Studies on the Syntheses of Heterocyclic Compounds. Part CCCLXXXV.† Pschorr Reactions of 1-(2-Aminobenzyl)- and 1-(2-Aminophenethyl)-1,2,3,4-tetrahydroisoquinolines (Total Synthesis of Thalicsimidine)

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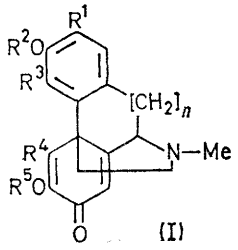
In order to obtain dienones coupled between the 8a- and 2'-positions, 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,8-dimethoxy-2-methylisoquinoline (IIIa) and the corresponding 5,6,7-trimethoxy- (IIIb) and 6-hydroxy-7-methoxy- (IIIc) derivatives were subjected to the Pschorr reaction. Compound (IIIb) afforded thalicsimidine (XIXa); compound (IIIc) gave 3-nitropredicentrine (XIXb) and the (2-hydroxybenzyl)isoquinoline (IIIj), together with the normal product (predicentrine) (XIXc) and the diosphenol-type compound (Ib) in poor yield. However, Pschorr reactions of 1-(2-amino-3,4,5-trimethoxyphenethyl)- (IIId) and 1-(2-amino-4-benzyloxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (IIIn) gave abnormal products, 1',2',3',4'-tetrahydro-5,6,6',7,7'-pentamethoxy-2'-methylspiro[indan-1,1'-isoquinoline] (XXXIa) and its 6-benzyloxy-analogue (XXXIb).

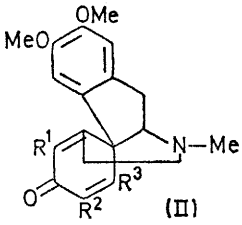
RECENTLY, we reported a general synthesis of morphinandienone-type alkaloids such as salutaridine (Ia) by the Pschorr reaction,[1-5] which has been widely applied to the synthesis of the aporphine alkaloids.[6] Battersby[7] and Osbond,[8] independently, also obtained morphinandienone-type compounds by the same method. We suggested [1] that the formation of another type of dienone (II), a hypothetical intermediate in the biogenesis of the erythrina [9] and hasbanan alkaloids,[10] would be theoretically possible. We have attempted to synthesise compounds of type (II) from benzylisoquinolines (IIIa—c) activated only at position 8a, or prevented from coupling to the 4a-position by steric hindrance, or activated at position 8a rather than at position 4a by appropriate substitution. We expected a better yield than in the formation of a morphinandienone from compound (IIIc), because of an increased electron density on the aromatic ring caused by the presence of a hydroxy-group, and also anticipated a one-step synthesis of the dehydrodiosphenol (Ib), which is a model compound in a synthesis of sinomenine.[11,12] We have also attempted to synthesise androcymbine (Ic) [13,14] by the Pschorr reaction of the 1-(2-aminophenethyl)isoquinoline (IIId).

Pschorr reactions of 6,7-dialkoxylated [1-5,8,11,12] and 6,7,8-trialkoxylated isoquinolines [7] have afforded only morphinandienone-type compounds and no dienones of type (II). We therefore deduced that nucleophilic attack of C-8a on an aromatic cation would only be possible for a 6,8-dialkoxylated isoquinoline lacking a 7-alkoxy-group, and examined the Pschorr reaction of 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,8-dimethoxy-2-methylisoquinoline (IIIa) in an attempt to make the dienone (IIb).



	R^1	R^2	R^3	R^4	R^5	n
a;	H	Me	OH	H	Me	1
b;	OMe	Me	H	H	H	1
c;	OMe	H	OMe	H	Me	2
d;	OMe	Me	H	OMe	Me	1
e;	OMe	Me	H	H	Me	2
f;	OMe	Me	OMe	H	Me	1

(I)



	R^1	R^2	R^3
a;	H	OMe	H
b;	H	H	OMe
c;	OMe	OMe	H

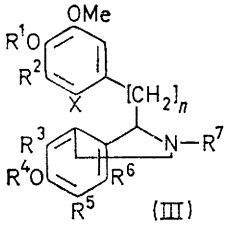
(II)

The aminoisoquinoline (IIIa) was synthesised in the usual way: a benzyne reaction [15] of 1-bromo-2,4-dimethoxybenzene (IV) [16] with acetonitrile in the presence of sodium amide gave 3,5-dimethoxybenzyl cyanide (V), which was reduced to 3,5-dimethoxyphenethylamine (VIa). Condensation of the amine with methyl 3,4-dimethoxyphenylacetate (VIIa), followed by a cyclisation of the amide (VIIIa), gave the 3,4-dihydro-

† Part CCCLXXXIV, T. Kametani, S. Takano, and T. Kobari, preceding paper.

[1] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968, 1398; *J. Chem. Soc.* (*C*), 1969, 520.
[2] T. Kametani, K. Fukumoto, and T. Sugahara, *Tetrahedron Letters*, 1968, 5459; *J. Chem. Soc.* (*C*), 1969, 801.
[3] T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1969, 1063.
[4] T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 2245.
[5] T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc.* (*C*), 1969, 2030.
[6] D. F. DeTar, *Org. Reactions*, 1967, **9**, 409.
[7] A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber, and J. Staunton, *Chem. Comm.*, 1968, 1214.
[8] B. Gregson-Allcott and J. M. Osbond, *Tetrahedron Letters*, 1969, 1771.
[9] D. H. R. Barton, R. James, G. W. Kirby, R. W. Turner, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1968, 1529.
[10] A. R. Battersby, 'Oxidative Coupling of Phenols,' ed. A. R. Battersby and W. I. Taylor, Marcel Dekker, New York, 1967, p. 133.
[11] T. Kametani, T. Sugahara, and K. Fukumoto, *Chem. and Ind.*, 1969, 833.
[12] T. Kametani, T. Sugahara, H. Yagi, K. Fukumoto, B. R. Pai, and R. Charubala, *J. Chem. Soc.* (*C*), 1970, 624.
[13] A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228.
[14] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968, 1001.
[15] T. Kametani, K. Ogasawara, T. Terui, K. Yamaki, and K. Fukumoto, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 1584.
[16] G. P. Rice, *J. Amer. Chem. Soc.*, 1926, **48**, 3125.

isoquinoline (IXa), the methiodide (Xa) of which was treated with sodium borohydride to afford 1,2,3,4-tetrahydro-2-methylisoquinoline (IIIe). Nitration of this isoquinoline gave the 2′-nitroisoquinoline (IIIf),

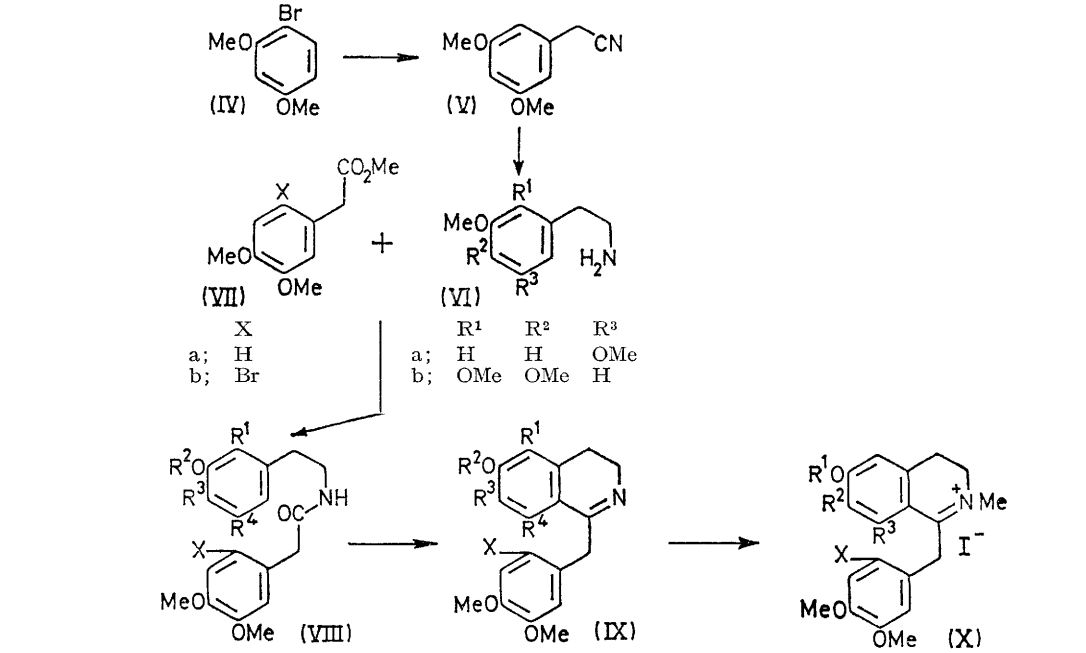


(III)

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	X	n
a;	Me	H	H	Me	H	OMe	Me	NH_2	1
b;	Me	H	OMe	Me	OMe	H	Me	NH_2	1
c;	Me	H	H	H	OMe	H	Me	NH_2	1
d;	Me	OMe	H	Me	OMe	H	Me	NH_2	2
e;	Me	H	H	Me	H	OMe	Me	H	1
f;	Me	H	H	Me	H	OMe	Me	NO_2	1
g;	Me	H	OMe	Me	OMe	H	H	H	1
h;	Me	H	OMe	Me	OMe	H	Me	H	1
i;	Me	H	OMe	Me	OMe	H	Me	NO_2	1
j;	Me	H	H	H	OMe	H	Me	OH	1
k;	Me	H	H	CH_2Ph	OMe	H	H	Br	1
l;	Me	H	H	Me	OMe	H	Me	NH_2	2
m;	Me	H	H	Me	OCH_2Ph	H	Me	NH_2	2
n;	CH_2Ph	OMe	H	Me	OMe	H	Me	NH_2	2
o;	Me	OMe	H	Me	OMe	H	Me	H	2

reduction of which afforded the 2′-aminoisoquinoline (IIIa). However, diazotisation of this compound, followed by thermal decomposition, gave only a deaminated product (IIIe) and no dienone (IIb).

