Phenol Oxidation and Biosynthesis. Part XXV.† New Syntheses of Bis-(2-arylethyl)amines of Biosynthetic Importance

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Two efficient routes to bis-(2-arylethyl)amines have been developed by using regiospecific alkylation of dialkylnitrosamine anions and homologation of aromatic aldehydes with methoxyacetonitrile anion as the respective key steps. The hitherto uncharacterised 1,3-diaryl-2-azonia-allene ions have been prepared in isolable form. Attempted insertion of C_1 fragments into these systems as a third route to the title compounds failed.

In connection with work on *Erythrina* alkaloid biogenesis,[1] we required efficient preparations of bis-(2-arylethyl)amines and of benzyltetrahydroisoquinolines. Existing syntheses [2-4] are unsatisfactorily long, although they give reasonable overall yields. This is largely because of the cumbersome homologation procedures used in the generation of $Ar-C_2$ units. A recent, improved homologation process [5] may offer some advantages, but we considered that more direct syntheses could be developed. These are conceptually expressed in Scheme 1. Availability directs the use of Ar–C units as a starting point. Scheme 1a shows the simplest formation

a; 2 Ar–C + C–N–C ⟶ (Ar–C–C)$_2$N

b; 2 Ar–C + N ⟶ Ar–C–N–C–Ar ⟶ (Ar–C–C)$_2$N

c; 2 Ar–C + 2C ⟶ 2 Ar–C–C + N ⟶ (Ar–C–C)$_2$N

SCHEME 1

of symmetrical bis-(2-arylethyl)amines from such units. Scheme 1b shows a carbon insertion alternative and Scheme 1c the homologation route. Each could be manipulated to produce unsymmetrical analogues or allow cyclisation to benzyltetrahydroisoquinolines.

For the *Erythrina* alkaloid work the Ar–C unit available was *O*-benzylisovanillin. If this is to be subject to two-fold nucleophilic attack then the simplest C–N–C unit capable of acting as such is the anion of dimethylnitrosamine.[6] Accordingly this anion was generated from the nitrosamine with lithium di-isopropylamide in tetrahydrofuran at −80° and treated with *O*-benzylisovanillin. The intermediate adduct (I) anion was quenched with water to give the mixed *E*- and *Z*-isomers of the adduct (I; R = H) (94%). Quenching with trimethylsilyl chloride gave the trimethylsilyl ethers (I; R = $SiMe_3$) and with benzoic anhydride furnished the benzoates (I; R = Bz). The addition of the second Ar–C unit was attempted *in situ*. The solution containing the intermediate anion of the adduct (I) at −80° was treated with a further 1·1 equiv. of lithium di-isopropylamide, and *O*-benzylisovanillin. Only 12% of the dialkylation product (II; R = H) was isolated. The remainder consisted of the unchanged intermediate (I; R = H) (50%) and 3-benzoyloxy-4-methoxybenzyl alcohol (35%). The benzyl alcohol arose from a hydride reduction of the aldehyde with di-isopropylamide ion,[7] and

† Part XXIV, ref. 1; preliminary communication, D. H. R. Barton, R. D. Bracho, and D. A. Widdowson, *J.C.S. Chem. Comm.* 1973, 781.

[1] D. H. R. Barton, R. D. Bracho, C. J. Potter, and D. A. Widdowson, *J.C.S. Perkin I*, 1974, 2278 and previous papers of this Series.

[2] K. Kindler and W. Peschke, *Arch. Pharm.*, 1932, **270**, 410.

[3] M. U. Tsao, *J. Amer. Chem. Soc.*, 1951, **73**, 5495.

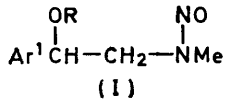
[4] F. Benington and R. D. Morin, *J. Amer. Chem. Soc.*, 1951, **73**, 1353.

[5] K. Ogura and G. Tsuchihashi, *Tetrahedron Letters*, 1972, **1383**.

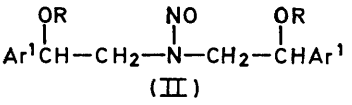
[6] D. Seebach and D. Enders, *Angew. Chem. Internat. Edn.*, 1972, **11**, 301.

[7] For a review, see R. W. Hoffmann, ' Dehydrobenzene and Cycloalkynes,' Academic Press, New York, 1967, p. 102.

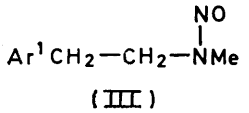
could be avoided by the use of 2,2,6,6-tetramethylpiperidine anion as base.[8] However, this modification did not significantly improve the yield of the double addition product (II; R = H). The intermediate anion



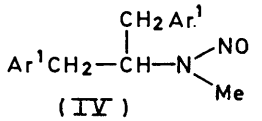
(I)



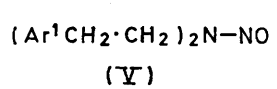
(II)



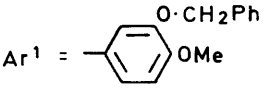
(III)



(IV)

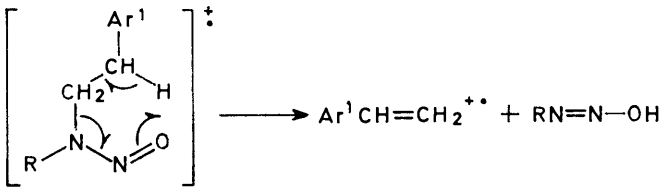


(V)



of (I) precipitated during the reaction. Solubilisation by use of hexamethylphosphoric triamide as co-solvent again gave no improvement.

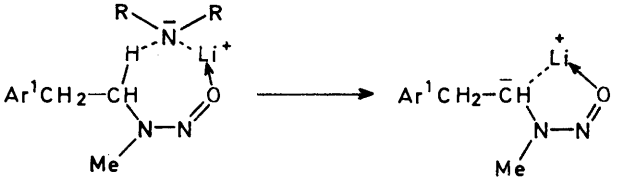
In order to simplify the system, the aldehyde component (*O*-benzylisovanillin) was converted into the derived benzyl bromide [9] and chloride. Alkylation of dimethylnitrosamine anion, generated with lithium di-isopropylamide, at −80°, with the chloride gave low yields, but the bromide gave 84% of the monoalkylation product (III), shown by n.m.r. spectroscopy to be a 3 : 1 mixture of the *E*- and *Z*-forms, respectively [10] (see below). The mass spectrum of (III) (and its analogues) was dominated by a McLafferty-type fragmentation (Scheme 2) the



SCHEME 2

occurrence of which was confirmed by accurate mass measurements.

A sequential double alkylation of dimethylnitrosamine at −80° gave a product different from a reference sample of the *N*-nitrosobis(arylethyl)amine (V). High resolution mass spectroscopy indicated the molecular formula $C_{32}H_{34}N_2O_5$, but the base peak, formed by the McLafferty process, was not at *m/e* 240 for the styrene (Scheme 2) but at *m/e* 466. The n.m.r. spectrum showed the product to be an isomeric mixture of *E*- and *Z*-forms and to contain an *N*-methyl group (τ 7·48 or 6·82 for *E*- or *Z*-, respectively). These data identify the compound as the unsymmetrical dialkylation product (IV). This substitution at the less acidic secondary position was unexpected and in order to gain insight into the process, low temperature n.m.r. studies were made. The α-protons of a nitrosamine *syn* to the nitroso-group resonate at higher field than those in the *anti*-position.[10] Thus at low temperature, where the equilibration of the two forms is suppressed, the position of reaction in the nitrosamine could be observed. It was found that the initial alkylation product of dimethylnitrosamine anion was the less stable *Z*-isomer. On warming the reaction mixture to ambient temperature, the equilibration to the previously observed *ca.* 3 : 1 ratio of *E*- and *Z*-forms could be followed. Even at 20°, equilibration was sufficiently slow for the two forms to be separated by preparative layer chromatography (p.l.c.). When the second alkylation process was carried out at −80°, as above, the substitution occurred at the same carbon centre as the first substitution, even though the protons would be expected *a priori* to be less acidic [11] and the anion more sterically crowded. It appeared therefore that the nitroso-group was directing the anion formation, either *via* complexation of the cation and the approaching base and/or by



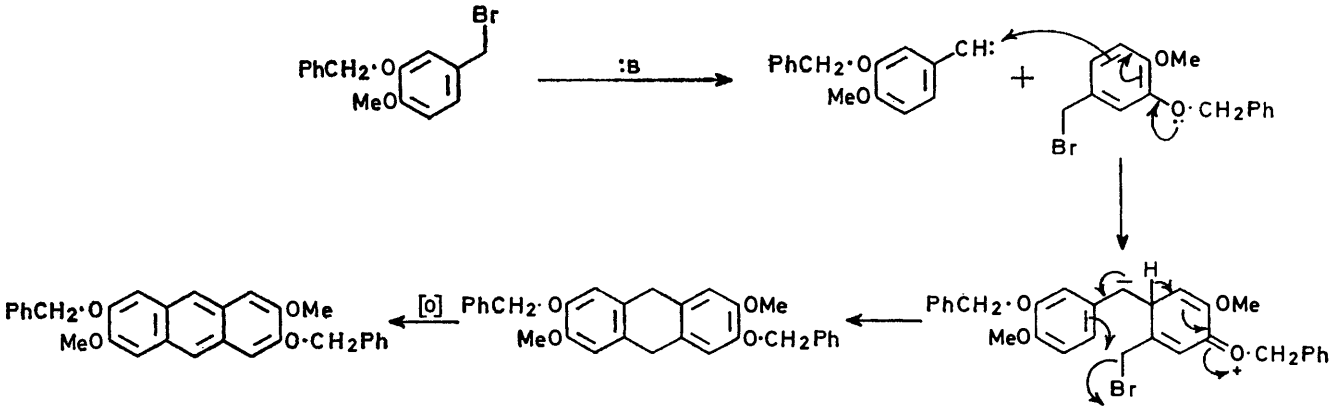
SCHEME 3

stabilisation of the resulting salt (Scheme 3).[12-14] On this basis, equilibration of the initial product [*Z*-(III)] prior to the second alkylation step should produce the desired symmetrical compound (V). In the event, alkylation of the equilibrated nitrosamine (III) (*E* : *Z* *ca.* 3 : 1) gave 75% of the symmetrical nitrosodiarylethylamine (V) (near the theoretical limit). The pure *E*-isomer of (III), obtained quantitatively by a slow crystallisation of the *E*–*Z*-mixture,[15] gave 94% of the required product (V) when the preferred base (see below) was used.

