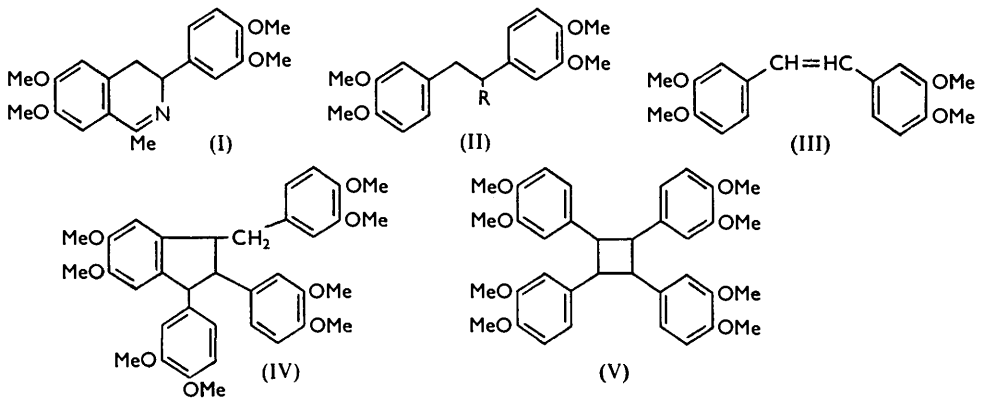
880. *Pavine. Part III.* Related Synthetic Work.*

By A. R. Battersby and R. Binks.

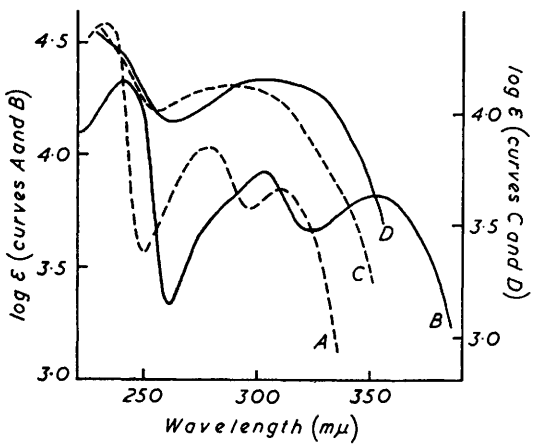
The action of phosphoric oxide on *N*-acetyl-1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine in boiling toluene yields, not the expected 3 : 4-dihydro-*iso*quinoline (I), but a dimer of 3 : 4 : 3′ : 4′-tetramethoxystilbene, which can be obtained directly from 3 : 4 : 3′ : 4′-tetramethoxystilbene under the same conditions. The 1 : 2 : 3 : 4-tetrahydro*iso*quinoline (VI) results from attempted methylation of 1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (II; R = NH_2) with formaldehyde and formic acid; when the latter base reacts with acetaldehyde and sulphuric acid, the 1 : 2 : 3 : 4-tetrahydro-1-methyl-*iso*quinoline (VII) is obtained. This is dehydrogenated in good yield by mercuric acetate to give the corresponding 3 : 4-dihydro-1-methyl*iso*-quinoline (I). Other related experiments are described.

In connection with work on pavine [1] and 1 : 2-dihydro*iso*quinolines,[2] we wished to synthesise the 3 : 4-dihydro*iso*quinoline (I). The obvious route is by Bischler–Napieralski ring-closure of the amide (II; R = NHAc) for which the necessary starting material is the amine (II; R = NH_2). This had previously been prepared [3] by reducing the oxime

and its ultraviolet absorption confirmed the absence of conjugated olefinic and veratrole residues. Determination of its molecular weight showed that the neutral product is a dimer of the stilbene (III) initially produced in the reaction and a number of structures is possible for this product, for example, the indane (IV), based upon that of anethole dimer,[6] or the *cyclo*butane (V).