1,2,3,4-tetrahydroisoquinoline (IIIg), which was subjected to the Eschweiler–Clarke reaction to give the 1,2,3,4-tetrahydro-2-methylisoquinoline (IIIh). Nitration of this compound afforded the (2-nitrobenzyl)-



(IV) (V) (VII) (VI) (VIII) (IX) (X)

	X
a;	H
b;	Br

	R^1	R^2	R^3
a;	H	H	OMe
b;	OMe	OMe	H

	R^1	R^2	R^3	R^4	X
a;	H	Me	H	OMe	H
b;	OMe	Me	OMe	H	H
c;	H	CH_2Ph	OMe	H	Br

	R^1	R^2	R^3	R^4	X
a;	H	Me	H	OMe	H
b;	OMe	Me	OMe	H	H
c;	H	CH_2Ph	OMe	H	Br

	R^1	R^2	R^3	X
a;	Me	H	OMe	H
b;	CH_2Ph	OMe	H	NO_2

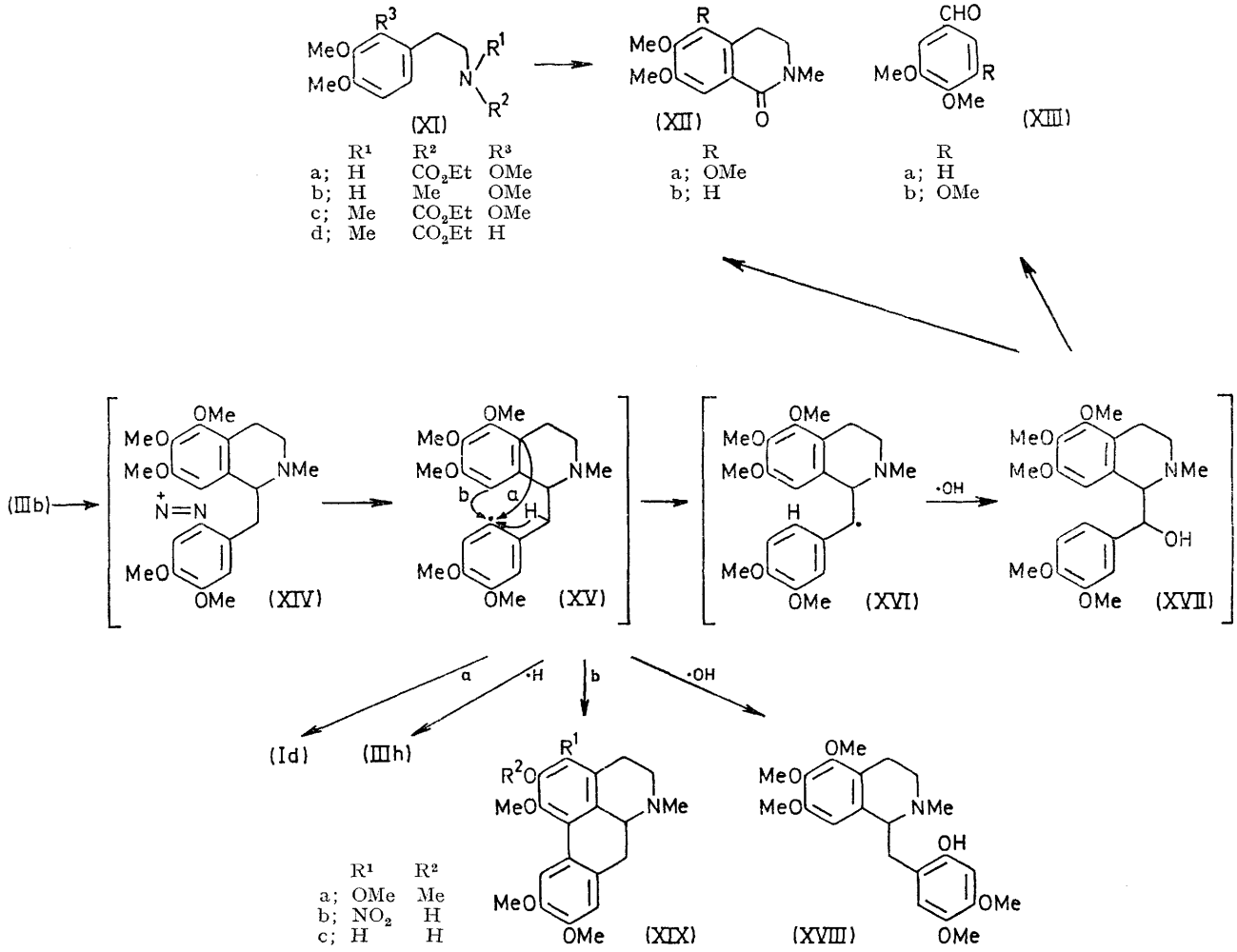
We expected that the introduction of a 5-substituent into the isoquinoline ring would hinder the access of an aromatic cation to C-4a, and would thus allow coupling at C-8a. We therefore investigated the Pschorr reaction of the 5,6,7-trimethoxyisoquinoline (IIIb), which was synthesised as follows. Fusion of 2,3,4-trimethoxyphenethylamine (VIb) [17] with methyl 3,4-dimethoxyphenylacetate (VIIa) [18] gave the corresponding amide (VIIIb), which was subjected to the Bischler–Napieralski reaction. The resulting 3,4-dihydroisoquinoline (IXb) was reduced with sodium borohydride to give the isoquinoline (IIIi). Reduction of the nitro-group gave compound (IIIb), and also an unidentified dimethyl derivative.

Pschorr reaction of the aminoisoquinoline (IIIb) followed by silica gel chromatography afforded six compounds. The first was identified as veratraldehyde (XIIIa), by spectral comparison with an authentic

[17] S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, 1966, **31**, 516.

[18] H. R. Snyder, J. S. Buck, and W. S. Ide, *Org. Synth.*, Coll. Vol. II, 1950, 333.

sample. The second showed n.m.r. signals for three *O*-methyl groups, an *N*-methyl group [τ ($CDCl_3$) 6·87], two pairs of methylene protons (A_2X_2 type), and an aromatic proton (τ 2·55), and its i.r. spectrum revealed an amide carbonyl absorption. It was therefore identified as 3,4-dihydro-5,6,7-trimethoxy-2-methylisoquinolin-1(2*H*)-one (XIIa), and was identical (i.r. spectrum) with an authentic sample prepared by the standard method as follows. The amine (VIb) was ethoxycarbonylated,



and the resulting amide (XIa) was reduced to give the *N*-methylphenethylamine (XIb). This was again ethoxycarbonylated, and cyclisation of the resulting urethane (XIc) followed by methylation with diazomethane gave the isoquinolone. We rationalise the formation of compounds (XIIIa) and (XIIa) as follows. An aromatic radical (XV) derived from the diazonium salt (XIV) abstracts one benzylic hydrogen atom to form the radical (XVI), which reacts with a hydroxy-radical to give the alcohol (XVII).[19] This could then be oxidised with an excess of nitrous acid.

The third product showed the betaine i.r. absorption and its u.v. spectrum indicated it to be a 1-benzyl-1,2,3,4-tetrahydroisoquinoline. Its n.m.r. spectrum showed an *N*-methyl group, five *O*-methyl groups, and three isolated aromatic protons. Therefore, it was tentatively assigned structure (XVIII). The u.v. spectrum of the fourth product showed typical 1,2,3,9,10-pentaoxygenated aporphine absorption[20] [$\lambda_{max.}$ (MeOH) 281, 301, and 311sh nm.] and the n.m.r. spectrum supported the presence of this system [τ ($CDCl_3$) 2·04 (11-H) and 3·21 (8-H)]. These data indicated this product to be thalicsimidine (XIXa), an alkaloid isolated from *Thalictrum simplex*,[21] and agree well with published values.[21,22]

The fifth product was a deamino-compound (IIIh), identical (spectra and m.p.) with an authentic sample.

The last product had the molecular formula $C_{21}H_{25}NO_5$, and its i.r. and u.v. spectra showed the presence of an α-methoxylated cross-conjugated cyclohexadienone

[19] T. Kametani, K. Fukumoto, M. Kawazu, and M. Fujihara, *J. Chem. Soc.* (*C*), 1970, 922.
[20] M. Shamma, R. J. Shine, and B. S. Dudock, *Tetrahedron*, 1967, **23**, 2887.
[21] Z. F. Ismailov, M. V. Jelezhenetskaya, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 136.
[22] Z. F. Ismailov, M. R. Yagudaev, and S. Yu. Yunusov, *Khim. prirod. Soedinenii*, 1968, **4**, 202; A. F. Ismailov and S. Yu. Yunusov, *ibid.*, p. 196.

system; this fact was also supported by the mass spectrum. The n.m.r. spectrum revealed an *N*-methyl and four *O*-methyl resonances, and signals for one olefinic and two aromatic protons, thus unambiguously confirming the structure (Id). No trace of compound (IIc) was observed.

In a third attempt to obtain a dienone of type (II) we used the 6-hydroxy-7-methoxyisoquinoline (IIIc), in which the electron density at position 8a is higher than that at position 4a. We also expected in this reaction to achieve a one-step synthesis of the dehydrodiosphenol-type compound (Ib), which was synthesised, in extremely low yield, during model experiments for the synthesis of sinomenine.[11,12] Diazotisation of the phenolic (2-aminobenzyl)isoquinoline (IIIc), prepared by the reduction of the nitroisoquinoline methiodide (Xb),[12] was carried out as before and the diazonium sulphate was thermally decomposed in an acidic medium to give five compounds.

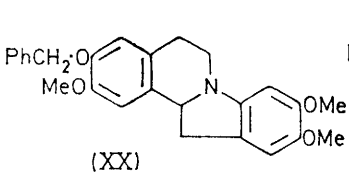
The first showed typical aporphine absorption in the u.v. spectrum, and signals for two aromatic protons (8-H and 11-H) at τ 3·20 and 1·98 in the n.m.r. spectrum. The i.r. spectrum showed absorptions for a nitro-group and an associated phenolic hydroxy-group, the latter disappearing on acetylation. These data indicated the compound to be 3-nitropredicentrine (XIXb).

The second product (M^+ *m/e* 357) showed i.r. absorptions characteristic of an ammonium salt and a phenolic hydroxy-group, and its n.m.r. spectrum revealed the presence of one *N*- and three *O*-methyl groups. The u.v. spectrum showed an absorption maximum at 280 nm. We first thought that this compound was the 6,7,12,12a-tetrahydrodibenzo[*b*,*g*]-indolizinium salt (XXIc), formed by the intramolecular coupling of an aromatic cation (or an aromatic radical), derived from the diazonium salt, with the nitrogen atom. However, direct comparison with an authentic sample, prepared by the benzyne reaction described later, proved our assumption to be incorrect, and the compound remained unidentified because of a shortage of material.

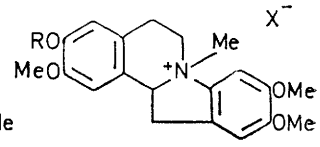
The third product had a betaine structure, showing broad i.r. absorptions centred at 2550 and 1790 cm.$^{-1}$. Its n.m.r. spectrum showed the presence of four isolated aromatic protons, three *O*-methyl groups, and an *N*-methyl group. The u.v. spectrum was of the 1-benzyl-1,2,3,4-tetrahydro-6,7-dioxygenated-isoquinoline type, and the mass spectrum (*m/e* 192) indicated a 1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-2-methylisoquinoline skeleton. Since the compound had a betaine structure, the second phenolic hydroxy-group was assigned to the 2′-position, and the structure (IIIj) was deduced.

The fourth product was identified as (±)-predicentrine (XIXc) by comparison with an authentic sample [13] (spectroscopic and chromatographic methods). The fifth, obtained in poor yield, showed dienone absorption in its i.r. and u.v. spectra, and t.l.c. comparison with an authentic specimen [12] indicated it to be the diosphenol-type compound (Ib). No compounds of type (II) were observed.