If lithium di-isopropylamide was used to generate the anion (Scheme 3; R = Pr^i), alkylation with the benzylic bromide produced a by-product, identified spectroscopically and by microanalysis as 2,6-dibenzyloxy-3,7-dimethoxyanthracene. This arose by a base-catalysed dimerisation of the alkylating agent. A reasonable mechanism is given in Scheme 4.

In order to circumvent this, a number of alternative bases were examined. Sodium hexamethyldisilazide [16]

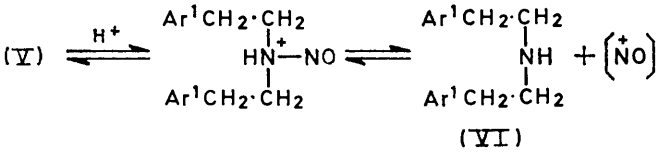
[8] R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, 1973, **95**, 582.
[9] E. J. Corey, C. V. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339.
[10] G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 1964, **86**, 4373.
[11] For a review see D. J. Cram, ' Fundamentals of Carbanion Chemistry,' Academic Press, New York and London, 1965.
[12] *Cf.* D. Seebach and D. Enders, *Angew. Chem. Internat. Edn.*, 1972, **11**, 1101.
[13] R. R. Fraser, G. Boussard, I. D. Postescu, J. J. Whiting, and Y. Y. Wigfield, *Canad. J. Chem.*, 1973, **51**, 1109.
[14] R. R. Fraser and Y. Y. Wigfield, *Tetrahedron Letters*, 1971, 2515.
[15] A. Mannschreck, *Angew. Chem. Internat. Edn.*, 1965, **4**, 985.
[16] V. Wannagat and H. Niederprum, *Chem. Ber.*, 1961, **94**, 1540.



SCHEME 4

was found to give products free from the anthracene and the highest yield (see above).

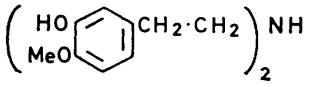
The denitrosation step (Scheme 5) would reportedly require acid catalysis [12,13,17,18] whatever the nature of the



SCHEME 5

reagent used to remove the nitrosonium ion. Dry hydrogen chloride in benzene in the presence of urea as nitroso-acceptor did however selectively denitrosate the nitrosamine (V) in 51% yield. Catalytic debenzylation as before [19] gave the required diphenolic amine (VII) (95%). Because of ease of handling, this two-step process was marginally preferred to a one-step debenzylation–denitrosation reaction with hydrogen chloride in ethanol, with urea again as nitrosonium ion acceptor [45% conversion into (VII)]. Other nitroso-acceptors (malonic ester, resorcinol, acetylacetone) proved less efficient than urea.

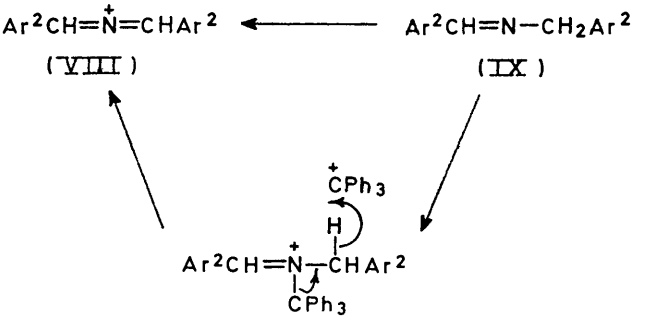
The overall process from *O*-benzylisovanillin to the diphenolic amine (VII) has now been reduced to a five-step sequence with *ca.* 40% overall yield, a significant improvement on previous routes.[2-4] The poor yield step in the synthesis was the denitrosation. Further effort would surely improve this.



(VII)

The novelty of the second approach (Scheme 1b) warranted an investigation of this alternative.

Here the simplest system with the potential for insertion processes is the 2-azonia-allene ion (VIII). Such species have been proposed as reactive intermediates [20-24] but have never been obtained as stable entities. To this end, a series of Schiff's bases (IX) was prepared. The generation of the cations (VIII) (Scheme 6) was attempted with trityl fluoroborate as oxidant [25] in dichloromethane. Reactions were followed by n.m.r. spectroscopy. When Ar^2 was Ph, only quaternisation of the nitrogen atom occurred, but the more nucleophilic 3-benzyloxy-4-methoxyphenyl analogue showed a process of quaternisation (downfield shift of the methylene and methine signals) and collapse to a new species, formulated as the 2-azonia-allene ion (VIII) on the evidence presented below. The use of 1·2 equiv. of trityl cation gave a five-fold increase in the rate of collapse of the intermediate



SCHEME 6

quaternary salt, indicative of a hydride (or analogous electron + hydrogen atom) abstraction from this salt. In this particular series, a complication arose from the use of an excess of trityl cation in the concurrent abstraction of a hydride ion from the protecting *O*-benzyl group. This was avoided by the use of the 2,6-dichlorobenzyl residue for phenol protection (see below).

At this stage no azonia-allene ion had been isolated in crystalline form. The structural assignment rested on

[17] For a review, see C. G. Overberger, J. P. Anselme and J. G. Lombardino, 'Organic Compounds with Nitrogen–Nitrogen Bonds,' Ronald Press, New York, 1966, p. 83.

[18] F. W. C. Stewart, *Austral. J. Chem.*, 1969, **22**, 2451.

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

[20] H. Ahlbrecht and S. Fischer, *Tetrahedron*, 1973, **29**, 659.

[21] W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Coster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.*, 1973, **38**, 943.

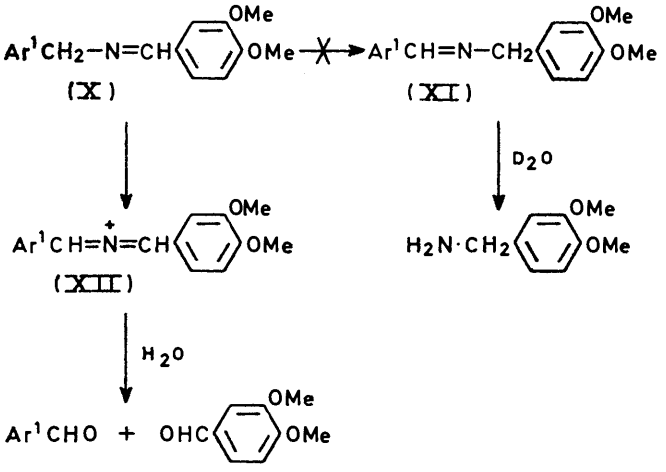
[22] L. D. Cama and B. G. Christensen, *Tetrahedron Letters*, 1973, 3505.

[23] P. G. Gassmann, D. K. Dygos, and J. E. Trent, *J. Amer. Chem. Soc.*, 1970, **92**, 2084.

[24] M. P. Doyle, M. A. Zaleta, J. E. DeBoer, and W. Wirenga, *J. Org. Chem.*, 1973, **38**, 1663.

[25] *Cf.* H. Volz and H. H. Kiltz, *Tetrahedron Letters*, 1970, 1917.

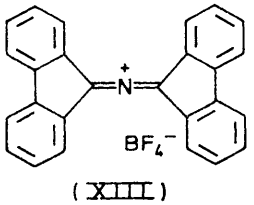
the spectroscopic evidence (n.m.r. indicated the lack of the $N{\cdot}CH_2$ group and symmetrisation of the system to include low-field iminium CH protons) and on the formation of *O*-benzylisovanillin as the sole aromatic product of hydrolysis. No benzylamines were detected. This degradative evidence was further checked by the use of the unsymmetrical system (X) (Scheme 7), prepared from



SCHEME 7

3-benzyloxy-4-methoxybenzylamine and veratraldehyde. The reaction with trityl cation was quenched with water when 70% complete (by n.m.r.). Product analysis by p.l.c. showed the presence of triphenylmethane, a trace of benzaldehyde (from the *O*-benzyl group), *O*-benzylisovanillin, and veratraldehyde. No veratrylamine, indicative of an isomerisation process *via* imine (XI), was detected. The *O*-benzylisovanillin must have arisen therefore from the azonia-allene ion (XII).