In extension of the foregoing work 3 : 4 : 3′ : 4′-tetramethoxystilbene (III) was made by Hofmann degradation of the methiodide of the base (II; R = NMe_2). A simpler route to the stilbene (III) involves acid-catalysed dehydration of the alcohol (II; R = OH) resulting from the hydrogenation of 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin. When the stilbene (III) was heated in toluene with phosphoric oxide, it afforded the dimer which had been isolated earlier from the attempted Bischler–Napieralski reaction.



Ultraviolet absorption spectra in ethanol of:
(*A*) *the* 3 : 4-*dihydro*isoquinoline (I).
(*B*) *the* 3 : 4-*dihydro*isoquinoline (I) *as the hydrogen oxalate.*
(*C*) *the dimethylaminomethylstilbene derivative* (IX).
(*D*) 3 : 4 : 3′ : 4′-*tetramethoxystilbene* (III).

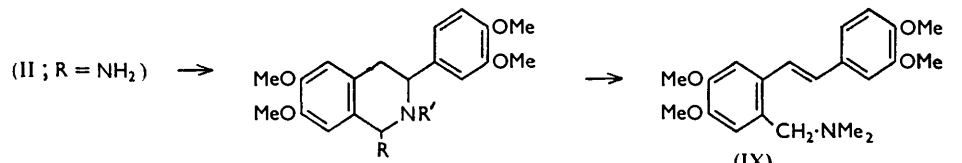
After the completion of this work, the action of phosphorus oxychloride on the amide (II; R = NHAc) was described [7] as yielding the stilbene (III). Dr. Walker has very kindly compared his material with our sample of the dimer by mixed m. p. and by infrared absorption, and the two products are identical.

Before the successful preparation of the methiodide (II; R = $NMe_3^+I^-$), the action of formic acid and formaldehyde on the base (II; R = NH_2) was examined with the aim of preparing the tertiary amine (II; R = NMe_2), $C_{20}H_{27}O_4N$. The product, $C_{20}H_{25}O_4N$, yielded a methiodide which underwent Hofmann degradation to a base, $C_{21}H_{27}O_4N$, having one double bond (micro-hydrogenation) and an ultraviolet absorption spectrum very similar to that of 3 : 4 : 3′ : 4′-tetramethoxystilbene (Figure). These results are

[6] Baker and Enderby, *J.*, 1940, 1094.
[7] Walker, *J. Amer. Chem. Soc.*, 1954, **76**, 3999.

interpreted in the following scheme in which the first step is an example where a Pictet–Spengler ring closure is preferred to *N*-dimethylation.[8]

The differences observed in the absorption spectra of the two stilbene derivatives are no doubt due to the steric effect [9] of the $CH_2 \cdot NMe_2$ group in the base (IX).



The ease of formation of the tetrahydro*iso*quinoline (VI) suggested the acid-catalysed condensation of acetaldehyde with the amine (II; R = NH_2) which gave the tetrahydro-*iso*quinoline (VII) in 74% yield together with a small amount of the stilbene (III); the formation of the latter emphasises the ease with which elimination occurs in this series. The base (VII) showed only very weak infrared absorption in the NH stretching region, but doubts about the secondary nature of the nitrogen atom were removed by the preparation, in high yield, of the neutral acetyl derivative of (VII) which had the expected strong band at 1655 cm.$^{-1}$ (–CO·NRR'). There have been a few other examples of piperidine derivatives which show weak or negligible NH stretching absorption.[10]

Dehydrogenation of the base (VII) with mercuric acetate gave 71% of a base, $C_{20}H_{23}O_4N$, having an ultraviolet absorption (Figure) identical with that obtained by summing the absorptions of 4-alkylveratrole and 3 : 4-dihydro-6 : 7-dimethoxy-1-methyl-*iso*quinoline. The ultraviolet absorption also underwent the expected bathochromic shift when the nitrogen was protonated. This product is therefore the required 3 : 4-dihydro-*iso*quinoline (I) and confirmation was obtained when the infrared spectrum of this base showed bands at 1622, 1606, and 1573 cm.$^{-1}$, a group which is characteristic of this type of 3 : 4-dihydro*iso*quinoline.[11] That no rearrangement of the skeleton had occurred during dehydrogenation was shown by reducing the base (I) catalytically to the tetrahydro*iso*-quinoline (VII).