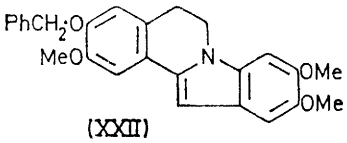
An authentic sample of compound (XXIc) was synthesised by application of the benzyne reactions to the (2-bromobenzyl)isoquinoline (IIIk) as follows. Fusion of 3-benzyloxy-4-methoxyphenethylamine with methyl 2-bromo-4,5-dimethoxyphenylacetate (VIIb) gave the corresponding amide (VIIIc), cyclisation of which afforded the 3,4-dihydroisoquinoline (IXc). Reduction of this, followed by benzyne reaction of the resulting 1,2,3,4-tetrahydroisoquinoline (IIIk) with sodium amide in liquid ammonia, gave the 5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizine (XX) and the 5,6-dihydro-analogue (XXII). Methylation of the former, followed by debenzylation of the quaternary iodide (XXIa) with hydrochloric acid, gave the 5,6,12,12a-tetrahydro-3-hydroxy-2,9,10-trimethoxy-7-methyldibenzo[*b*,*g*]indolizinium salt (XXIb), which was treated with wet silver oxide to afford compound (XXIc).



(XX)



(XXI)



(XXII)

	R	X
a;	CH_2Ph	I
b;	H	I
c;	H	OH

Our lack of success in obtaining compounds of type (II) is probably due to the fact that the approach of C-8a to an aromatic cation would be sterically hindered by the 1-benzyl group. The Pschorr reactions of our phenolic (2-aminobenzyl)isoquinolines proved unsuitable for syntheses of morphinandienone- and aporphine-type compounds, because of the many side reactions.

Finally, the synthesis of androcymbine (Ic) was attempted by a Pschorr method. We have previously reported the synthesis of the homomorphinandienone-type compound (Ie) by Pschorr reactions of the (2-aminophenethyl)isoquinolines (IIIl and m),[23] and have also synthesised c-norandrocymbine (If) [24] by the same method. We therefore examined the Pschorr reactions of the (2-aminophenethyl)isoquinolines (IIId and n) under a variety of conditions.

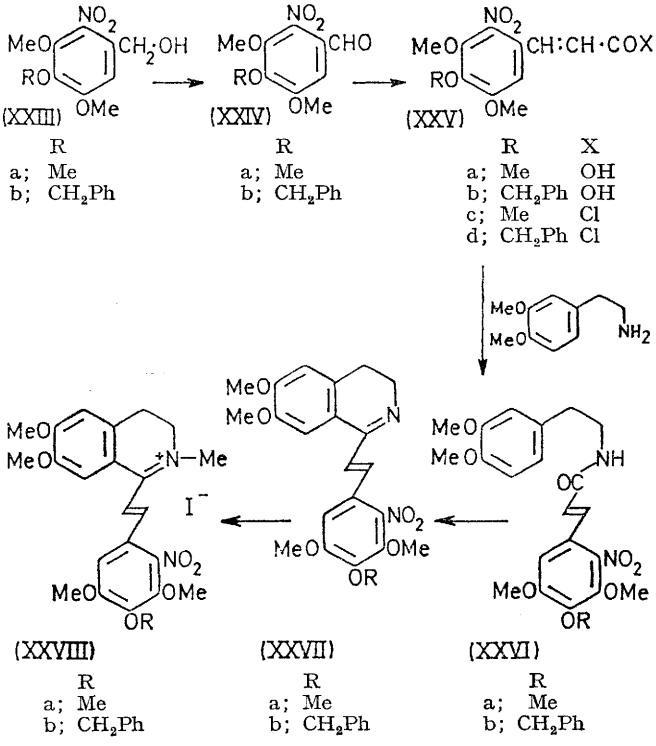
The starting aminoisoquinolines were synthesised as follows. 3,4,5-Trimethoxy-2-nitrobenzyl alcohol (XXIIIa) [25] and its 4-benzyloxy-analogue (XXIIIb) were oxidised with active manganese dioxide and the

[23] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *J. Chem. Soc.* (*C*), 1968, 3084.

[24] T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 1809.

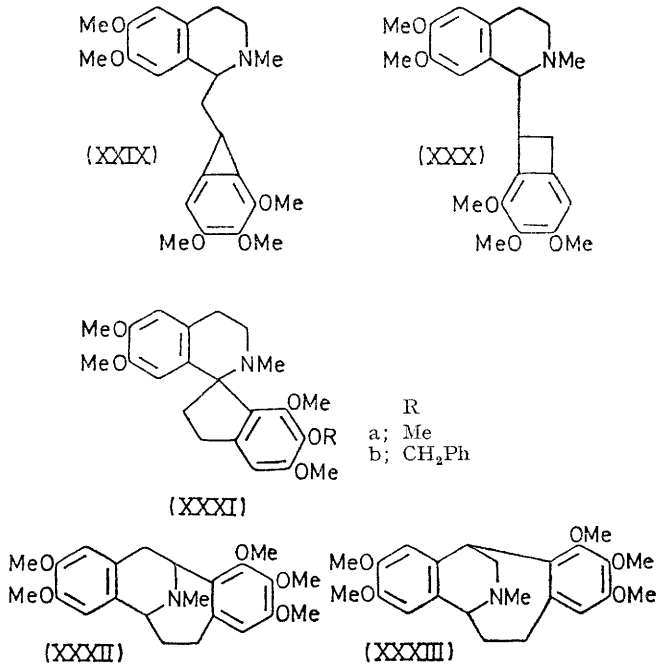
[25] K. Hirai and K. Harada, *J. Pharm. Soc. Japan*, 1960, **80**, 1429.

aldehydes (XXIVa and b) obtained were subjected to the Knoevenagel reaction with malonic acid to give the corresponding cinnamic acids (XXVa and b).[26] Schotten–Baumann reaction of the cinnamoyl chlorides (XXVc and d) (prepared with phosphorous pentachloride) with 3,4-dimethoxyphenethylamine afforded the amides (XXVIa and b), Bischler–Napieralski cyclisation of which gave the corresponding 3,4-dihydroisoquinolines (XXVIIa and b). The methiodides (XXVIIIa and b) were then reduced first by zinc and hydrochloric acid and then with hydrogen over Adams catalyst.



The (2-aminophenethyl)isoquinoline (IIId) was diazotised with sodium nitrite (6 equiv.) in sulphuric acid and the mixture was heated to give three compounds.

The first was identified as 3,4,5-trimethoxybenzaldehyde (XIIIb) by comparisons (m.p. and spectroscopy) with an authentic sample. The second was 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolin-1(2*H*)-one (XIIb), identical with an authentic sample [27] prepared from the urethane (XId). The third (36% yield) had the molecular formula $C_{23}H_{29}NO_5$, and its u.v. spectrum showed the presence of a 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline system but not of a homoaporphine system.[28] The n.m.r. spectrum revealed signals for three aromatic protons and one *N*- and five *O*-methyl groups. The *N*- and *O*-methyl resonances were at abnormally high field, probably owing to the existence of several groups on the same ring. Possible structures for this compound could then be limited to (XXIX), (XXX), (XXXIa), (XXXII), and (XXXIII). All but (XXXIa) were ruled out as follows.

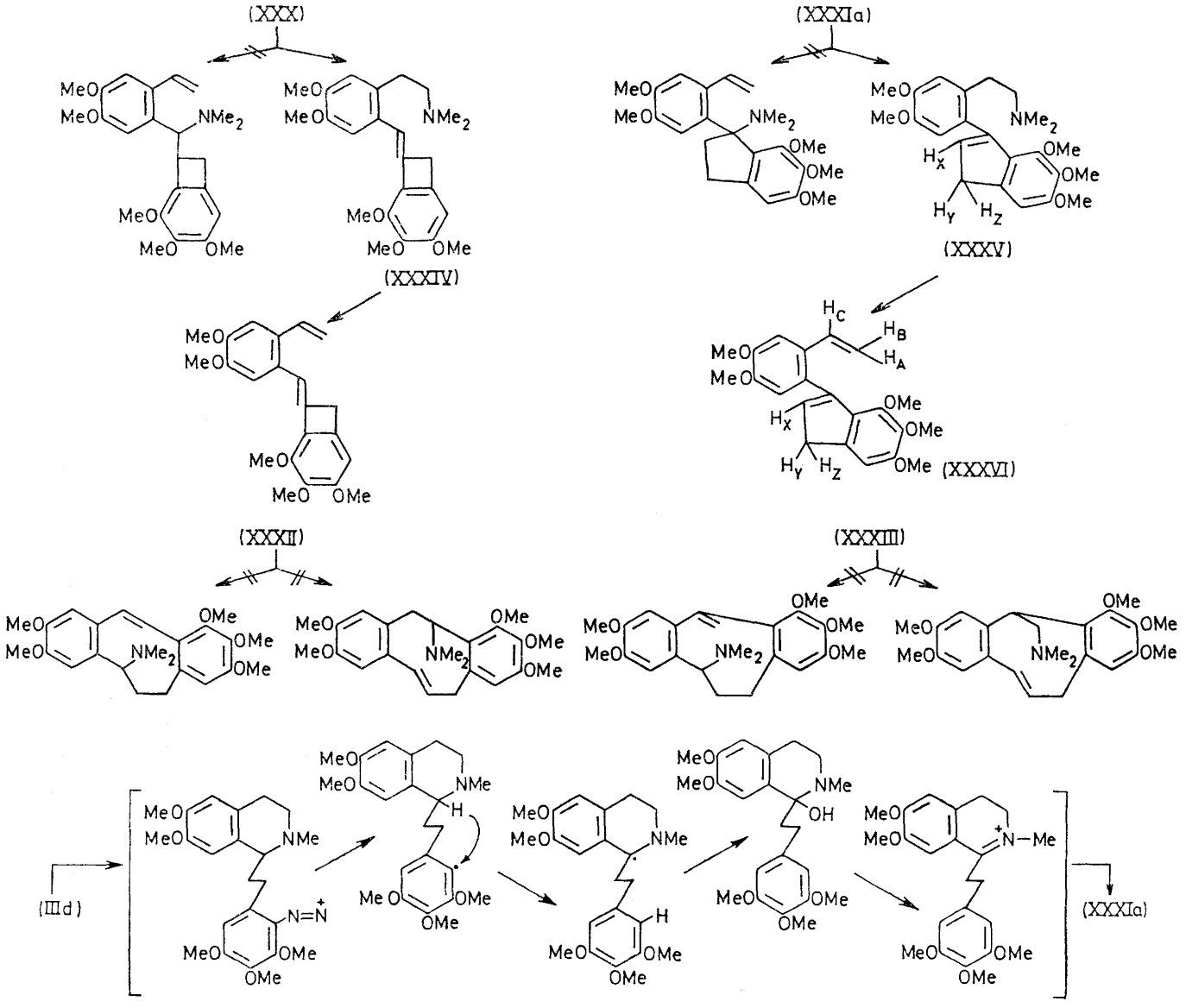


Treatment of the compound with cold concentrated sulphuric acid had no effect; this fact ruled out the cyclopropene structure (XXIX).[29] Hofmann degradation gave a methine base, the n.m.r. spectrum of which showed a signal for only one olefinic proton [τ 3·84 (t, J 1·7 Hz)], and the mass spectrum (M^+ *m/e* 413) of which showed a strong fragment ion [$M^+ - (CH_2{\cdot}NMe_2)$] at *m/e* 355. The methine base must then be either (XXXIV) or (XXXV). A second Hofmann degradation caused loss of trimethylamine, and the n.m.r. spectrum of the product showed the presence of a vinyl group as a typical ABX pattern. Moreover, the spectrum revealed an olefinic proton signal at τ 3·84 (t, J 1·7 Hz) coupled with a methylene doublet at τ 6·55 (proved by decoupling). Both chemical shifts were closely similar to those for indene,[30] and the coupling constant between an olefinic proton and its neighbouring methylene protons in cyclopentene is known to be J 1·4 Hz,[31] in contrast with the coupling constant of the allylic system in *cis*-benzylidenebenzocyclobutene [32] (J 0·9 Hz). This product was therefore assigned structure (XXXVI), which implies that the Pschorr reaction product has structure (XXXIa). Furthermore, oxidation of the Pschorr product with an excess of potassium per-