When 1,3-bis-[3-(2,6-dichlorobenzyloxy)-4-methoxyphenyl]-2-azonia-allene fluoroborate was prepared as above, the solution in dichloromethane deposited bright yellow crystals during 3 days. These were washed with dichloromethane [to m.p. 173—178° (decomp.)] but could not be recrystallised. The i.r. spectrum showed a cumulene band at 1910 cm^{-1} consistent with the azonia-allene formulation, but the material was not amenable to purification. Mild hydrolysis gave the starting *O*-(2,6-dichlorobenzyl)isovanillin together with the corresponding imine. This was identified by further hydrolysis to aldehyde and by reduction with sodium borohydride to the amine (see Experimental section).



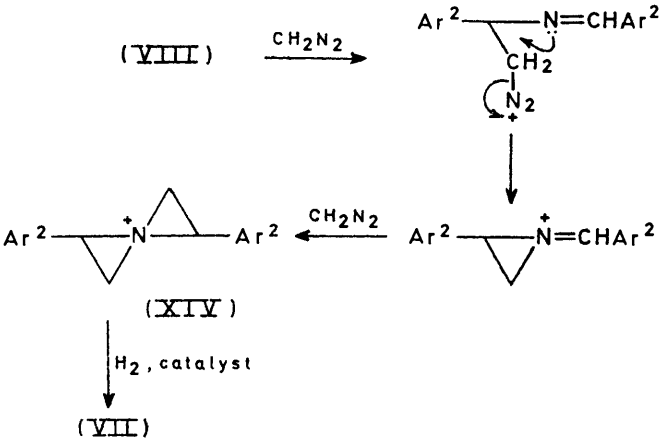
(XIII)

In an analogous manner, difluorenylideneneammonium tetrafluoroborate (XIII) was prepared as red crystals, deposited from dichloromethane solution, $\nu_{max.}$ 1880 cm^{-1} which again proved to be extremely water-sensitive and could not be purified. Hydrolysis gave fluorenone and the imine, which was again identified by further hydrolysis to fluorenone and borohydride reduction to fluoren-9-ylamine.

With the existence of the cations (VIII) well proven, the carbon insertion process was investigated. It was envisaged that diazomethane could undergo a double addition to generate the azoniaspiropentane system (XIV) (Scheme 8).[26] This could undergo hydrogenolysis to generate the bis(arylethyl)amine system with concurrently deprotection of the phenolic groups. In the event, traces of trityl cation in the system caused catalytic decomposition of even large excesses of diazomethane. The reaction with the cation (VIII; Ar^2 = 3-benzyloxy-4-methoxyphenyl) gave a multitude of products, and none ascribable to an insertion process were isolated.

Although other C_1 units are available, this approach was not continued in view of the success of the previously described nitrosamine route.

The approaches described above were aimed specifically at bis(arylethyl)amine systems with little scope beyond these. In order to produce a more generally applicable



SCHEME 8

synthesis, we investigated a third route based on the concept given in Scheme 1c—the homologation process.

We required a product from the homologation process which was capable of acylating an amino-function. The approach chosen is shown in Scheme 9.

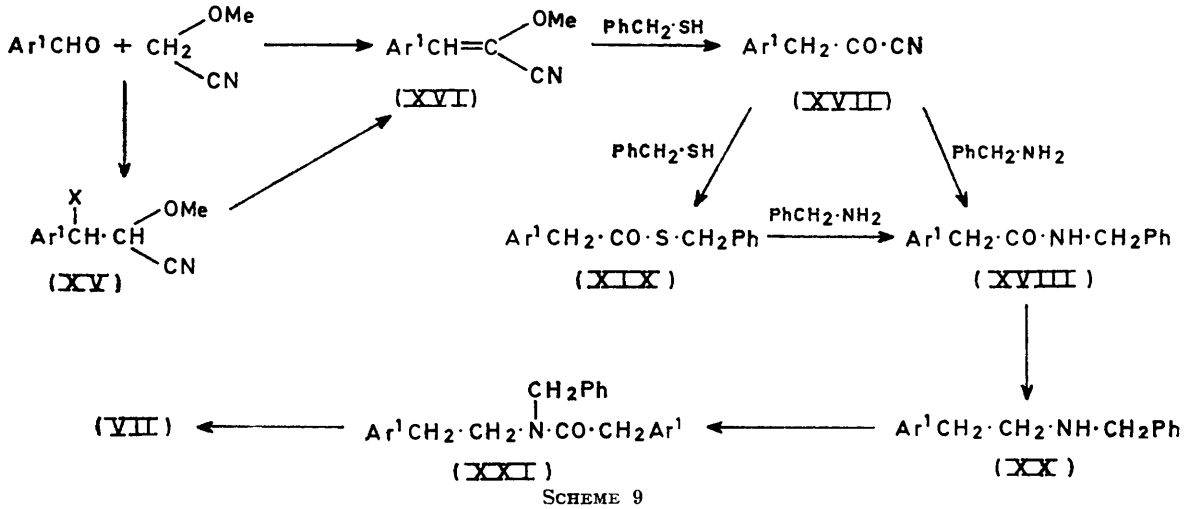
O-Benzylisovanillin was condensed with the sodium salt of methoxyacetonitrile,[27] generated with sodium hydride, in dimethylformamide containing an excess of the methoxyacetonitrile. Initially, the reaction was carried out at ambient temperature and the intermediate adduct (XV; X = OH) was isolated. This was converted into the chloride (XV; X = Cl) with thionyl chloride and the product was dehydrochlorinated with triethylamine to generate the aryl(methoxy)acrylonitrile (XVI). Subsequently, it was found that, at 110°, the intermediate

[26] *Cf.* T. R. Keenan and N. J. Leonard, *J. Amer. Chem. Soc.*, 1971, **93**, 6567.

[27] G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, 1971, **93**, 5286.

adduct anion (XV; X = O^-) underwent a smooth dehydration to the cinnamonitrile directly (81% conversion). The enol ether was characterised spectroscopically (see Experimental section) and by demethylation with sodium toluene-α-thiolate [28] and hydrolysis of the resultant acyl cyanide (XVII) to *O*-benzylhomoisovanillic acid. Alternatively we conceived that the intermediate acyl cyanide (XVII) should be aminolysed by benzylamine to generate the benzamide (XVIII).

Alternatively, the aryl cyanide could also acylate the thiol present in the medium. The resulting thiol ester



SCHEME 9

(XIX) would however also undergo aminolysis to the amide (XVIII). In the event the benzamide (XVIII) was formed in excellent yield (95%) although we did not determine which of the alternative pathways was followed.

The intermediate amide (XVIII) was reduced with lithium aluminium hydride to the *N*-benzylarylethylamine (XX) (75%). This was in turn used to aminate the acyl cyanide (XVII) as before to give the tertiary amide (XXI) (80%). Reduction with lithium aluminium hydride and catalytic debenzylation of the product to give the bis(arylethyl)amine (VII) have been described by us previously.[19]

As with the first synthesis above, this route consists of five stages but the overall yield (*ca.* 30% from *O*-benzylisovanillin) is lower. However, the route has the added alternative possibility of cyclisaton of the intermediate amide (XXI) to produce biosynthetically important 1-benzyl-1,2,3,4-tetrahydroisoquinoline intermediates.

EXPERIMENTAL

Unless otherwise stated, m.p.s were determined on a Kofler hot-stage apparatus. Unless specified to the contrary n.m.r. spectra were run for solutions in deuteriochloroform and i.r. spectra for solutions in chloroform. T.l.c. and p.l.c. were carried out on silica GF plates of 0·1 and 1 mm thickness, respectively. Light petroleum refers to the fraction of b.p. 40—60°.

α-Lithio-derivatives of Nitrosamines: General Method of Preparation and Reaction with Electrophiles.—A serum-stoppered three-necked flask containing a magnetic stirrer was fitted with a three-way tap for making connections either to a dry nitrogen source or to a vacuum pump. The system was thereby repeatedly flushed with nitrogen, after which the tube leading to the pump was disconnected and attached to a mercury bubbler. Nitrogen was passed through the system at a rate sufficient to maintain a positive pressure. All reagents were introduced by the use of syringe techniques. First, di-isopropylamine in tetrahydrofuran was added. The flask was cooled to −80° and methyllithium in ether was introduced into the stirred solution. After 30 min the nitrosamine in tetrahydrofuran was added to the lithium di-isopropylamide, followed after a further 10—15 min by the electrophile in tetrahydrofuran. The mixture was stirred at −80° until reaction was complete (t.l.c. control). The mixture was either worked up (see below for general work-up procedure) or transferred to another flask containing lithium di-isopropylamide prepared *in situ* as above, for reaction with a second batch of the electrophile. When the reaction was complete (t.l.c. control), the mixture was equilibrated between ether and brine. The aqueous layer was washed several times with ether and chloroform. The combined organic phase was dried (K_2CO_3) and evaporated under reduced pressure to give the crude product.