Leonard and his co-workers [12] have recently studied the action of mercuric acetate on simple quinolizidines and piperidines, but the dehydrogenation of simple tetrahydro*iso*-quinolines by this reagent has not previously been examined. The result obtained here has, besides its general interest as a mild method for converting 1 : 2 : 3 : 4-tetrahydro- into the corresponding 3 : 4-dihydro-*iso*quinolines, also that of serving as a model for the first stage in the dehydrogenation of emetine by mercuric acetate.[13]

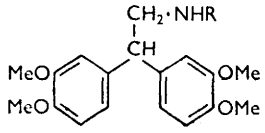
The preparations of the tetrahydro-2-methyl*iso*quinoline (VIII) and the corresponding methiodide are described in the Experimental section.

Other model experiments related to work on *iso*pavine [14] required the preparation of a base of the type (X). Veratrole condensed with *N*-benzyl-2 : 2-dimethoxyethylamine, to give a mixture of bases from which the ethylamine (X; R = CH_2Ph) and the dihydro-anthracene (XI) were isolated by fractional crystallisation of the picrates. The picrate of the base (XI) was stable, but the free base gradually changed and, after being dried at 100°, was shown by its ultraviolet absorption to contain about 10% of the corresponding

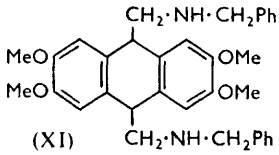
[8] Cf. Castrillon, *ibid.*, 1952, **74**, 558; Baltzly, *ibid.*, 1953, **75**, 6038.
[9] Braude, *Experientia*, 1955, **11**, 457.
[10] Marion, Ramsay, and Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 305.
[11] Battersby, Davidson, and Harper, forthcoming publication.
[12] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279, and earlier papers.
[13] Battersby and Openshaw, *J.*, 1949, S 67.
[14] Battersby and Yeowell, *J.*, 1958, 1988.

anthracene (XII). This ready aromatisation of 9 : 10-dihydroanthracenes has been encountered previously.[15]

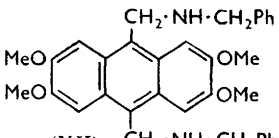
When the base (X; R = CH_2Ph) was methylated with formic acid and formaldehyde, a ring-closure occurred similar to that discussed above. The product was shown to be the tetrahydro*iso*quinoline (XIII) by analysis of its crystalline methiodide and by Hofmann



(X)



(XI)



(XII)

camphor on a veratrole derivative of unequivocal structure (compound I; R = $CH_2 \cdot NMe_2$; ref. 13) all gave results 17—25% low. The m. p. of the dimer was depressed to 130—142° in admixture with 3 : 4 : 3′ : 4′-tetramethoxystilbene prepared as below.

The same dimer was obtained when phosphorus oxychloride (1 ml.) replaced the phosphoric oxide in the above experiment.

1 : 2-*Bis*-(3 : 4-*dimethoxyphenyl*)*ethyltrimethylammonium Iodide*.—Methyl iodide (6 ml.) was heated for 10 hr. under reflux with a solution of 1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (1 g.) and anhydrous sodium carbonate (0·5 g.) in water (30 ml.) and purified dioxan (45 ml.). Addition of aqueous sodium thiosulphate to the cooled solution removed the iodine, and the solution was then evaporated until free from dioxan and methyl iodide. The resulting suspension was extracted thrice with ether–chloroform (10 : 1) which removed a solid (0·1 g.) crystallising from ethanol as needles (30 mg.), m. p. 117—118°.