[26] E. Hardegger and H. Corrodi, *Pharm. Acta Helv.*, 1964, **39**, 101.
[27] T. Kametani, M. Koizumi, and K. Fukumoto, *J. Pharm. Soc. Japan*, 1970, **90**, 1331.
[28] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1968, 1003.
[29] E. P. Kohler and J. B. Conant, *J. Amer. Chem. Soc.*, 1917, **39**, 1404.
[30] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, 'N.M.R. Spectra Catalog,' No. 227, Varian Associates, Palo Alto, California, 1962.
[31] K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, 1961, **83**, 226; G. V. Smith and H. Kriloff, *ibid.*, 1963, **85**, 2016.
[32] A. T. Vlomquist and V. J. Hruby, *J. Amer. Chem. Soc.*, 1967, **89**, 4996.

manganate did not furnish the isoquinolone (XIIb), indicating that it was not the cyclobutane derivative (XXX).

The spiro-compound was characterised by spectroscopic comparison with the spiroisoquinoline (XXXIa). A slight modification of the reaction conditions in the case



SCHEME

Products of the Pschorr reaction of the (2-aminophenethyl)isoquinoline (IIId) under various conditions

(IIId) (mole)	$NaNO_2$ (moles)	5% H_2SO_4 (moles)	Medium	Decomp. Temp.	Time (hr.)	Yield (%) (XXXIa)	(XIIIb)	(XIIb)	(XId)
1	6	14·5	H_2SO_4	70°	1	36	2·5	4·8	
1	1·7	6	H_2SO_4	70	1	34·5			
1	1	6	AcONa	20—30	3				
1	6	5	H_2SO_4	70	1	9	3·4	4·0	4·8

A mechanism for the formation of compound (XXXIa) is shown in the Scheme.

Similar treatment of the 4′-benzyloxy-analogue (IIIn) afforded the 5′-benzyloxy-analogue (XXXIb) of the spiroisoquinoline (XXXIa), along with 4-benzyloxy-3,5-dimethoxybenzaldehyde and the isoquinolone (XIIb).

of the aminoisoquinoline (IIId) gave a deaminated product (Io), identical with an authentic sample,[24] as well as compounds (XXXIa), (XIIIb), and (XIIb). The results are summarised in the Table.

We are now investigating the synthesis of androcymbine and related compounds by the same method.

EXPERIMENTAL

I.r. spectra were measured with a Hitachi EPI-3 recording spectrophotometer, u.v. spectra with a Hitachi recording spectrophotometer, n.m.r. spectra with a Hitachi H-60 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi RMU-7 spectrometer.

3,5-Dimethoxybenzyl Cyanide (V).—To a stirred solution of sodium (26 g.) in liquid ammonia (1 l.) was added a small amount of iron(III) chloride and the mixture was stirred for 2 hr. Acetonitrile (36 g.) was added and then 1-bromo-2,4-dimethoxybenzene (IV) [16] (48 g.) with stirring, and stirring was continued for a further 3·5 hr. The excess of sodium amide was decomposed with ammonium chloride (80 g.) and the mixture was poured into water and extracted with benzene. The extract was washed with 10% hydrochloric acid, 10% sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to leave a brown oil, which was distilled *in vacuo* to give the nitrile (V) (10·8 g.) as an oil, b.p. 152—155°/6 mm., which gradually solidified and afforded needles, m.p. 50—53° (from benzene–hexane) (lit.,[33] 53°), $\nu_{max.}$ ($CHCl_3$) 2250 cm.$^{-1}$ (C≡N).

3,5-Dimethoxyphenethylamine (VIa).—A mixture of the cyanide (V) (35 g.) and ethanol (200 ml.) was saturated with ammonia gas, and the resulting mixture was reduced with hydrogen (100 atmos.) at 80° over W-2 Raney nickel (15 g.) for 4·5 hr., with shaking in an autoclave. The nickel was filtered off and the filtrate was evaporated to leave an oil, which was distilled in a current of nitrogen *in vacuo* to give the phenethylamine (VIa) (30 g.) as an oil, b.p. 130—141°/6 mm.; the hydrochloride afforded scales, m.p. 156° (from ethanol–ethyl acetate) (lit.,[34] 157—158°).

N-(3,5-Dimethoxyphenethyl)-3,4-dimethoxyphenylacetamide (VIIIa).—A mixture of the phenethylamine (VIa) (11·9 g.) and methyl 3,4-dimethoxyphenylacetate (VIIa) (12·5 g.) was heated at 180° for 2·5 hr. under a current of nitrogen, cooled, and recrystallised from benzene–hexane to give the *amide* (VIIIa) (20 g.) as pale yellow needles, m.p. 88—91° (Found: C, 67·2; H, 7·15. $C_{20}H_{25}NO_5$ requires C, 66·85; H, 7·0%), $\nu_{max.}$ ($CHCl_3$) 3370 (NH) and 1653 cm.$^{-1}$ (C=O).

3,4-Dihydro-6,8-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (IXa).—A solution of the amide (VIIIa) (20 g). and phosphoryl chloride (20 g.) in dry benzene (100 ml.) was refluxed for 1·5 hr. and the solvent was then distilled off. The residue was poured into hexane and the separated solid afforded the *3,4-dihydroisoquinoline* (IXa) *hydrochloride* (19 g.) as prisms, m.p. 159—162° (from ethanol–ether) (Found: C, 62·2; H, 6·55. $C_{20}H_{23}NO_4$,HCl,0·5H_2O requires C, 62·05; H, 6·5%), $\nu_{max.}$ ($CHCl_3$) 3350—3500 cm.$^{-1}$ (OH) (water of crystallisation).

1,2,3,4-Tetrahydro-6,8-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methylisoquinoline (IIIe).—To the 3,4-dihydroisoquinoline [prepared from the foregoing hydrochloride (19 g.)] was added methyl iodide (30 ml.) and the mixture was set aside overnight at room temperature in a current of nitrogen. The excess of methyl iodide was then evaporated off and the residue was triturated with ether to give the methiodide (Xa) (17·6 g.) [$\nu_{max.}$ ($CHCl_3$) 1615 cm.$^{-1}$]. This was dissolved in ethanol (100 ml.), and sodium borohydride (3 g.) was added in portions; the mixture was then set aside for 2 hr. at room temperature. The solvent was distilled off and the residue was decomposed with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *1,2,3,4-tetrahydro-2-methylisoquinoline* (IIIe) (14·5 g.), which yielded prisms, m.p. 106·5—109° (from ethanol–ether) (Found: C, 70·25; H, 7·7. $C_{21}H_{27}NO_4$ requires C, 70·55; H, 7·6%), τ ($CDCl_3$) 7·62 (NMe, 3H, s), 6·25 (2 × OMe, 6H, s), 6·23 (OMe, 3H, s), 6·20 (OMe, 3H, s), 3·80 (7-H, 1H, d, *J* 2 Hz), 3·70 (5-H, 1H, d, *J* 2 Hz), and 3·25br (ArH, 3H, s).

1,2,3,4-Tetrahydro-6,8-dimethoxy-1-(4,5-dimethoxy-2-nitrobenzyl)-2-methylisoquinoline (IIIf).—Concentrated nitric acid (*d* 1·38; 25 ml.) in glacial acetic acid (10 ml.) was added dropwise to a solution of the 1,2,3,4-tetrahydroisoquinoline (IIIe) (10 g.) in glacial acetic acid (60 ml.) with stirring at room temperature during 0·5 hr. The mixture was then stirred for a further 0·5 hr. with cooling, poured into water, and basified with ammonia. The separated oil was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated to leave the nitroisoquinoline (IIIf) (11 g.) as a brown viscous syrup, τ ($CDCl_3$) 7·51 (NMe, 3H, s), 6·40 (OMe, 3H, s), 6·27 (2 × OMe, 6H, s), 6·10 (OMe, 3H, s), 3·80br (5-H and 7-H, 2H, s), 3·53 (6′-H, 1H, s), and 2·57 (3′-H, 1H, s).

1-(2-Amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,8-dimethoxy-2-methylisoquinoline (IIIa).—(a) *Reduction with zinc.* Zinc powder (20 g.) was added to a mixture of the nitroisoquinoline (IIIf) (11 g.), concentrated hydrochloric acid (200 ml.), and water (50 ml.) with stirring at room temperature during 80 min.; the mixture was then stirred for 1 hr. at the same temperature, basified with ammonia, and extracted with chloroform. The extract was washed with 10% sodium hydroxide and water, dried (Na_2SO_4), and evaporated to leave a brown viscous syrup, which was purified by silica gel (100 g.) column chromatography with chloroform–methanol (98 : 2 v/v) as eluant to afford the aminoisoquinoline (IIIa) (1·7 g.) as a pale yellow viscous syrup, τ ($CDCl_3$) 7·60 (NMe, 3H, s), 6·28 (OMe, 3H, s), 6·25 (OMe, 3H, s), 6·20 (OMe, 3H, s), 6·15 (OMe, 3H, s), 5·75br (NH_2, 2H, exchangeable), 3·82 (7-H, 1H, d, *J* 2 Hz), 3·68 (5-H, 1H, d, *J* 2 Hz), 3·77 (3′-H, 1H, s), and 3·52 (6′-H, 1H, s). The *picrate* gave yellow needles, m.p. 118—119° (from chloroform–ether) (Found: C, 51·4; H, 4·75. $C_{27}H_{31}O_{11}N_5$,0·33$CHCl_3$ requires C, 51·15; H, 4·9%), and gave a positive Beilstein test.