Reaction of N-*Lithiomethyl*-N-*methylnitrosamine with* O-*Benzylisovanillin.*—To a solution of the nitrosamine [2 mmol; prepared [6] from di-isopropylamine (0·3 ml), methyllithium (1·42M-solution; 1·4 ml), and dimethylnitrosamine (0·15 g) in tetrahydrofuran; total volume 4 ml] was added a solution of *O*-benzylisovanillin (0·48 g, 2 mmol) in tetrahydrofuran (2 ml) as above. After 2·5 h at −80° the mixture was quenched with (i) water, (ii) trimethylsilyl chloride, or (iii) benzoic anhydride and worked up as above.

(i) Quenching with water afforded a mixture of (E)- and (Z)-2-(3-*benzyloxy*-4-*methoxyphenyl*)-2-*hydroxy*-N-*methyl*-N-*nitrosoethylamine* (I; R = H) as a pale yellow non-distillable oil (0·58 g, 94%), $\nu_{max.}$ (neat), 3405, 3025, 2965, 2865, 1607, 1590, 1467, 1463, 1450, and 1430 cm^{-1}, τ 2·40—2·90 (5H, m, ArH), 2·90—3·30 (3H, m, ArH), 4·90 (2H, s, $O{\cdot}CH_2$), 5·13 [1H, t, *J* 6 Hz, ArCH(O)C], 5·80 (72% of 2H, d, *J* 6 Hz, $CH_2{\cdot}N$), 6·17 (3H, s, OMe), 6·47 (28% of 3H, s, NMe), 5·00—6·50 (1H + 28% of 2H, m, 1H exchangeable with D_2O, OH

[28] D. M. Jones and N. F. Wood, *J. Chem. Soc.*, 1964, 5600.

and CH_2·N), and 7·03 (72% of 3H, s, NMe) (Found: M^+, 316·1418. $C_{17}H_{20}N_2O_4$ requires M, 316·1423. Found: *m/e*, 256·1096. $C_{16}H_{16}O_3$ requires 256·1099).

(ii) Quenching with trimethylsilyl chloride gave a mixture of (*E*)- and (*Z*)-2-(3-benzyloxy-4-methoxyphenyl)-*N*-methyl-*N*-nitroso-2-trimethylsilyloxyethylamine (I; R = $SiMe_3$) was obtained as a yellow gum, $\nu_{max.}$ 1600 and 1450br cm^{-1}, *m/e* 388 (M^+), 373, 343, 328, 315 (100%), 299, 243, 244, and 91.

(iii) Quenching the mixture with benzoic anhydride afforded a mixture of (E)- and (Z)-2-*benzoyloxy*-2-(3-*benzyloxy*-4-*methoxyphenyl*)-N-*methyl*-N-*nitrosoethylamine* (I; R = Bz) as a thick yellow oil, $\nu_{max.}$ (neat) 1720, 1600, and 1460br cm^{-1}, τ 1·80—2·20 (2H, m, ArH), 2·40—2·80 (8H, m, ArH), 2·90—3·20 (3H, m, ArH), 3·73 [1H, q, *J* 4 Hz, ArCH(O)C], 4·83 (2H, s, OCH_2), 5·50 (75% of 2H, t, *J* 4 Hz, N·CH_2), 5·83 (25% of 2H, t, *J* 4 Hz, N·CH_2), 6·17 (3H, s, OMe), 6·40 (25% of 3H, s, NMe), and 7·03 (75% of 3H, s, NMe), *m/e* 420 (Found: M^+, 420·1678. $C_{24}H_{24}N_2O_5$ requires M, 420·1685. Found: *m/e* 360·1373. $C_{23}H_{20}O_4$ requires 360·1362).

Sequential Reaction of Dimethylnitrosamine with O-*Benzylisovanillin*.—(i) The monosubstitution product (I; R = —ve charge) (10 mmol in 30 ml) was transferred to a freshly prepared solution of lithium di-isopropylamide (11 mmol, 15 ml) at −80°. After *ca.* 15 min the solution was treated with *O*-benzylisovanillin (2·40 g, 10 mmol) in tetrahydrofuran (5 ml). Stirring was continued at −80° for 5 h and then the solution was allowed to attain room temperature. Work-up by the general method afforded a brown gum (5·37 g), t.l.c. of which showed the presence of three compounds. These were separated by p.l.c. (eluant 5% methanol in chloroform) to give (*a*) 3-benzyloxy-4-methoxybenzyl alcohol (1·4 g, 35%) as needles, m.p. and mixed m.p. 70—71° (from ether–light petroleum) (lit.,[29] 72°), *m/e* 244 (M^+), 227, 214, 153, 136, and 91 (100%); (*b*) unchanged (I; R = OH) (2·1 g, 53%) obtained as a yellow oil the identity of which was confirmed by direct comparison (i.r., n.m.r., and mass spectra) with an authentic sample; and (*c*) the desired *bis*-[2-(3-*benzyloxy*-4-*methoxyphenyl*)-2-*hydroxyethyl*]*nitrosamine* (II; R = H) (0·5 g, 12%) as a yellow gum, $\nu_{max.}$ (neat) 3400, 3020, 2965, 2860, 1605, 1590, and 1450br cm^{-1}, τ 2·40—2·90 (10H, m, ArH), 2·90—3·30 (6H, m, ArH), 4·93 (4H, s, O·CH_2), 6·20 (6H, s, OMe), and 4·80—7·00 (8H, complex m, 2H exchangeable with D_2O aliphatic + OH), *m/e* 558 (M^+), 540, 528, 492, 480, 333, 286, 268, 257, 243, 227, and 91 (100%).

(ii) This reaction was repeated with 2,2,6,6-tetramethylpiperidine in place of di-isopropylamine; otherwise the procedure was identical with that of (i). The n.m.r. spectrum of the product mixture indicated the presence of *ca.* 15% of the desired nitrosamine (II; R = H), unchanged *O*-benzylisovanillin and the nitrosamine (I; R = H). T.l.c. revealed the additional presence of the benzyl alcohol (trace).

(iii) The addition of hexamethylphosphoramide (2 ml) in the lithiation procedure (ii) produced no marked improvement in the yield of the nitrosamine (II; R = H) as indicated by the n.m.r. spectrum of the crude product.

3-*Benzyloxy*-4-*methoxybenzyl Chloride*.—This was prepared according to the method of Baxter and his co-workers[29] in 96% yield as needles, m.p. 78—79° (from ether–light petroleum) (lit.,[29] 77°), $\nu_{max.}$ (Nujol) 1611 and 1595 cm^{-1}, *m/e* 264/262 (M^+), 277, and 91 (100%).

Monoalkylation of N-*Lithiomethyl*-N-*methylnitrosamine with* 3-*Benzyloxy*-4-*methoxybenzyl Chloride*.—To a solution of the nitrosamine (0·01 mol) was added the benzyl chloride (2·6 g, 0·01 mol) in tetrahydrofuran (2·5 ml). After being stirred at −80° for 5 h and overnight at room temperature the mixture was worked up as before to yield a yellow oil, the n.m.r. spectrum of which indicated the presence of *ca.* 35% of the anticipated nitrosamine (III), together with *ca.* 65% of unchanged chloride. P.l.c. (eluant chloroform) gave 2-(3-benzyloxy-4-methoxyphenyl)-*N*-methyl-*N*-nitrosoethylamine (III) (0·9 g, 30%) as a pale yellow gum, $\nu_{max.}$ (neat) 3025, 2965, 2880, 1605, 1592, 1464, 1458, 1448, and 1436 cm^{-1}, τ 2·73 (5H, m, ArH), 3·13—3·37 (3H, m, ArH), 5·00 (2H, s, O·CH_2), 5·87 (2H, t, *J* 8 Hz, $ArCH_2$), 6·27 (3H, s, OMe), 6·70 (24% of 3H, s, NMe), 6·00—7·00 (2H, m, CH_2·N), and 7·23 (76% of 3H, s, NMe), *m/e* 300 (M^+), 240, and 91 (100%).

3-*Benzyloxy*-4-*methoxybenzyl Bromide*.—Dry *N*-bromosuccinimide (32·4 g, 0·18 mol) in dry dichloromethane (600 ml) was cooled to 0° and dimethyl sulphide (15·75 ml, 0·22 mol) in dichloromethane (30 ml) was added dropwise with rapid stirring. The mixture was cooled to −20°, then stirred for *ca.* 30 min, and the benzyl alcohol (29·28 g, 0·12 mol) in dichloromethane (60 ml) was added dropwise during 1 h. The mixture was allowed to warm to room temperature and stirring continued until a clear solution was obtained. This was equilibrated between brine and light petroleum. The organic layer was washed three times with brine, dried ($MgSO_4$), and evaporated to yield 3-*benzyloxy*-4-*methoxybenzyl bromide* (34·5 g, 98%) as needles, m.p. 94—95° (from chloroform–light petroleum), $\nu_{max.}$ (Nujol) 1607 and 1595 cm^{-1}, τ 2·60—2·80 (5H, m, ArH), 3·00—3·33 (3H, m, ArH), 4·90 (2H, s, OCH_2), 5·60 (2H, s, CH_2Br), and 6·17 (3H, s, OMe), *m/e* 308/306 (M^+), 227, and 91 (100%) (Found: C, 59·0; H, 5·1; Br, 25·9. $C_{15}H_{15}BrO_2$ requires C, 58·65; H, 4·9; Br, 26·0%).