The aqueous alkaline layer was acidified, treated with potassium iodide (10 g.), and extracted thrice with chloroform. Evaporation of the dried extract at 40° left crystals which, when recrystallised from ethanol, gave the *iodide* as rods (1·38 g., 89%), m. p. 179—180° (decomp.) unchanged by further recrystallisation (Found: C, 51·4; H, 6·4; I, 26·2. $C_{21}H_{30}O_4NI$ requires C, 51·7; H, 6·2; I, 26·4%).

3 : 4 : 3′ : 4′-*Tetramethoxystilbene* (III).—(*a*) A solution of the foregoing methiodide (0·8 g.) in warm water (40 ml.) was shaken for 30 min. with moist silver oxide (from 2 g. of silver nitrate), then filtered. The filtrate and washings (total 100 ml.) were treated with sodium hydroxide (80 g.), heated under reflux for 2 hr., then cooled and extracted thrice with ether. Evaporation of the dried ethereal solution left the stilbene as plates (0·45 g., 92%), m. p. 153—154° (from ethanol) (Found: C, 72·1; H, 6·5. Calc. for $C_{18}H_{20}O_4$: C, 72·0; H, 6·7%). Hydrogenation of this product in ethanol over platinum at 17°/751 mm. (uptake 1·06 mol.) gave 3 : 4 : 3′ : 4′-tetramethoxydibenzyl, m. p. and mixed m. p. 108—109°.

(*b*) When 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (1 g.) in ethanol (150 ml.) was shaken at 20°/758 mm. with hydrogen and 10% palladised charcoal, gas was absorbed (1 mol.) during 5 hr. The solution was filtered and evaporated to dryness to leave a crystalline residue. Part of this (0·3 g.) was heated under reflux with aqueous 2N-sulphuric acid (15 ml.) for 7 hr.; on cooling, crystals separated. These were recrystallised from ethanol to afford the stilbene (III), m. p. 152—154°, alone or on admixture with the sample from (*a*) above, $\lambda_{min.}$ 261 (log ε 3·95), $\lambda_{max.}$ 303 mμ (log ε 4·14) in EtOH.

Dimerisation of 3 : 4 : 3′ : 4′-*Tetramethoxystilbene*.—The stilbene (0·2 g.) in dry toluene (20 ml.) was heated under reflux for 8 hr. with phosphoric oxide (2 g.) which had been exposed to the air for *ca.* 1 min. The mixture was worked up as described above for the isolation of the neutral fraction in the attempted cyclisation. A gum was obtained which crystallised from ethanol to give the stilbene dimer (50 mg.), m. p. 153—156°, alone or on admixture with the product from the attempted cyclisation, but depressed to 133—140° when mixed with the stilbene (III).

3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinoline (VI) *and its Methiodide*.—1 : 2-Bis-(3 : 4-dimethoxyphenyl)ethylamine (1 g.) was heated at 100° for 8 hr. with 95% formic acid (5 ml.) and 37% aqueous formaldehyde (5 ml.), and the solution then poured into water and made alkaline. The precipitated base was extracted into ether–chloroform (10 : 1) and recovered from the dried solution by evaporation. Crystallisation from aqueous ethanol (30% ethanol by vol.) gave the *tetrahydro*isoquinoline (0·92 g.), m. p. 123—125° (Found: C, 69·9; H, 7·3; N, 4·3. $C_{20}H_{25}O_4N$ requires C, 69·95; H, 7·3; N, 4·1%).

A solution of this base (0·5 g.) in ether (20 ml.), methanol (5 ml.), and methyl iodide (5 ml.) was kept in the dark for 44 hr. The precipitated solid (0·7 g.) was washed with ether and recrystallised from aqueous ethanol, to give the *methiodide*, m. p. 250—252° (decomp.) (Found: C, 52·1; H, 5·9; I, 26·9. $C_{21}H_{28}O_4NI$ requires C, 52·0; H, 5·8; I, 26·2%).