(b) *Catalytic reduction.* The nitroisoquinoline (IIIf) (600 mg.) in ethanol (150 ml.) was hydrogenated over platinum oxide (200 mg.). After absorption of the calculated amount of hydrogen (*ca.* 100 ml.), the catalyst was filtered off, and the solution was distilled to leave the aminoisoquinoline (IIIa) (400 mg.), which was purified by silica gel chromatography.

Pschorr Reaction of the Aminoisoquinoline (IIIa).—To a solution of the aminoisoquinoline (IIIa) (1·7 g.) in 5% sulphuric acid (100 ml.) 10% sodium nitrite solution (13 ml.) was added drop by drop at 0—5° with stirring during 10 min. The mixture was stirred for 1 hr. at room temperature, then heated at 70° with stirring for a further 1 hr., basified with ammonia, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a gum (870 mg.), which was subjected to silica gel (20 g.) column chromatography. Elution with chloroform gave the deaminated product (IIIe) (50 mg.) as prisms, m.p. 106·5—109° (from ethanol–ether), identical (spectral data) with an authentic sample. Further elution, with

[33] R. Adams, S. MacKenzie, jun., and S. Loewe, *J. Amer. Chem. Soc.*, 1948, **70**, 664.

[34] F. Benington, R. D. Morin, L. C. Clark, jun., and R. P. Fox, *J. Org. Chem.*, 1958, **23**, 1979.

chloroform–methanol (99 : 1, 98 : 2, 96 : 4, and 95 : 5) gave tars, which could not be purified.

2-(3,4-*Dimethoxyphenyl*)-N-(2,3,4-*trimethoxyphenethyl*)-*acetamide* (VIIIb).—A mixture of 2,3,4-trimethoxyphenethylamine (VIb) (10·1 g.) and methyl 3,4-dimethoxyphenylacetate (VIIa) (10·0 g.) was heated at 180° for 1·5 hr., then cooled to give a brown solid, which yielded the *amide* (VIIIb) (18·2 g.) as needles, m.p. 102—103·5° (from benzene–hexane) (Found: C, 64·4; H, 6·7; N, 3·95. $C_{21}H_{27}NO_6$ requires C, 64·75; H, 7·0; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 3350 (NH) and 1650 cm.$^{-1}$ (amide C=O).

3,4-*Dihydro*-5,6,7-*trimethoxy*-1-(3,4-*dimethoxybenzyl*)*isoquinoline* (IXb).—A mixture of the amide (VIIIb) (15 g.), phosphoryl chloride (21 ml.), and dry toluene (120 ml.) was heated at 100° for 1 hr. Excess of toluene and phosphoryl chloride were evaporated off and the residue was washed with hot benzene (100 ml. × 2) and used immediately because of difficulty in crystallisation.

1-(3,4-*Dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-5,6,7-*trimethoxyisoquinoline* (IIIg).—To a stirred solution of the 3,4-dihydroisoquinoline (IXb) hydrochloride (15 g.) in methanol (200 ml.) sodium borohydride (6 g.) was added in portions during 1·5 hr. The mixture was stirred for a further 1 hr., then evaporated, and the residue was basified with 10% ammonia and extracted with ether (100 ml. × 3). The extract was washed with water (100 ml. × 2), dried (Na_2SO_4), and evaporated to leave the 1,2,3,4-tetrahydroisoquinoline (IIIg) (10·7 g.) as a yellowish-brown syrup, which was chromatographed on silica gel (200 g.) with chloroform [fractions (300 ml.) 1—7] and chloroform–methanol (99 : 1 v/v; fractions 8—24) as eluants. Evaporation of fractions 8—24 gave the 1,2,3,4-tetrahydroisoquinoline (IIIg) as a yellow syrup; the *hydrochloride* afforded colourless needles, m.p. 125—126° (from methanol–ether) (Found: N, 3·75. $C_{21}H_{27}NO_5$,HCl requires N, 3·4%).

1-(3,4-*Dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-5,6,7-*trimethoxy*-2-*methylisoquinoline* (IIIh).—To a stirred solution of the 1,2,3,4-tetrahydroisoquinoline (IIIg) (7·6 g.) in methanol (200 ml.) 37% formalin was added, and stirring was continued for 1·5 hr. Sodium borohydride (6 g.) was then added in portions during 30 min. and the resultant mixture was stirred for 1 hr. and evaporated. The residue was basified with 10% ammonia and extracted with ether (100 ml. × 3). The extract was washed with water (100 ml. × 2), dried (Na_2SO_4), and evaporated to give a yellow syrup (6·2 g.), which was chromatographed on silica gel (150 g.) with chloroform [fractions (300 ml.) 1—5] and chloroform–methanol (99 : 1 v/v; fractions 6—21) as eluants. Fractions 6—21 gave the 1,2,3,4-tetrahydroisoquinoline (IIIh) (5·7 g.) as a yellowish-brown syrup; the *perchlorate* yielded pale yellow prisms, m.p. 160—162° (from methanol–ether) (Found: C, 54·1; H, 6·2; N, 3·35. $C_{22}H_{29}NO_5$,$HClO_4$ requires C, 54·15; H, 6·2; N, 2·85%), τ ($CDCl_3$) 7·49 (NMe, 3H, s), 4·04 (8-H, 1H, s), 3·41 (ArH, 1H, s), and 3·28 (ArH, 2H, s).

1-(4,5-*Dimethoxy*-2-*nitrobenzyl*)-1,2,3,4-*tetrahydro*-5,6,7-*trimethoxy*-2-*methylisoquinoline* (IIIi).—To a stirred solution of the 1,2,3,4-tetrahydroisoquinoline (IIIh) (5·5 g.) in glacial acetic acid (35 ml.), concentrated nitric acid (15 ml.) was added dropwise during 30 min. with cooling. The mixture was stirred at 0—5° for 10 min., poured into ice–water (500 ml.), basified with ammonia, and extracted with chloroform (100 ml. × 5). The extract was washed with water (100 ml. × 2), dried (Na_2SO_4), and evaporated to leave a reddish-brown gum (6·0 g.); the *hydrochloride* gave yellow needles, m.p. 186—187° (from methanol–ether) (Found: C, 56·45; H, 6·25; N, 6·3. $C_{22}H_{28}N_2O_7$,HCl requires C, 56·35; H, 6·25; N, 5·95%), τ ($CDCl_3$) 7·57 (NMe, 3H, s), 6·30 (OMe, 3H, s), 6·22 (OMe, 3H, s), 6·18 (2 × OMe, 6H, s), 6·09 (OMe, 3H, s), 3·79 (8-H, 1H, s), 3·56 (6′-H, 1H, s), and 2·47 (3′-H, 1H, s).

1-(2-*Amino*-4,5-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-5,6,7-*trimethoxy*-2-*methylisoquinoline* (IIIb).—To a stirred solution of the nitroisoquinoline (IIIi) (6 g.) in concentrated hydrochloric acid (100 ml.) and water (25 ml.), zinc powder (15 g.) was added in portions during 1 hr., and the mixture was stirred for 3·5 hr. The excess of zinc was filtered off, and the aqueous layer was basified with ammonia and extracted with chloroform (100 ml. × 4). The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown gum (5·0 g.), which was chromatographed on silica gel (100 g.) with chloroform [fractions (200 ml.) 1—20], chloroform–methanol (99 : 1 v/v; fractions 21—36), and chloroform–methanol (98 : 2 v/v; fractions 37—53) as eluants. Fractions 21—36 gave the aminoisoquinoline (IIIb) (1·2 g.) as an orange-yellow syrup; the *hydrochloride* gave needles, m.p. 213—215° (from methanol–ether) (Found: C, 55·85; H, 6·9; N, 5·95. $C_{22}H_{30}N_2O_5$,2HCl requires C, 55·55; H, 6·8; N, 5·9%), τ ($CDCl_3$) 3·93 (3′-H, 1H, s), 3·80 (8-H, 1H, s), and 3·70 (6′-H, 1H, s).

Pschorr Reaction of Compound (IIIb).—To a stirred solution of the aminoisoquinoline (IIIb) (1·2 g.) in 5% sulphuric acid (100 ml.) aqueous 10% sodium nitrite (3 ml.) was added dropwise at 0—5° during 10 min. The mixture was stirred at 0—5° for 1 hr., then heated gradually to 70°. Stirring was continued for a further 1 hr. at this temperature, then the mixture was cooled, basified with ammonia, and extracted with chloroform (100 ml. × 5). The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown gum (1·0 g.), which was chromatographed on silica gel (50 g.) with chloroform [fractions (100 ml.) 1—18], chloroform–methanol (99·5 : 0·5 v/v; fractions 19—21), chloroform–methanol (99 : 1 v/v; fractions 22—31), chloroform–methanol (98 : 2 v/v; fractions 32—57), chloroform–methanol (97 : 3 v/v; fractions 58—69), and chloroform–methanol (95 : 5 v/v; fractions 69—75) as eluants; elution was monitored by t.l.c. and i.r. spectroscopy.

Fraction 5 gave 3,4-dimethoxybenzaldehyde (XIIIa) (5 mg.), identical (i.r. spectrum) with an authentic sample, $\nu_{max.}$ ($CHCl_3$) 1678 cm.$^{-1}$ (CHO). Fractions 14—18 gave the 3,4-dihydro-5,6,7-trimethoxy-2-methylisoquinolin-1(2*H*)-one (XIIa) (20 mg.) as prisms, m.p. 104—106° (lit.,[35] 104—106°), identical [i.r. spectrum; $\nu_{max.}$ ($CHCl_3$) 1640 cm.$^{-1}$] with the sample described later, τ ($CDCl_3$) 7·05 (ArCH_2·CH_2·N, 2H, t, *J* 6 Hz), 6·87 (NMe, 3H, s), 6·48 (ArCH_2·CH_2·N, 2H, t, *J* 6 Hz), 6·14 (OMe, 3H, s), 6·11 (OMe, 3H, s), 6·09 (OMe, s, 3H), and 2·55 (8-H, 1H, s). Fractions 20—21 gave the *benzylisoquinoline* (XVIII) (12 mg.) as a yellow viscous syrup [Found: *M* (*m/e*), 403. $C_{22}H_{29}NO_6$ requires *M*, 403], $\lambda_{max.}$ (MeOH) 283 nm., $\nu_{max.}$ ($CHCl_3$) 2750—2200 and 1950—1720 cm.$^{-1}$, τ ($CDCl_3$) 7·44 (NMe, 3H, s), 6·30 (OMe, 3H, s), 6·23 (2 × OMe, 6H, s), 6·20 (OMe, 3H, s), 6·17 (OMe, 3H, s), 3·69 (8-H, 1H, s), 3·60 (3′-H and 6′-H, 2H, s), *m/e* 403 (M^+), 386, 370, 354, 251, 237, and 236 (base peak). Fractions 22—30 gave thalicsimidine (XIXa) as a yellowish brown viscous syrup, τ ($CDCl_3$) 7·45 (NMe, 3H, s), 6·28 (OMe, 3H, s), 6·12 (OMe,

[35] N. M. Mollov and H. B. Dutschewska, *Tetrahedron Letters*, 1969, 1951.