Monoalkylation of N-*Lithiomethyl*-N-*methylnitrosamine with* 3-*Benzyloxy*-4-*methoxybenzyl Bromide*.—The nitrosamine (0·012 mol) was treated with the benzyl bromide (2·25 g, 0·0075 mol) in tetrahydrofuran (10 ml). After reaction was complete (2 h at −80°; t.l.c. control) the mixure was worked up as before to afford 2-(3-*benzyloxy*-4-*methoxyphenyl*)-N-*methyl*-N-*nitrosoethylamine* (III) (1·88 g, 84%) as pale yellow needles, m.p. 87—90° (from methanol–light petroleum). This had spectral characteristics (i.r., n.m.r., and mass) identical with those of the foregoing product (Found: C, 68·05; H, 6·7; N, 9·1. $C_{17}H_{20}N_2O_3$ requires C, 68·0; H, 6·7; N, 9·35%).

Sequential Dialkylation of Dimethylnitrosamine with the Benzyl Bromide.—(i) *N*-Lithiomethyl-*N*-methylnitrosamine (0·01 mol; total vol. 15 ml) obtained from lithium di-isopropylamide (0·01 mol) and dimethylnitrosamine (0·75 g, 0·01 mol) was treated with the benzyl bromide (1·50 g, 0·005 mol) in tetrahydrofuran (5 ml) as before. After 3 h at −80° the mixture was transferred to a freshly prepared solution of lithium di-isopropylamide (0·01 mol, 10 ml), stirred for *ca.* 15 min, at −80°, and treated with further benzyl bromide (1·40 g, 0·004 mol) in tetrahydrofuran (5 ml). The mixture was worked up after 30 min (t.l.c. control) to obtain a mixture of (E)- and (Z)-1-(3-*benzyloxy*-4-*methoxybenzyl*)-2-(3-*benzyloxy*-4-*methoxyphenyl*)-N-*methyl*-N-*nitrosoethylamine* (IV) (2·45 g, 93%) as a yellow gum, $\nu_{max.}$ (neat) 3025, 2965, 2880, 1608, 1592, and 1460—1430br cm^{-1}, τ 2·50—2·90 (10H, m, ArH), 3·12—3·50 (6H, m, ArH), 4·98 (4H, s, O·CH_2), 6·24 (6H, s, OMe), 6·82 (14% of 3H, s, NMe),

[29] I. Baxter, L. T. Allen, and G. A. Swan, *J. Chem. Soc.*, 1965, 3645.

7·12 (*ca.* 86% of 4H, d, *J* 8 Hz, CH_2Ar), 7·36 (*ca.* 14% of 4H, d, *J* 8 Hz, CH_2Ar), and 7·48 (86% of 3H, s, NMe), *m/e* 526, 466, 452, 413, 270, 240, 227, and 91 (Found: M^+, 526·2449. $C_{32}H_{34}N_2O_5$ requires *M*, 526·2449. Found: *m/e* 466·2135. $C_{31}H_{30}O_4$ requires 466·2144).

Bis-[2-(3-*benzyloxy*-4-*methoxyphenyl*)*ethyl*]*nitrosamine* (V).—A suspension of bis-[2-(3-benzyloxy-4-methoxyphenyl)-ethyl]amine hydrochloride (33 mg) in dry pyridine (3 ml) was cooled to 0° and gaseous nitrosyl chloride was passed in slowly until the solution turned brown. The mixture was stirred at 0° for 30 min (t.l.c. control), treated with dilute hydrochloric acid, and extracted with ether. The extract was dried (Na_2CO_3) and evaporated to yield the *nitrosamine* (V) (36 mg, 100%) as pale yellow needles, m.p. 63—66° (decomp.) (from chloroform–light petroleum), $\nu_{max.}$ 3025, 2965, 2880, 1605, 1590, 1464, 1458, 1448, and 1432 cm^{-1}, τ 2·50—2·90 (10H, m, ArH), 3·10—3·50 (6H, m, ArH), 4·98 (4H, s, O·CH_2), 6·10 (2H, m, CH_2·N), 6·24 (6H, s, OMe), 6·48 (2H, m, CH_2·N), and 7·34 (4H, m, CH_2Ar), *m/e* 526, 496, 404, 330, 286, 270, 240, 227, and 91 (Found: M^+, 526·2444. $C_{32}H_{34}N_2O_5$ requires *M*, 526·2449. Found: *m/e* 240·1165. $C_{16}H_{16}O_2$ requires 240·1150).

Alkylation of the Nitrosamine (III) *with the Benzyl Bromide.*—(i) A solution of lithium di-isopropylamide (0·005 mol, 7·5 ml) was treated with the nitrosamine (III) (1·50 g, 0·005 mol) in tetrahydrofuran (6 ml) with stirring, followed after 10 min by 3-benzyloxy-4-methoxybenzyl bromide (1·50 g, 0·005 mol) in tetrahydrofuran (4 ml). After 1·5 h at −80°, work-up as before gave a brown semi-solid. The n.m.r. spectrum (and t.l.c.) of this indicated the presence of *ca.* 40% unchanged nitrosamine (III).

(ii) The reaction was carried out with an excess of lithium di-isopropylamide (0·008 mol), otherwise as above. The product was obtained as a brown semi-solid (2·77 g). T.l.c. showed the presence of two compounds in addition to polar decomposition products. P.l.c. (eluant 20% ethyl acetate in benzene) afforded 2,6-*bisbenzyloxy*-3,7-*dimethoxyanthracene* (0·20 g, *ca.* 10%) as needles, m.p. 183—184° (from ethyl acetate), $\nu_{max.}$ 1600 cm^{-1}, $\lambda_{max.}$ 215 (log ε 4·44), 235 (4·24), 295 (4·26), 305 (4·33), 320 (4·45), 334 (4·51), and 345 nm (4·35), τ 2·50—2·73 (10H, m, ArH), 2·90—3·20 (6H, m, ArH), 4·80 (4H, s, O·CH_2), and 6·10 (6H, s, OMe), *m/e* 450 (M^+), 237, and 91 (100%) (Found: C, 77·55; H, 6·1. $C_{30}H_{26}O_4$,0·5EtOAc requires C, 77·7; H, 6·1%). Bis-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]nitrosamine (V) (2·0 g, 75%) was obtained as a yellow gum, identical (t.l.c.; i.r., n.m.r., and mass spectra) with an authentic sample.

Alkylation of N-*Methyl*-N-*sodiomethylnitrosamine with the Benzyl Bromide.*—Sodium hexamethyldisilazide (13·5 g, 0·075 mol) in tetrahydrofuran (125 ml) at −80° was treated (under nitrogen) with dimethylnitrosamine (5·0 g, 0·065 mol) in tetrahydrofuran (30 ml), followed after *ca.* 10 min by a solution of 3-benzyloxy-4-methoxybenzyl bromide (14·0 g, 0·045 mol) in tetrahydrofuran (45 ml). After being stirred for 3 h at −80° the mixture was worked up as before to obtain 2-(3-benzyloxy-4-methoxyphenyl)-*N*-methyl-*N*-nitrosoethylamine (III) (13·6 g, 97%) as a pale yellow solid identical (m.p.; i.r. and n.m.r. spectra; t.l.c.) with the previously obtained sample.

Alkylation of the Nitrosamine (III) *with the Benzyl Bromide* via *its* α-*Sodio-derivative.*—To a solution of sodium hexamethyldisilazide (3·83 g, 0·021 mol) in tetrahydrofuran (40 ml) was added a solution of the nitrosamine (III) (3·75 g, 0·012 mol) in tetrahydrofuran (30 ml) with stirring at −80°. The resulting α-sodio-derivative was treated after 10 min with a solution of 3-benzyloxy-4-methoxybenzyl bromide (3·40 g, 0·012 mol) in tetrahydrofuran (30 ml). The mixture was stirred for 5 h at −80° and worked up by the usual method to obtain bis-[2-(3-benzyloxy-4-methoxyphenyl)-ethyl]nitrosamine (V) (4·65 g, 75%) as a pale yellow amorphous solid, identical (i.r., n.m.r., and mass spectra; t.l.c.) with an authentic sample.

(E)-2-(3-*Benzyloxy*-4-*methoxyphenyl*)-N-*methyl*-N-*nitrosoethylamine.*—The *E*–*Z*-mixture of nitrosamines (III) (1·00 g; *E* : *Z* 76 : 24 by n.m.r.) was dissolved in the minimum volume of hot light petroleum (b.p. 60—80°). The colourless solution thus obtained was filtered and kept at 0° for 3 weeks, whereby the *E*-nitrosamine (III) was obtained as a pale yellow amorphous solid (0·91 g, 91% recovery), τ 2·50—2·80 (5H, m, ArH), 3·14—3·40 (3H, m, ArH), 4·84 (2H, s, O·CH_2), 5·72 (2H, t, *J* 6 Hz, CH_2·N), 6·14br (5H, s, OMe and $ArCH_2$), and 7·10 (3H, s, NMe).

Alkylation of the E-*Nitrosamine* (III) *with the Benzyl Bromide* via *its* α-*Sodio-derivative.*—This was carried out in a manner similar to the above alkylation reaction, but with the pure isomer. The nitrosamine (V) was obtained in 94% yield.