Hofmann Degradation of 3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2 : 2-*dimethyl*isoquinolinium *Iodide*.—The foregoing methiodide (0·412 g.) was degraded as for the preparation of the stilbene (III) above, by using water (30 ml.), silver nitrate (0·5 g.), potassium hydroxide (20 g.), and a period of reflux of 5 hr. The products were separated into a neutral (16 mg.) and a basic fraction (240 mg.) in the usual way. The latter crystallised from aqueous ethanol to give 2-*dimethylaminomethyl*-4 : 5 : 3′ : 4′-*tetramethoxystilbene* (IX) as stout prisms (0·17 g.), m. p. 101—103° (Found in material dried at 78°: C, 70·7; H, 7·6; N, 4·2. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6; N, 3·9%), $\lambda_{min.}$ 254 (log ε 4·0), $\lambda_{max.}$ 289 mμ (log ε 4·12) in EtOH.

This base (20·6 mg.) was hydrogenated in ethanol at 18°/743 mm. over platinum; uptake of hydrogen (1·03 mol.) ceased after 2 hr.

3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinoline* (VII).—To a solution of 1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (3 g.) in aqueous 6N-sulphuric acid (120 ml.) was added acetaldehyde (9 ml.), and the mixture was heated under reflux for 1 hr. A second portion (9 ml.) of acetaldehyde was added to the cooled solution which was then kept overnight. After addition of more acetaldehyde (6 ml.) next day, the solution was heated under reflux for 5 hr. Extraction of the tarry solution with ether removed a solid which crystallised from ethanol as colourless plates (0·28 g.), m. p. 151—152°, raised to 152—153° on admixture with the tetramethoxystilbene (III).

The main aqueous solution was made strongly alkaline with potassium hydroxide and extracted thrice with ether; evaporation of the dried extract left a crystalline residue. This was recrystallised from ether, to give the *tetrahydroisoquinoline* as plates (2·38 g., 74%), m. p. 125—128°, raised to 130—133° by repeated recrystallisation from aqueous ethanol (Found: C, 70·1; H, 7·5; N, 3·9. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3; N, 4·1%), $\lambda_{min.}$ 222 and 253, $\lambda_{max.}$ 229 and 281 mμ (log ε 4·18, 2·83; 4·2, 3·82 respectively) in EtOH.

When the tetrahydro*iso*quinoline (41 mg.) was heated on the steam-bath for 2 hr. with acetic anhydride (1 ml.), and the reaction mixture then worked up as usual for neutral material, the *N*-acetyl derivative was obtained as a colourless resin (45 mg., 98%).

3-(3 : 4-*Dimethoxyphenyl*)-3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*methyl*iso*quinoline* (I).—A solution of the foregoing base (2·2 g.) in water (35 ml.) and acetic acid (3·5 ml.) was treated with mercuric acetate (10 g.) and warmed gently until a clear solution was obtained. This was heated under reflux for 9 hr., then cooled and filtered, the mercurous acetate being washed with water and ethanol. Hydrogen sulphide was passed for 10 min. at 55° through the aqueous-alcoholic solution, which was then acidified with aqueous 2N-hydrochloric acid (25 ml.) and treated again with hydrogen sulphide for 1 hr. After coagulation of the precipitate so formed by heat, the solution was filtered and the filter pad was washed with hot water (3 × 30 ml.) and boiling ethanol (3 × 30 ml.), both solvents having been acidified with a few drops of 2N-hydrochloric acid. The combined filtrates and washings were evaporated until free from ethanol, then extracted thrice with ether, and the extracts were rejected. The aqueous layer was made strongly alkaline with potassium hydroxide and extracted with ether (3 × 100 ml.) which removed a crystalline base (1·85 g.). A solution of this base in ethanol was treated with a saturated solution of hydrated oxalic acid (1·5 g.) in ethanol, yielding a pasty precipitate. This crystallised well from ethanol (1·2 l.), to afford the *dihydroisoquinoline hydrogen oxalate* (cf. I) as fine needles (2·02 g.), m. p. 217° (decomp.), raised to 219° (decomp.) by further recrystallisation from ethanol (Found: C, 61·0; H, 5·9; N, 3·5. $C_{22}H_{25}O_8N$ requires C, 61·2; H, 5·8; N, 3·2%), $\lambda_{min.}$ 220, 261, and 323, $\lambda_{max.}$ 241, 303, and 352 mμ (log ε 4·10, 3·32, 3·66; 4·33, 3·93, 3·83) in EtOH. The *base* (I), recovered from the hydrogen oxalate by treatment with aqueous alkali and extraction with ether, crystallised from aqueous ethanol as prismatic needles (1·55 g., 71% overall), m. p. 115—116° (Found: C, 70·8; H, 6·8; N, 4·3. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·8; N, 4·1%), $\lambda_{min.}$ 249 and 296, $\lambda_{max.}$ 231, 278, and 310 mμ (log ε 3·56, 3·76; 4·58, 4·04, 3·85 respectively) in EtOH.