3H, s), 6·09 (2 × OMe, 6H, s), 6·05 (OMe, 3H, s), 3·21 (8-H, 1H, s), and 2·04 (11-H, 1H, s), *m/e* 385 (M^+), $\lambda_{max.}$ (MeOH) 281, 301, and 311sh nm.; the *perchlorate* (244 mg.) gave prisms, m.p. 220—225° (from methanol–ether) (Found: C, 54·05; H, 5·95; N, 3·15. $C_{22}H_{27}NO_5,HClO_4$ requires C, 54·35; H, 5·8; N, 2·9%). Fraction 35 gave the deaminated product (IIIh) (2 mg.) as a yellowish brown syrup; its *perchlorate* afforded pale yellow prisms, m.p. 160—162° (from methanol–ether), identical with the previous sample. Fractions 36—40 gave the *dienone* (Id) (14 mg.) as a yellow syrup [Found: *M* (*m/e*), 371·17208. $C_{21}H_{25}NO_5$ requires *M*, 371·1732], τ ($CDCl_3$) 7·53 (NMe, 3H, s), 6·22 (OMe, 3H, s), 6·14 (2 × OMe, 6H, s), 5·74 (OMe, 3H, s), 3·82 (8-H, 1H, s), 3·40 (1-H, 1H, s), and 2·67 (4-H, 1H, s), $\nu_{max.}$ ($CHCl_3$) 1665 and 1637 $cm.^{-1}$, $\lambda_{max.}$ (MeOH) 235sh nm., *m/e* 356 (*M* — Me), 340 (M^+ — OMe), and 328 (M^+ — COMe).

N-*Ethoxycarbonyl*-2,3,4-*trimethoxyphenethylamine* (XIa).—To a stirred mixture of 2,3,4-trimethoxyphenethylamine (VIb) (4·6 g.), triethylamine (2·5 g.), and benzene (100 ml.) ethyl chlorocarbonate (2·5 g.) was added dropwise at 10—15° during 15 min., and stirring was continued for 1 hr.; triethylamine hydrochloride was precipitated. The mixture was then washed with water (50 ml. × 2), dried (Na_2SO_4), and evaporated to give a pale yellow oil (6·0 g.), $\nu_{max.}$ ($CHCl_3$) 3430 (NH) and 1710 $cm.^{-1}$ (C=O), which was used without purification.

2,3,4-*Trimethoxy*-N-*methylphenethylamine* (XIb).—To a stirred suspension of lithium aluminium hydride (1·6 g.) in tetrahydrofuran (40 ml.) a solution of the urethane (XIa) (6 g.) in tetrahydrofuran (60 ml.) was added dropwise during 45 min. Stirring was continued at room temperature for 2 hr. and at 60° for 30 min. The solvent was removed and the residue was extracted with ether (100 ml. × 3). The extract was washed with water (100 ml. × 2), dried (Na_2SO_4), and evaporated to leave a pale yellow oil, which was distilled *in vacuo* to give an oil (2·8 g.), b.p. 96—100°/0·01 mm. Its *oxalate* gave needles, m.p. 182—183° (from methanol–ether) (Found: C, 53·15; H, 6·45; N, 4·55. $C_{12}H_{19}NO_3,C_2H_2O_4$ requires C, 53·3; H, 6·7; N, 4·45%).

N-*Ethoxycarbonyl*-2,3,4-*trimethoxy*-N-*methylphenethylamine* (XIc).—To a stirred solution of the amine (XIb) (3·3 g.) in aqueous 10% sodium hydroxide (10 ml.) a solution of ethyl chlorocarbonate (2 g.) in benzene (5 ml.) was added dropwise during 15 min., and stirring was continued for 1 hr. The aqueous layer was extracted with benzene (10 ml. × 3) and the combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to leave the urethane (XIc) (3·1 g.) as an oil, $\nu_{max.}$ ($CHCl_3$) 1680 $cm.^{-1}$ (C=O) τ ($CDCl_3$), 8·79 (CH_3·CH_2, 3H, t, *J* 8 Hz), 7·14 (NMe, 3H, s), 6·20 (OMe, 3H, s), 6·18 (OMe, 3H, s), 6·12 (OMe, 3H, s), 5·94 (CH_3·CH_2, 2H, q, *J* 8 Hz), 3·48 (5-H, 1H, d, *J* 9 Hz), and 3·21 (6-H, 1H, d, *J* 9 Hz).

3,4-*Dihydro*-5,6,7-*trimethoxy*-2-*methylisoquinolin*-1(2H)-*one* (XIIa).—To polyphosphoric acid [freshly prepared from 85% phosphoric acid (18 ml.) and phosphorous pentoxide (30 g.) at 100° for 3 hr.] was added the urethane (XIc) (3·0 g.). The mixture was heated at 140—145° for 2·5 hr., poured into ice–water (500 ml.) and extracted with chloroform (100 ml. × 3). The extract was washed with water (100 ml. × 2), dried (Na_2SO_4), and evaporated to leave a yellow oil, which was chromatographed on silica gel (10 g.) with chloroform [fractions (20 ml.) 1—16] as eluant. Fractions 8—9 gave 3,4-dihydromonohydroxydimethoxy-2-methylisoquinolin-1(1*H*)-one (30 mg.) as a powder [$\nu_{max.}$ 3480 (OH) and 1640 $cm.^{-1}$ (C=O)], which was methylated with diazomethane [prepared from *N*-methyl-*N*-nitroso-toluene-*p*-sulphonamide (3 g.)] in ether at room temperature for 24 hr. to afford 3,4-dihydro-5,6,7-trimethoxy-2-methylisoquinolin-1(1*H*)-one (XIIa), identical with the previous sample.

1-(2-*Amino*-4,5-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methylisoquinoline* (IIIc).—To a solution of 6-benzyloxy-1-(4,5-dimethoxy-2-nitrobenzyl)-3,4-dihydro-7-methoxyisoquinoline methiodide (Xb) (5 g.) in concentrated hydrochloric acid (100 ml.) and water (27 ml.) zinc powder (11·5 g.) was added in small portions during 0·5 hr. at room temperature with stirring, and stirring was continued for 0·5 hr. at the same temperature and then at 90° for 0·5 hr. Inorganic material was filtered off, and the filtrate was poured into 10% ammonia, cooled with ice, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a reddish-brown viscous oil (3 g.), $\nu_{max.}$ ($CHCl_3$) 3500 $cm.^{-1}$ (OH), τ ($CDCl_3$) 7·45 (NMe, 3H, s), 6·35, 6·30, and 6·20 (OMe, each 3H, s), and 3·85, 3·75, 3·63 and 3·40 (ArH, each 1H, s), which was labile in air and therefore used without purification.

Modified Pschorr Reaction of the Aminoisoquinoline (IIIc).—Sodium nitrite solution (10%; 7 ml.) was added dropwise during 0·5 hr. to a stirred and cooled (0—5°) solution of the aminoisoquinoline (IIIc) (2·5 g.) in 5% sulphuric acid (98 ml.) and acetic acid (40 ml.); stirring was continued at 5° for 1 hr. and the mixture was then heated at 70° for 2 hr., cooled, basified with 10% ammonia, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a reddish viscous syrup (1·8 g.), which was chromatographed on silica gel (45 g.) with chloroform and chloroform–methanol (99 : 1) as eluants.

Elution with chloroform first gave 3-*nitropredicentrine* (XIXb) as yellow rods (80 mg.) (from methanol), m.p. 205—210° (decomp.) [Found: C, 62·3; H, 6·05; N, 7·2%; *M* (*m/e*), 386·1506. $C_{20}H_{22}N_2O_6$ requires C, 62·15; H, 5·75; N, 7·25%; *M*, 386·1477], $\nu_{max.}$ (KBr) 3400—3200 (OH), 1510, and 1370 $cm.^{-1}$ (NO_2), $\lambda_{max.}$ (MeOH) 280 and 313 nm., τ ($CDCl_3$) 7·45 (NMe, 3H, s), 6·30, 6·08, and 6·05 (OMe, each 3H, s), 3·20 (8-H, 1H, s), and 1·98 (11-H, 1H, s), and then a pale yellow syrup which gave yellowish rods (15 mg.), m.p. 197—200° (decomp.) (from methanol), $\nu_{max.}$ ($CHCl_3$) 3500 (OH) and 2500—2200 $cm.^{-1}$ (salt), $\lambda_{max.}$ (MeOH) 280 nm., *m/e* 357 (M^+), the structure of which remained unclear.

Elution with chloroform–methanol (99 : 1) gave 4,5-*dimethoxy*-1-(2-*hydroxybenzyl*)-1,2,3,4-*tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methylisoquinoline* (IIIj) (35 mg.) as a reddish syrup [Found: *M* (*m/e*), 359·1760. $C_{20}H_{25}NO_5$ requires M^+ 359·1732], $\nu_{max.}$ ($CHCl_3$) 3500 (OH) and 2550—1700 $cm.^{-1}$ (betaine), $\lambda_{max.}$ (MeOH) 288 nm., τ ($CDCl_3$) 7·38 (NMe, 3H, s), 6·26, 6·18, and 6·12 (OMe, each 3H, s), and 3·61, 3·51, 3·46, and 3·38 (ArH, each 1H, s), *m/e* 359·1760 (M^+) and 192.

Further elution with chloroform–methanol (99 : 1) gave (±)-predicentrine (XIXc) (150 mg.) as a green viscous syrup, identified by comparison (spectra and chromatography) with an authentic sample, and the diosphenol-type compound (Ib) (2 mg.) as a reddish syrup, characterised by comparison (spectra and t.l.c.) with an authentic sample.

Acetylation of 3-*Nitropredicentrine* (XIXb).—A mixture of

3-nitropredicentrine (20 mg.), acetic anhydride (0·5 ml.), and pyridine (0·1 ml.) was set aside for 24 hr. at room temperature then poured into ice–water, basified with 10% ammonia, and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4). Evaporation gave 2-acetyl-1,9,10-trimethoxy-3-nitroaporphine as reddish viscous syrup, τ ($CDCl_3$) 7·63 (OAc, 3H, s), 7·45 (NMe, 3H, s), 6·42, 6·10, and 6·06 (OMe, each 3H, s), 3·20 (8-H, 1H, s), 2·09 (11-H, 1H, s).

N-(3-*Benzyloxy*-4-*methoxyphenethyl*)-2-*bromo*-4,5-*dimethoxyphenylacetamide* (VIIIc).—A mixture of 3-benzyloxy-4-methoxyphenethylamine (8·5 g.) and methyl 2-bromo-4,5-dimethoxyphenylacetate (VIIb) (10 g.) was heated at 180—190° for 4·5 hr. in a current of nitrogen, cooled to room temperature, and recrystallised from ethanol to give the *amide* (VIIIc) (13 g.) as needles, m.p. 133—135° (Found: C, 60·8; H, 5·2; N, 3·1. $C_{26}H_{28}BrNO_5$ requires C, 60·7; H, 5·5; N, 2·7%), $\nu_{max.}$ ($CHCl_3$) 3380 (NH) and 1660 $cm.^{-1}$ (amide C=O).