Denitrosation of the Nitrosamine (V).—(i) Urea (1·50 g) was suspended in a solution of the nitrosamine (V) (1·40 g) in dry benzene (60 ml), and into this was passed dry hydrogen chloride with stirring at room temperature for 1 h (t.l.c. control). The solution was filtered and the filtrate swept with nitrogen to remove excess of hydrogen chloride. Evaporation, and trituration of the residue with ether afforded *bis-*[2-(3-*benzyloxy*-4-*methoxyphenyl*)*ethyl*]*amine* (VI) *hydrochloride* (0·72 g, 51%) as needles, m.p. 173—174° (from methanol), τ ($CDCl_3$–D_2O) 2·50—2·83 (10H, m, ArH), 3·30br (6H, s, ArH), 5·00 (4H, s, O·CH_2), 6·23 (6H, s, OMe), and 6·90br (8H, s, $ArCH_2$·CH_2·N), *m/e* 497 (M^+), 406, 270 (100%), 241, 228, 215, and 91 (Found: C, 71·7; H, 6·65; N, 2·3. $C_{32}H_{35}NO_4$,HCl requires C, 71·95; H, 6·8; N, 2·6%).

Hydrogenolyis of this amine (VI) hydrochloride (0·40 g) in ethanol (15 ml) containing concentrated hydrochloric acid (2 drops) over 10% palladium–charcoal afforded bis-[2-(3-hydroxy-4-methoxyphenyl)ethyl]amine (VII) hydrochloride (0·25 g, 95%) as plates, m.p. 225—227° (decomp.) (from ethanol) (lit.,[19] 228—233°), τ (D_2O–NaOH) 3·33 (2H, d, *J* 8 Hz, H-5 of Ar), 3·60 (2H, d, *J* 2 Hz, H-2 of Ar), 3·83 (2H, dd, *J* 8 and 2 Hz, H-6 of Ar), 6·30 (6H, s OMe), and 7·43br (8H, t, *J* 6 Hz, $ArCH_2$·CH_2·N), *m/e* 317 (M^+), 180 (100%), 151, 137, and 127.

(ii) A solution of the nitrosamine (V) (86 mg) and urea (100 mg) in ethanol (10 ml) was treated with hydrogen chloride for 1 h with stirring at room temperature. The denitrosation was sluggish at this temperature (as indicted by t.l.c.). Therefore the mixture was refluxed on a steam-bath for 1·5 h, after which it was flushed with nitrogen. The solution was concentrated and cooled to yield bis-[2-(3-hydroxy-4-methoxyphenyl)ethyl]amine (VII) hydrochloride (26 mg, 45%) as plates, m.p. and mixed m.p. 225—227° (decomp.) (from ethanol) (lit.,[19] 228—233°).

Reaction of N-*Benzylidenebenzylamine with Trityl Tetrafluoroborate.*—To a solution of *N*-benzylidenebenzylamine (IX; Ar^2 = Ph) [30] (80 mg, 0·4 mmol), in [^{2}H]chloroform (1 ml) was added trityl tetrafluoroborate [31] (165 mg, 0·5

[30] R. E. Jorday and H. Adkins, *J. Amer. Chem. Soc.*, 1955, **77**, 4559.

[31] H. J. Dauben, L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, 1960, **25**, 144.

mmol). The reaction was monitored by n.m.r. for 24 h but no triphenylmethane was produced. This was confirmed by t.l.c. The n.m.r. spectrum indicated quaternisation of the nitrogen atom; τ ($CDCl_3$) 1·05 ($CH{=}\overset{+}{N}$) and 5·07 ($CH_2{\cdot}\overset{+}{N}$).[26]

O-Benzylisovanillin Oxime.—A mixture of *O*-benzylisovanillin (8·0 g) and hydroxylamine hydrochloride (8·0 g) in ethanol (160 ml) and pyridine (40 ml) was refluxed on a water-bath for 14 h (t.l.c. control). Evaporation under reduced pressure and trituration of the resulting oil with cold water yielded needles of *O-benzylisovanillin oxime* (7·30 g, 86%), m.p. 90—92° (from ethanol–water), $\nu_{max.}$ (Nujol) 1529 cm^{-1}, *m/e* 257 (M^+), 240, 166, and 91 (100%) (Found: C, 70·3; H, 6·05; N, 5·3. $C_{15}H_{15}NO_3$ requires C, 70·0; H, 5·9; N, 5·45%).

3-Benzyloxy-4-methoxybenzylamine Hydrobromide.—To a stirred solution of *O*-benzylisovanillin oxime (7·0 g) in absolute ether (150 ml) was added a suspension of lithium aluminium hydride (7·0 g) in absolute ether (150 ml) under dry nitrogen. After 72 h at 60° (t.l.c. control) the mixture was cooled and water (300 ml) was added dropwise under nitrogen followed by 10% sodium hydroxide (100 ml). The aqueous phase was extracted with ether (5 × 500 ml) and the collected *ether* extracts were dried (Na_2SO_4) and evaporated to yield the crude amine as a yellow oil. A solution of this in methanol was saturated with gaseous hydrogen bromide. Trituration with ether gave *3-benzyloxy-4-methoxybenzylamine hydrobromide* as needles (6·0 g, 67%), m.p. 215—217° (decomp.) (from methanol), $\nu_{max.}$ (Nujol) 1593 cm^{-1}, τ (CD_3OD–D_2O) 2·50—2·75 (5H, m, ArH), 2·80—3·00 (3H, m, ArH), 4·80 (2H, s, $CH_2{\cdot}O$), 5·93 (2H, s, $CH_2{\cdot}N$), and 6·13 (3H, s, OMe) (Found: C, 55·5; H, 5·8; N, 4·3. $C_{15}H_{18}BrNO_2$ requires C, 55·6; H, 5·6; N, 4·3%).

N-(3-Benzyloxy-4-methoxybenzylidene)-3-benzyloxy-4-methoxybenzylamine (IX; Ar^2 = 3-$PhCH_2O$-4-$MeO{\cdot}C_6H_3$).—3-Benzyloxy-4-methoxybenzylamine (1·56 g, 6·4 mmol; liberated from the foregoing salt with aqueous $NaHCO_3$) was treated with *O*-benzylisovanillin (1·56 g, 6·4 mmol) in benzene, with azeotropic removal of the water produced, to obtain the *imine* (IX; Ar^2 = 3-$PhCH_2O$-4-$MeO{\cdot}C_6H_3$) as needles (2·84 g, 94%), m.p. 115—118° (from benzene–light petroleum), $\nu_{max.}$ (Nujol) 1643 cm^{-1}, $\lambda_{max.}$ 212 (ε 22,400), 227 (18,000), 246 (11,000), and 302 nm (7400), τ 1·80 (1H, s, CH=N), 2·40—2·80 (13H, m, ArH), 2·97—3·20 (3H, m, ArH), 4·85 (2H, s, $CH_2{\cdot}O$), 4·88 (2H, s, $CH_2{\cdot}O$), 5·33 (2H, s, $CH_2{\cdot}N$), 6·13 (3H, s, OMe), and 6·17 (3H, s, OMe), *m/e* 467 (M^+), 376, 332, 242, 227 (100%), and 91 (Found: C, 76·9; H, 6·45; N, 2·9. $C_{30}H_{29}NO_4$ requires C, 77·05; H, 6·25; N, 3·0%).

Reaction of the Imine (IX; Ar^2 = 3-$PhCH_2O$-4-$MeO{\cdot}C_6H_6$) *with Trityl Tetrafluoroborate*.—(i) The imine (93 mg, 0·2 mmol) in [^{2}H]chloroform (1 ml) was treated with trityl tetrafluoroborate (66 mg, 0·20 mmol, 1 mol. equiv.). The reaction was monitored by n.m.r., which showed slow disappearance of the $ArCH_2N$ signal and a corresponding appearance of a singlet at τ 4·47. The n.m.r. spectrum after 36 h indicated *ca.* 62% reaction. Addition of D_2O caused rapid appearance of a low-field signal at τ 0·23. The peaks at τ 4·47 and 0·23 were shown to be due to Ph_3CH and the *O*-benzylisovanillin aldehyde proton, respectively, by the peak enhancement method. After hydrolysis these resonances were in the ratio 1 : 2.

(ii) The imine (47 mg, 0·1 mmol) was treated with trityl tetrafluoroborate (40 mg, 0·12 mmol, 1·2 mol equiv.) in [^{2}H]chloroform (0·5 ml). The reaction was monitored as in (i) and showed *ca.* 60% hydride abstraction in 7 h.

(iii) The imine (1·17 g, 2·5 mmol) in dry dichloromethane (15 ml) was treated (in a dry box) with trityl tetrafluoroborate (1·00 g, 3·0 mmol, 1·2 mol. equiv.) to obtain a clear red solution. After 14 h (*ca.* 65% reaction by n.m.r.) it was treated with water (10 ml) and extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to yield a yellow gum. This was separated by p.l.c. (alumina; benzene) to give triphenylmethane (0·365 g, 60%), m.p. 92—94° (from light petroleum), mixed m.p. with an authentic sample 90—92° (lit.,[32] 92°), benzaldehyde (trace; isolated as the 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 237—238°), and *O*-benzylisovanillin (0·70 g, 58%), m.p. 61° (from ether), mixed m.p. with an authentic sample 60—63°.