A sample (23·6 mg.) of this base was hydrogenated in ethanol (5 ml.) in the presence of platinum (10 mg.) at 19°/747 mm. Hydrogen (1·0 mol.) was absorbed for 12 min. and uptake then ceased. The product, isolated in the usual way, had m. p. 127—128°, raised to 130—133° on admixture with the tetrahydro*iso*quinoline (VII).

3-(3 : 4-*Dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1 : 2-*dimethyl*iso*quinoline and its Methiodide*.—A solution of the tetrahydro*iso*quinoline (VII) (0·2 g.) in 95% formic acid (4 ml.) and aqueous formaldehyde (8 ml.) was heated at 100—110° for 15 hr., then poured into aqueous 0·1N-hydrochloric acid (20 ml.). After extraction thrice with ether, the aqueous solution was made alkaline with sodium hydroxide and extracted thrice again with ether. Evaporation of the dried second set of ether-extracts left a gum which yielded the crystalline *perchlorate* (0·25 g.) of the tetrahydro-2-methyl*iso*quinoline (VIII). Recrystallised from aqueous ethanol, this had m. p. 211—212° (Found: C, 55·5; H, 6·4. $C_{21}H_{28}O_8NCl$ requires C, 55·1; H, 6·2%).

The tertiary base (VIII), recovered as usual from the perchlorate, was dissolved in dry ether and kept with an excess of methyl iodide overnight. The crystals which separated were recrystallised from ethanol to give the *methiodide*, m. p. 170°, with gas evolution to a resin which flows at 208—209° (decomp.) (Found: C, 52·8; H, 6·2. $C_{22}H_{30}O_4NI$ requires C, 53·0;

H, 6·1%). The same methiodide (by m. p. and mixed m. p.) was formed when the secondary base (VII) (80 mg.) was heated in methanol (2 ml.) with methyl iodide (0·5 ml.) and an excess of aqueous sodium carbonate solution for 4 hr.

N-*Benzyl*-2 : 2-*bis*-(3 : 4-*dimethoxyphenyl*)*ethylamine* (X).—*N*-Benzyl-2 : 2-dimethoxyethylamine (14·8 g.) was added during 3 hr. to a stirred solution of veratrole (20 g.) in glacial acetic acid (70 ml.) and concentrated sulphuric acid (70 ml.). Stirring was continued for a further 2 hr. and the mixture was then poured on ice (250 g.). The resultant solution was extracted with ether (2 × 250 ml.), and the aqueous layer was basified and extracted with ethyl acetate. Evaporation of the dried organic extracts left a gum which was heated at 100°/0·1 mm. for 5 hr. to remove volatile bases. The resinous product (11·7 g.) in ethanol (200 ml.) was treated with picric acid (11 g.), a solid being precipitated. The solid was extracted with hot acetone and the sparingly soluble picrate (1·27 g.), m. p. 223—224°, was reserved. Concentration of the acetone extract yielded crystals and the same material was obtained when the original ethanolic