6-*Benzyloxy*-1-(2-*bromo*-4,5-*dimethoxybenzyl*)-3,4-*dihydro*-7-*methoxyisoquinoline* (IXc) *Hydrochloride*.—A mixture of the amide (VIIIc) (11 g.), phosphoryl chloride (16 ml.), and dry benzene (250 ml.) was refluxed on a water-bath for 2 hr., and an excess of n-hexane was then added. A syrup which was deposited overnight was separated by decantation and washed with ether several times. Recrystallisation from methanol–ether gave yellowish *rods* (IXc) (9·4 g.), m.p. 180—181° (Found: C, 59·1; H, 5·45; N, 2·85. $C_{26}H_{27}BrClNO_4$ requires C, 58·6; H, 5·1; N, 2·65%), $\nu_{max.}$ ($CHCl_3$) 2300—2750 (=NH^+) and 1645 $cm.^{-1}$ (C=NH^+).

6-*Benzyloxy*-1-(2-*bromo*-4,5-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxyisoquinoline* (IIIk).—To a solution of the isoquinoline (IXc) hydrochloride (9·0 g.) in methanol (96 ml.) and water (3 ml.) sodium borohydride (6 g.) was added in small portions with stirring at 0° and stirring was continued for 0·5 hr. at 0° and then for 0·5 hr. at room temperature. The mixture was then refluxed for 0·5 hr., methanol was distilled off, and the residue was decomposed with water and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give the *tetrahydroisoquinoline* (IIIk) (9 g.), which yielded prisms, m.p. 118—120° (from benzene–n-hexane) (Found: C, 63·1; H, 5·65; N, 3·3. $C_{26}H_{28}BrNO_4$ requires C, 62·65; H, 5·65; N, 2·8%).

Benzyne Reaction of 1,2,3,4-*Tetrahydroisoquinoline* (IIIk).—To a mixture of sodium (8 g.) and liquid ammonia (300 ml.) was added a solution of the 1,2,3,4-tetrahydroisoquinoline (IIIk) (4 g.) in tetrahydrofuran (20 ml.) with stirring, and stirring was continued for 3 hr. An excess of crystalline ammonium chloride (25 g.) was added; and the product was mixed with water and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to give a reddish viscous oil (3·6 g.), which was chromatographed on alumina (90 g.) in the dark. Elution with chloroform gave 3-benzyloxy-5,6,12,12a-tetrahydro-2,9,10-trimethoxydibenzo[*b*,*g*]indolizine (XX) as a reddish viscous syrup (200 mg.), $\lambda_{max.}$ (MeOH) 317 and 285 nm., τ ($CDCl_3$) 6·30, 6·20, and 6·14 (OMe, each 3H, s), 5·25 (12a-H, 1H, q, *J* 3·5 and 9 Hz), 5·02 (PhCH_2·O, 2H, s), 3·72 and 3·53 (ArH, each 1H, s), 3·38 (ArH, 2H, s), and 2·71 (C_6H_5·CH_2O, 5H, s); the *methiodide* (XXIa) gave needles, m.p. 230—232° (from methanol) (Found: C, 57·85; H, 5·2; N, 2·85. $C_{27}H_{30}INO_4$ requires C, 57·95; H, 5·4; N, 2·5%).

Further elution gave 3-*benzyloxy*-5,6-*dihydro*-2,9,10-*trimethoxydibenzo*[b,g]*indolizine* (XXII) as a green viscous syrup, which yielded needles (1·3 g.), m.p. 195—198° (from ethyl acetate) (Found: C, 75·5; H, 6·1; N, 3·7. $C_{26}H_{25}NO_4$ requires C, 75·15; H, 6·05; N, 3·35%), $\lambda_{max.}$ 235, 290, 320, 325 and 335, nm., τ ($CDCl_3$) 6·97 (5-H_2, 2H, t, *J* 7 Hz), 6·08 (OMe, 9H, s), 5·90 (6-H_2, 2H, t, *J* 7 Hz), 4·89 (PhCH_2·O, 2H, s), 3·28 (ArH, 2H, s), 3·0 (ArH, 1H, s), 2·85 (ArH, 1H, s), and 2·63 (C_6H_5·CH_2O, 5H, s).

5,6,12,12a-*Tetrahydro*-3-*hydroxy*-2,9,10-*trimethoxy*-7-*methyldibenzo*[b,g]*indolizinium Iodide* (XXIb).—A mixture of the 5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizinium iodide (XXIa) (50 mg.), ethanol (2 ml.), and concentrated hydrochloric acid (2 ml.) was heated on a water-bath for 4 hr., and ethanol and hydrochloric acid were then distilled off. The residue was dissolved in ethanol and potassium iodide (50 mg.) was added; the resultant mixture was heated for 2 hr. Inorganic material was then filtered off, and the filtrate was concentrated to give a reddish viscous syrup, which yielded reddish needles (30 mg.), m.p. 225—228° (from methanol) (Found: N, 2·85. $C_{20}H_{24}INO_4$ requires N, 3·0%).

3,4,5-*Trimethoxy*-2-*nitrobenzaldehyde* (XXIVa).—A mixture of 3,4,5-trimethoxy-2-nitrobenzyl alcohol (XXIIIa) [25] (12 g.), manganese dioxide [36] (18 g.), and chloroform (200 ml.) was refluxed for 30 hr. with stirring, cooled to room temperature, and filtered. The filtrate was evaporated and the resultant pale yellow syrup was chromatographed on silica gel with chloroform as eluant to give pale yellow prisms (8 g.), m.p. 76° (lit.,[26] 76°).

4-*Benzyloxy*-3,5-*dimethoxy*-2-*nitrobenzaldehyde* (XXIVb).—A mixture of 4-benzyloxy-3,5-dimethoxy-2-nitrobenzyl alcohol (XXIIIb) [25] (14 g.), manganese dioxide [36] (21 g.), and chloroform (350 ml.) was heated at 40° for 60 hr. with stirring, then treated as in the preceding experiment to give a pale yellow syrup (10 g.), which was used without purification.

3,4,5-*Trimethoxy*-2-*nitrocinnamic Acid* (XXVa).—A mixture of the aldehyde (XXIVa) (24 g.), malonic acid (24 g.), piperidine (1 ml.), and pyridine (100 ml.) was refluxed for 1·5 hr., cooled to room temperature, and poured into ice and concentrated hydrochloric acid (1 : 1). The precipitate gave yellow needles (16 g.), m.p. 183—185° (from methanol) (lit.,[26] 175—178°), $\nu_{max.}$ ($CHCl_3$) 1691 (C=O) and 1648 $cm.^{-1}$ (C=C).

4-*Benzyloxy*-3,5-*dimethoxy*-2-*nitrocinnamic Acid* (XXVb).—A mixture of the aldehyde (XXIVb) (5·5 g.), malonic acid (5·5 g.), piperidine (0·3 ml.), and pyridine (28 ml.) was refluxed for 2 hr., then treated as just described to give a powder, which yielded pale yellow needles (4 g.), m.p. 160—161° (from methanol–water) (Found: C, 59·7; H, 5·0; N, 3·45. $C_{18}H_{17}NO_7$ requires C, 60·1; H, 4·8; N, 3·9%), $\nu_{max.}$ ($CHCl_3$) 1695 (C=O) and 1640 $cm.^{-1}$ (C=C).

N-(3,4-*Dimethoxyphenethyl*)-3,4,5-*trimethoxy*-2-*nitrocinnamamide* (XXVIa).—To a suspension of the acid (XXVa) (16 g.) in dry chloroform (120 ml.) phosphorous pentachloride (12 g.) was added in small portions with stirring during 0·5 hr. The mixture was set aside for a further 1 hr. and then filtered. The filtrate was evaporated below 40° and n-hexane (100 ml.) was added to the residue. The separated acid chloride (XXVc) was filtered off, washed with n-hexane, dissolved (15 g.) in chloroform (50 ml.), and added dropwise to a solution of 3,4-dimethoxyphenethylamine (11·2 g.) in 5% sodium hydroxide (80 ml.)

[36] J. Attenburro, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

with stirring at 18—22°. Stirring was continued for 2 hr., then the organic layer was separated, washed with 10% hydrochloric acid, 5% sodium hydroxide, and water, dried (Na_2SO_4), and evaporated. Methanol (5 ml.) was added to separate the crystals. Filtration, followed by recrystallisation from methanol, gave yellow *needles* (21 g.), m.p. 142—143° (Found: C, 59·45; H, 5·95; N, 6·5. $C_{22}H_{26}N_2O_8$ requires C, 59·2; H, 5·9; N, 6·3%), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1667 (amide C=O), and 1630 cm.$^{-1}$ (C=C).

4-*Benzyloxy*-N-(3,4-*dimethoxyphenethyl*)-3,4-*dimethoxy*-2-*nitrocinnamamide* (XXVIb).—A similar condensation of the acid (XXVb) (4 g.) with 3,4-dimethoxyphenethylamine (3 g.) gave the *amide* as yellow needles (4·2 g.), m.p. 182—183° (from methanol) (Found: C, 64·35; H, 6·05; N, 5·5. $C_{28}H_{30}N_2O_8$ requires C, 64·4; H, 5·8; N, 5·4%), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1666 (amide C=O), and 1629 cm.$^{-1}$ (C=C).

3,4-*Dihydro*-6,7-*dimethoxy*-1-[(3,4,5-*trimethoxy*-2-*nitrophenyl*)*vinyl*]*isoquinoline Methiodide* (XXVIIIa).—A mixture of the amide (XXVIa) (17 g.), phosphoryl chloride (17 ml.), and dry chloroform (170 ml.) was heated under reflux for 0·5 hr. An excess of n-hexane (800 ml.) was added and the yellow precipitate, which was collected by decantation, was washed with n-hexane (2 × 100 ml.), dissolved in chloroform (200 ml.), and poured into cooled ammonia with stirring. The solvent layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give a yellow syrup (XXVIIa) (15 g.), τ ($CDCl_3$) 6·09 (2 × OMe, 6H, s), 6·06 (2 × OMe, 6H, s), 6·02 (OMe, 3H, s), 3·28 (1H), 3·09 (1H), 2·98 (1H), and 2·95 (2H). A mixture of the crude 3,4-dihydroisoquinoline and methyl iodide (25 ml.) was set aside at room temperature for 24 hr.; the *methiodide* (XXVIIIa) was obtained in quantitative yield and gave yellow needles, m.p. 127—128° (from methanol–ether) (Found: C, 48·15; H, 4·85; N, 5·1. $C_{23}H_{27}IN_2O_7$ requires C, 48·4; H, 4·8; N, 4·9%).