N-(3,4-Dimethoxybenzylidene)-3-benzyloxy-4-methoxybenzylamine (X).—Condensation of 3-benzyloxy-4-methoxybenzylamine (0·522 g, 2·1 mmol) with veratraldehyde (0·356 g, 2·1 mmol) as before afforded the *imine* (X) a needles (0·740 g, 90%), m.p. 80—81° (from benzene–light petroleum), $\nu_{max.}$ (Nujol) 1653 cm^{-1}, τ 1·90 (1H, s, CH=N), 2·63—3·30 (11H, m, ArH), 4·93 (2H, s, $CH_2{\cdot}O$), 5·33 (2H, s, $CH_2{\cdot}N$), 6·13 (6H, s, OMe), and 6·20 (3H, s, OMe), *m/e* 391 (M^+), 300, 256, 227, and 91 (100%) (Found: C, 73·85; H, 6·3; N, 3·5. $C_{24}H_{25}NO_4$ requires C, 73·75; H, 6·45; N, 3·6%).

Reaction of the Imine (X) *with Trityl Tetrafluoroborate*.—In a pilot experiment the imine (X) (78 mg, 0·2 mmol) in [^{2}H]chloroform (1 ml) was treated with 1·2 mol. equiv. of trityl tetrafluoroborate (80 mg). The reaction was monitored by n.m.r. for triphenylmethane (see above). Hydrolysis (D_2O) after *ca.* 70% reaction produced two low-field singlets in the n.m.r. spectrum, at τ 0·18 and 0·22. These were shown to be due to *O*-benzylisovanillin and veratraldehyde, respectively, by peak enhancement. The ratio of these two aldehydes to triphenylmethane was 2 : 1.

The imine (X) (0·39 g, 1 mmol) in dry dichloromethane (5 ml) was treated with trityl tetrafluoroborate (0·40 g, 1·2 mmol). After 20 h (*ca.* 70% reaction by n.m.r.), aqueous sodium hydrogen carbonate was added and the mixture extracted with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated to yield a yellow gum. This was separated by p.l.c. (eluant CH_2Cl_2) into (in order of increasing polarity) triphenylmethane (0·16 g, 66%), benzaldehyde (trace; obtained as 2,4-dinitrophenylhydrazone, m.p. 237—239°), *O*-benzylisovanillin (0·14 g, 60%; 2,4-dinitrophenylhydrazone, m.p. 200—201°), and veratraldehyde (0·11 g, 66%; 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 263—265°). T.l.c. [alumina; chloroform–methanol (20 : 1)] of the crude mixture after hydrolysis showed the absence of veratrylamine.

O-(2,6-Dichlorobenzyl)isovanillin.—Isovanillin (4·0 g) was benzylated with 2,6-dichlorobenzyl bromide [33] as above to give the *ether* as cubes (6·0 g, 73%), m.p. 168—170° (from benzene), $\nu_{max.}$ (Nujol) 1679 cm^{-1}, τ 0·08 (1H, s, CHO), 2·50—3·20 (6H, m, ArH), 4·67 (2H, s, $O{\cdot}CH_2$), and 6·13 (3H, s, OMe), *m/e* 312/310 (M^+) and 161/159 (100%) (Found: C, 57·9; H, 3·8. $C_{15}H_{12}Cl_2O_3$ requires C, 57·9; H, 3·9%).

O-(2,6-Dichlorobenzyl)isovanillin Oxime.—A mixture of the above aldehyde (5·0 g) and hydroxylamine hydrochloride (5·0 g) in ethanol (70 ml), pyridine (20 ml), and

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[33] N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, 1952 5044.

benzene (10 ml) was refluxed on a water-bath for 3 h (t.l.c. control) under nitrogen. Solvents were removed under reduced pressure and the residue triturated with cold water to yield the *oxime* as plates (5·28 g, 100%), m.p. 182—184° (from ethanol–water), $\nu_{max.}$ (Nujol) 3300 and 1568 cm^{-1}, *m/e* 327/325 (M^+) and 161/159 (100%) (Found: C, 55·35; H, 3·85; N, 4·4. $C_{15}H_{13}Cl_2NO_3$ requires C, 55·25; H, 4·0; N, 4·3%).

3-(2,6-*Dichlorobenzyloxy*)-4-*methoxybenzylamine Hydrochloride*.—The above oxime (1·63 g) was reduced with lithium aluminium hydride (1·00 g) as reported [34] to obtain the amine as a yellow oil, which when treated with methanolic hydrogen chloride afforded the *hydrochloride* as needles (0·87 g, 50%), m.p. 232—234° (from methanol–ether), $\nu_{max.}$ (Nujol) 3400, 1599, 1591, and 1573 cm^{-1}, τ ($CDCl_3$–D_2O–NaOH) 2·60—3·17 (6H, m, ArH), 4·70 (2H, s, O·CH_2), 6·20 (3H, s, OMe), and 6·23 (2H, s, CH_2·N), *m/e* 313/311 (M^+), 161/159, and 152 (100%) (Found: C, 51·8; H, 4·85; Cl^-, 10·05; N, 3·95. $C_{15}H_{15}Cl_2NO_2$,HCl requires C, 51·7; H, 4·65; Cl^-, 10·25; N, 4·0%).

N-[3-(2,6-*Dichlorobenzyloxy*)-4-*methoxybenzylidene*]-3-(2,6-*dichlorobenzyloxy*)-4-*methoxybenzylamine*.—Condensation of the above amine (0·60 g, 1·9 mmol) with *O*-(2,6-dichlorobenzyl)isovanillin (0·59 g, 1·9 mmol) as before afforded the *imine* as rosettes (1·04 g, 90%), m.p. 154—156° (from benzene–light petroleum), $\nu_{max.}$ (Nujol) 1640, 1590, and 1580 cm^{-1}, τ 1·70 (1H, s, CH=N), 2·27—3·17 (12H, m, ArH), 4·63 (4H, s, O·CH_2), 5·27 (2H, s, CH_2·N), and 6·17 (6H, s, OMe), *m/e* 605 (M^+), 571/569, 470, 446/444, 297/295 (100%), 261, 180, and 161/159 (Found: C, 59·45; H, 4·35; Cl, 22·85; N, 2·3. $C_{30}H_{25}Cl_4NO_4$ requires C, 59·55; H, 4·15; Cl, 22·4; N, 2·3%).

1,3-*Bis*-[3-(2,6-*dichlorobenzyloxy*)-4-*methoxyphenyl*]-2-*azonia-allene Tetrafluoroborate*.—A pilot reaction of the above imine (121 mg, 0·2 mmol) with trityl tetrafluoroborate (80 mg, 0·24 mmol) in [^{2}H]chloroform (0·5 ml) monitored by n.m.r. indicated *ca.* 70% hydride abstraction in 13 h.

The above imine (0·48 g, 0·8 mmol) in dry dichloromethane (2 ml) was treated (in a dry box) with trityl tetrafluoroborate (0·32 g, 0·96 mmol) to obtain a greenish yellow solution. This, during 3 days, deposited a bright yellow solid which was washed with dry dichloromethane to afford a pale yellow crystalline *solid* (0·15 g, 28%), m.p. 173—178° (decomp.), $\nu_{max.}$ (Nujol) 1910, 1665 (hydrolysis product), and 1660 cm^{-1} (Found: C, 48·65; H, 3·65; N, 1·6. $C_{30}H_{24}BCl_4F_4NO_4$,0·5CH_2Cl_2 requires C, 49·95; H, 3·45; N, 1·9%). The supernatant liquid was chromatographed over a small alumina (grade III) column to obtain triphenylmethane as a solid (120 mg, 61%). T.l.c. of the supernatant liquid also showed the presence of 3-(2,6-dichlorobenzyloxy)-4-methoxybenzaldehyde, traces of the corresponding amine and triphenylmethanol and also the absence of 2,6-dichlorobenzaldehyde. The azonia-allene salt (120 mg) was quenched in chloroform–methanol. T.l.c. showed the production of two compounds, which were separated by p.l.c. (eluant dichloromethane). The faster-running was identified (m.p., t.l.c., and n.m.r. spectrum) as *O*-(2,6-dichlorobenzyl)isovanillin (58 mg, 54%). The lower band afforded a pale yellow amorphous solid (65 mg, 52%). On t.l.c. this was found to undergo partial hydrolysis to give a spot corresponding to the above aldehyde. Hence it was suspected to be the corresponding imine. A portion (*ca.* 10 mg) of this was boiled briefly with methanolic aqueous 6N-hydrochloric acid, basified ($NaHCO_3$), and extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase yielded *O*-(2,6-dichlorobenzyl)isovanillin (identified by t.l.c. and mass spectrum). The second portion (40 mg) in MeOH (1·5 ml) was treated with sodium borohydride (50 mg). After 14 h the methanol was evaporated off, water was added, and the solution was extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated to yield a yellow gum. Addition of methanolic hydrogen chloride followed by ether precipitated the benzylamine hydrochloride as needles (8 mg), m.p. and mixed m.p. 230—231°.

