.
[19] F. Ramirez and S. Dershowitz, *J. Org. Chem.*, 1957, **22**, 41.