1-[(4-*Benzyloxy*-3,5-*dimethoxy*-2-*nitrophenyl*)*vinyl*]-3,4-*dihydro*-6,7-*dimethoxyisoquinoline Methiodide* (XXVIIIb).—A Bischler–Napieralski reaction of the amide (XXVIb) (4·2 g.) with phosphoryl chloride (4·2 g.) in chloroform (40 ml.), followed by methylation with methyl iodide (8 ml.), gave the *methiodide* as yellow needles, m.p. 145—146° (from methanol) (Found: C, 52·35; H, 5·1; N, 4·65. $C_{29}H_{31}IN_2O_7,H_2O$ requires C, 52·4; H, 5·0; N, 4·2%), $\nu_{max.}$ ($CHCl_3$) 3370 cm.$^{-1}$ (OH, water of crystallisation).

1-(2-*Amino*-3,4,5-*trimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* (IIId).—Zinc powder (112 g.) was added in small portions to a stirred mixture of the methiodide (XXVIIIa) (15 g.), concentrated hydrochloric acid (380 ml.), glacial acetic acid (100 ml.), and water (190 ml.) during 0·5 hr., and the mixture was stirred for 5 hr. at room temperature. The excess of zinc was filtered off and the filtrate was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to leave an aminoisoquinoline (13 g.), which was hydrogenated over Adams catalyst (1·0 g.) to give a pale brown viscous syrup (12 g.), τ ($CDCl_3$) 7·56 (NMe, 3H, s), 6·24 (OMe, 3H, s), 6·18 (OMe, 3H, s), 6·15 (3 × OMe, 9H, s), 3·62 (6′-H, 1H, s), 3·47 (5-H and 8-H, 2H, s).

1-(2-*Amino*-4-*benzyloxy*-3,5-*dimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* (IIIn).—Reduction of methiodide (XXVIIIb) (4·2 g.) with zinc powder (27 g.), concentrated hydrochloric acid (105 ml.), and glacial acetic acid (105 ml.), followed by catalytic hydrogenation over Adams catalyst (0·3 g.), gave a pale brown viscous syrup (3 g.), τ ($CDCl_3$) 7·54 (NMe, 3H, s), 6·25 (OMe, 3H, s), 6·18 (OMe, 3H, s), 6·16 (2 × OMe, 6H, s), 5·00 (O·CH_2Ph, 2H, s), 3·60 (6′-H, 1H, s), and 3·46 (5-H and 8-H, 2H, s).

Pschorr Reaction of 1-(2-*Amino*-3,4,5-*trimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* (IIId).—To a solution of the aminoisoquinoline (IIId) (2 g.) in 5% sulphuric acid (140 ml.) 10% sodium nitrite solution (20 ml.) was added dropwise with stirring at 5° during 20 min., and stirring was continued at 5° for 1 hr. and then at 70° for 1 hr. The cooled mixture was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a dark brown gum (1·6 g.), which was chromatographed on silica gel (25 g.) with chloroform [fractions (50 ml.) 1—24], chloroform–methanol (99 : 1 v/v; fractions 25—30), chloroform–methanol (98 : 2 v/v; fractions 31—55), and chloroform–methanol (97 : 3 v/v; fractions 56—60) as eluants; elution was monitored by t.l.c. and i.r., and u.v. spectra. Fraction 3 gave 3,4,5-trimethoxybenzaldehyde (XIIIb) (23 mg.) as pale yellow prisms, m.p. 73—74° (lit.,[37] 74°) (from ethanol), identical (i.r. spectrum) with an authentic sample.[37] Fractions 4—6 gave 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolin-1(2*H*)-one (XIIb) (48 mg.) as plates, m.p. 124—125° (lit.,[27] 124—125°) (from ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 1640 cm.$^{-1}$ (C=O), identical with an authentic sample prepared from the urethane (XId). Fractions 7—13 gave 1′,2′,3′,4′-*tetrahydro*-5,6,6′,7,7′-*pentamethoxy*-2′-*methylspiro*[*indan*-1,1′-*isoquinoline*] (XXXIa) (720 mg.), b.p. 220° (bath)/0·01 mm., as a hygroscopic viscous syrup (Found: C, 67·35; H, 7·4; N, 3·7%; M^+, 399·204. $C_{23}H_{29}NO_5,0{\cdot}5H_2O$ requires C, 67·6; H, 7·4; N, 3·45%; *M*, 399·204], τ ($CDCl_3$) 7·85 (NMe, 3H, s), 6·76 (OMe, 3H, s), 6·41 (OMe, 3H, s), 6·25 (OMe, 3H, s), 6·17 (OMe, 3H, s), 6·15 (OMe, 3H, s), 3·86 (ArH, 1H, s), 3·50 (ArH, 1H, s), and 3·47 (ArH, 1H, s), $\lambda_{max.}$ (MeOH) 283 nm.

Pschorr Reaction of Compound (IIIn).—To a solution of the aminoisoquinoline (IIIn) (3 g.) in 5% sulphuric acid (106 ml.) 10% sodium nitrite solution (5·2 ml.) was added dropwise with stirring at 5° during 30 min., and stirring was continued at 5° for 1 hr. and then at 70° for 1 hr. The mixture was then treated as in the preceding experiment to give 4-benzyloxy-3,5-dimethoxybenzaldehyde (49 mg.) as a pale yellow glass; 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolin-1(2*H*)-one (XIIb) (37 mg.) and the spiro-derivative (XXXIb) (1·2 g.) as a pale yellow viscous syrup, τ ($CDCl_3$) 7·79 (NMe, 3H, s), 6·77 (OMe, 3H, s), 6·42 (OMe, 3H, s), 6·17 (2 × OMe, 6H, s), 5·10 (O·CH_2Ph, 2H, s), 3·84 (4-H, 1H, s), and 3·45 (5′-H and 8′-H, 2H, s), *m/e* 475 (M^+) and 384 (M − 91), $\lambda_{max.}$ (MeOH) 280 nm.

Oxidation of the Spiro-compound (XXXIa) *with Potassium Permanganate*.—To a solution of compound (XXXIa) (200 mg.) in acetone (40 ml.), 1% potassium permanganate solution in acetone (20 ml.) was added dropwise with stirring at room temperature, and stirring was continued for 4 hr. Methanol was then added to decompose the excess of permanganate, and the mixture was filtered. The filtrate was evaporated to dryness under a stream of nitrogen and the residue was extracted with ether. The extract was washed with 5% potassium carbonate, 2% sulphuric acid, and water, dried (Na_2SO_4), and evaporated to give a brown syrup (67 mg.), which was chromatographed on silica gel

[37] M. Tomita and K. Okui, *J. Pharm. Soc. Japan*, 1956, **76**, 632.

(3 g.) with chloroform [fractions (25 ml.) 1—4] and chloroform–methanol (99·5 : 0·5 v/v; fractions 5—10) as eluants (monitored by t.l.c. and i.r. and u.v. spectra). Fractions 3—5 gave a pale yellow viscous syrup (7 mg.), $\nu_{max.}$ ($CHCl_3$) 1648 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 282 nm. Fractions 9—10 gave a syrup (3 mg.), $\nu_{max.}$ ($CHCl_3$) 1675 cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 283 nm. Neither product was identified.

Hofmann Degradation of Compound (XXXIa).—A mixture of the spiro-derivative (XXXIa) (200 mg.) and methyl iodide (1 g.) was set aside at room temperature overnight; the excess of methyl iodide was then evaporated off to leave the methiodide (230 mg.), which was suspended in 50% sodium hydroxide (7 ml.) and heated on a water-bath for 2 hr. in a current of nitrogen. The mixture was cooled to room temperature, and the oil which separated was extracted with chloroform (10 ml. × 3). The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown gum; this was dissolved in 10% hydrochloric acid (20 ml.) and washed with ether (10 ml. × 2). The acidic layer was basified with 10% ammonia and the separated syrup was extracted with ether (20 ml. × 3). The extract was washed with water, dried (Na_2SO_4), and evaporated to give the methine base (XXXV) (150 mg.) as a reddish viscous syrup, τ ($CDCl_3$) 7·88 (2 × NMe, 6H, s), 6·65 (OMe, 3H, s), 6·18 (2 × OMe, 6H, s), 6·12 (OMe, 3H, s), 6·09 (OMe, 3H, s), 6·55 (H_Y and H_Z, 2H, d, J 1·7 Hz), 3·84 (H_X, 1H, t, J 1·7 Hz), 3·22 (ArH, 2H, s), and 3·12 (ArH, 1H, s), *m/e* 413 (M^+) and 355 (M − 58).

A second Hofmann degradation, of the methiodide (135 mg.) obtained by methylation of the base (XXXV) (130 mg.) with methyl iodide (1 g.), was carried out as follows. A suspension of the methiodide in 50% sodium hydroxide (4 ml.) was heated at 120—130° in a stream of nitrogen and the gas evolved was passed through a trap containing 5% hydrochloric acid. [Concentration of the hydrochloric acid solution from the trap gave trimethylamine hydrochloride (21 mg.), m.p. 277—278° (lit.,[38] 278°).] After 3 hr. heating the oil which had separated was extracted with ether (10 ml. × 3). The extract was washed with 5% hydrochloric acid (10 ml. × 2) and water, dried (Na_2SO_4), and evaporated to leave the (*vinylphenyl*)-*indene* (XXXVI) (66 mg.) as a pale yellow viscous syrup, which gave pale yellow prisms, m.p. 176—178° (from ether–hexane) (Found: C, 71·35; H, 6·25. $C_{22}H_{24}O_5$ requires C, 71·7; H, 6·55%), τ ($CDCl_3$) 6·61 (OMe, 3H, s), 6·17 (OMe, 3H, s), 6·14 (OMe, 3H, s), 6·11 (OMe, 3H, s), 6·05 (OMe, 3H, s), 6·55 (H_Y and H_Z, 2H, d, J 1·7 Hz), 3·84 (H_X, 1H, t, J 1·7 Hz), 4·99 (H_A, 1H, q, J_{AC} 10·5; J_{AB} 1·7 Hz), 4·49 (H_B, 1H, q, J_{BC} 17·5, J_{AB} 1·7 Hz), 3·25 (H_C, 1H, q, J_{BC} 17·5, J_{AC} 10·5 Hz), 3·18 (ArH, 2H, s), and 3·09 (ArH, 1H, s), *m/e* 368 (M^+), 353 (M − 15), 337 (M − 31), 323 (M − 45), and 307 (M − 61).

We thank Mr. S. Hirata, Miss A. Kawakami, Miss C. Yoshida, Miss T. Tadano, Miss T. Yoshida, Miss R. Kato, and Miss R. Suzuki, Pharmaceutical Institute, Tohoku University, for i.r., n.m.r., and mass spectral determinations and microanalyses.

[0/490 *Received, April 1st,* 1970]

[38] R. Adams and C. S. Marvel, *Org. Synth.*, Coll. Vol. I, 1950, 531.