Difluoren-9-ylideneammonium Tetrafluoroborate (XIII).—Fluoren-9-ylideneaminofluorene [35] (186 mg, 0·54 mmol) in dry dichloromethane (1 ml) was treated (in a dry box) with trityl tetrafluoroborate (360 mg, 1·1 mmol). After 3 days the solvent was evaporated off to yield a red crystalline mass, $\nu_{max.}$ (Nujol) 1880 cm^{-1}. Attempted recrystallisation from dichloromethane–ether afforded orange needles of crude fluoren-9-iminium tetrafluoroborate (70 mg, 48%), m.p. 230—240° (decomp.). Treatment of a portion of this with aqueous sodium hydrogen carbonate gave fluoren-9-imine as a pale yellow amorphous solid, m.p. 120—124° (lit.,[36] 123—124°). The iminium salt (30 mg) was dissolved in absolute methanol (1 ml) and treated with sodium borohydride (50 mg) for 15 h, after which the solvent was evaporated off. The pale yellow solid obtained was treated with water and extracted into ether. Extracts were dried ($MgSO_4$) and evaporated to yield a yellow oil, which when treated with methanolic hydrogen chloride afforded pale yellow needles (10 mg) of fluoren-9-ylamine hydrochloride, m.p. and mixed m.p. 248—253°. Brief treatment of the crude fluoren-9-iminium tetrafluoroborate (27 mg) in methanol with aqueous hydrochloric acid yielded fluorenone (11 mg, 61%). The mother liquors from the above recrystallisation afforded triphenylmethane (61 mg, 46%) and fluorenone (44 mg).

3-(3-*Benzyloxy*-4-*methoxyphenyl*)-2-*methoxyacrylonitrile* (XVI).—(*a*) To a cooled solution of sodium hydride (240 mg) in dimethylformamide (5 ml) and methoxyacetonitrile (710 mg) was added a solution of *O*-benzylisovanillin (2·42 g) and methoxyacetonitrile (2 ml) in dimethylformamide (20 ml). The mixture was stirred at room temperature for 3 h and poured into water. The aqueous mixture was extracted with ether and the extract was washed once with water, dried (Na_2SO_4), and finally evaporated under reduced pressure. The residue was separated by preparative t.l.c. to give the adduct (XV; X = OH) (2·03 g, 67%), τ 2·21 (1H, s, OH), 2·60—3·33 (8H, complex, ArH), 4·98 (2H, s, O·CH_2Ar), 5·30 [1H, m, *H*C(CN)OMe], 6·00 [1H, m, C*H*(OH)ArC], 6·26 (3H, s, OMe), and 6·63 (3H, s, OMe), $\nu_{max.}$ 3600, 2850, 2250, and 1600 cm^{-1}.

To a cooled mixture of the adduct (XV; X = OH) (0·471 g) and pyridine (1·5 ml), thionyl chloride (0·4 ml) was added, and the mixture was stirred for 16 h. The excess of thionyl chloride was removed under reduced pressure and the remaining black oil was diluted with water (50 ml). The mixture was extracted with ether to give the chloride (XV; X = Cl) (0·344 g, 70%), m.p. 109—110°. Without further purification, this compound (250 mg) was refluxed in benzene (2 ml) with a few drops of triethylamine for 1 h to give the nitrile (XVI) (200 mg, 90%) (see below).

(*b*) Methoxyacetonitrile (710 mg) was added dropwise to a cooled solution of sodium hydride (240 mg) in freshly dis-

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[35] A. Schönberg and E. Singer, *Chem. Ber.*, 1965, **98**, 812.

[36] J. P. Anselme, *Org. Prep. Procedures*. 1969, **1**, 201.

tilled dimethylformamide (20 ml) under nitrogen. Once the sodium hydride had reacted, *O*-benzylisovanillin (2·42 g) in methoxyacetonitrile (2 ml) and dimethylformamide (10 ml) were added, together with triethylamine (1 ml), and the mixture was heated at 110° until t.l.c. analysis showed that all the aldehyde had reacted. The mixture was poured into water (500 ml) and extracted with benzene–light petroleum. The combined extracts were washed once with water (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed over alumina with benzene as eluant to give the *nitrile* (XVI) (24 g, 81%), m.p. 85—87° (from chloroform–light petroleum), τ 2·66—3·30 (8H, complex, ArH), 3·96 (1H, s, olefinic), 4·82 (2H, s, O·CH_2Ph), 6·10 (3H, s, OMe), and 6·20 (3H, s, OMe), $\nu_{max.}$ 2250, 1520, 1275, 1218, 1150, and 1020 cm^{-1}, $\lambda_{max.}$ 208 (ε 26,800), 233 (18,950), 293 (21,200), and 315 nm (19,600), *m/e* 295 (M^+) and 91 (Found: C, 73·05; H, 5·6; N, 4·45. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·75; N, 4·75%).

O-Benzylhomoisovanillic Acid.—The enol ether (XVI) (200 mg) was stirred with powdered sodium hydroxide in freshly distilled dimethylformamide and toluene-α-thiol (84 mg), and sodium hydride (200 mg) was added under nitrogen. The mixture was heated at 110° for 2 h then poured into water and treated with carbon dioxide. The aqueous phase was separated, cooled, and acidified with aqueous 10% hydrochloric acid and then extracted with ether. The extract was dried (Na_2SO_4) and concentrated to give the acid (143·8 mg, 68%), m.p. 125—128° (lit.,[37] 128—129°), τ 2·60 (5H, s, ArH), 3·00—3·40 (3H, complex, ArH), 4·87 (2H, s, O·CH_2Ph), 6·12 (3H, s, OMe), 6·40 (3H, s, CH_2), and 6·47 (1H, s, CO_2H), $\nu_{max.}$ 3000, 2500, 1700, 1600, 1440, 1280, and 920 cm^{-1}, *m/e* 272 (M^+, 100%) 227, 213, 181, 137, 106, and 91.

N-*Benzyl*-N-[2-(3-*benzyloxy*-4-*methoxyphenyl*)]*acetamide* (XVIII).—The nitrile (XVI) (735 mg) and benzylamine (266 mg) in freshly distilled dimethylformamide (3 ml) were treated with toluene-α-thiol (309 mg) and sodium hydride (78 mg) in dimethylformamide (5 ml), under nitrogen. The mixture was heated for 5 min at 100°, cooled to room temperature, and poured into water, to precipitate the *amide* (XVIII) (854·4 mg, 95%), m.p. 136—138° (from chloroform–light petroleum), τ 2·69—2·83 (10H, complex, ArH), 3·23 (3H, s, ArH), 4·13 (1H, m, exchangeable with D_2O, NH), 4·96 (2H, s, O·CH_2Ph), 5·66 (2H, d, CH_2·NH), 6·16 (3H, s, OMe), and 6·53 (2H, s, $ArCH_2$), $\nu_{max.}$ 3420, 2850, 1660, 1530, and 1270 cm^{-1}, *m/e* 361 (M^+, 100%), 270, 255, 227, 228, 167, 137, 106, and 91 (Found: C, 76·35; H, 6·2; N, 3·6. $C_{23}H_{23}NO_3$ requires C, 76·45; H, 6·4; N, 3·85%).

N-*Benzyl*-N-2-(3-*benzyloxy*-4-*methoxyphenyl*)*ethylamine* (XX) *Hydrochloride.*—The amide (XVIII) (1·2 g) in dry tetrahydrofuran (50 ml) was added dropwise to a slurry of lithium aluminium hydride (300 mg) in tetrahydrofuran (10 ml). The mixture was refluxed overnight, then carefully poured into water (100 ml) and extracted with ether (10 × 15 ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue, in ethanol, was saturated with hydrogen chloride. Addition of ether precipitated the amine (XX) hydrochloride (0·95 g, 75%), m.p. 208—210° (from chloroform–light petroleum) (lit.,[19] 208—211°), τ 2·46—2·86 (10H, complex, ArH), 3·27 (3H, s, ArH), 4·90 (2H, s, O·CH_2Ph), 6·13 (3H, s, OMe), 6·26 (2H, s, N·CH_2Ph), and 7·27 (4H, m, CH_2·CH_2), $\nu_{max.}$ (Nujol) 3400, 2600, 1610, and 1595 cm^{-1}, *m/e* 345 (M^+), 345, 254, 243, 228, 137 (100%), 103, and 91 (100%).

N-*Benzyl*-N-[2-(3-*benzyloxy*-4-*methoxyphenyl*)*ethyl*]-(3-*benzyloxy*-4-*methoxyphenyl*)*acetamide* (XXI).—The nitrile (XVI) (231 mg) in freshly distilled dimethylformamide (5 ml) was added dropwise to a solution of toluene-α-thiol (97 mg) and the amine (XX) (300 mg) with sodium hydride (56 mg) in dimethylformamide (2 ml) under nitrogen. The mixture was stirred until all the enol ether had reacted (t.l.c. analysis), then poured into water and extracted with ether. The combined extracts were washed once with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in chloroform; addition of a few ml of light petroleum precipitated the previously uncrystallised [19] amide (XXI) (376 mg, 80%), m.p. 140—141°, τ 2·63—3·34 (21H, ArH), 4·96 (2H, s, O·CH_2Ph), 5·06 (2H, s, O·CH_2Ph), 5·63 (2H, m, N·CH_2Ph), 6·27 (6H, s, OMe), 6·43—6·93 (4H, m, CH_2·CH_2), and 7·30 (2H, ABq, *J* 8 Hz, CO·CH_2Ar), *m/e* 601 (M^+), 361, 240, 227, 120, and 91 (100%).

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