Pavine. Part I. The Structure and Chemistry of Pavine.

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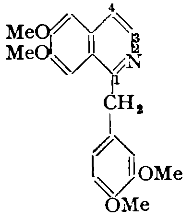
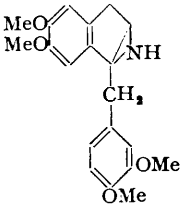
Pavine has been shown to possess the structure (IX) by degradation to 2 : 2′-dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV). The latter is obtained from pavine by two applications of Hofmann's degradation, with hydrogenation after the first, and oxidation of the final neutral product. Both stages of the Hofmann degradation have been found to proceed without rearrangement. In addition to several new derivatives of 2′ : 3′ : 2″ : 3″-tetramethoxy-1 : 2-5 : 6-dibenzo*cyclo*octa-diene and -triene, the corresponding tetraene has been prepared. A number of reactions of pavine derivatives have been explained and the mechanism of formation of pavine is discussed.

REDUCTION of papaverine (I), $C_{20}H_{21}O_4N$, with tin and hydrochloric acid affords 1 : 2 : 3 : 4-tetrahydropapaverine and a crystalline base, originally named " tetrahydropapaverine " (Goldschmiedt, *Monatsh.*, 1886, **7**, 485; 1898, **19**, 324), but renamed pavine by Pyman and Reynolds (*J.*, 1910, **97**, 1320) after its molecular formula had been shown to be $C_{20}H_{23}O_4N$ (Pyman, *J.*, 1909, **95**, 1610). Pavine is a secondary base, resistant to attempted reduction or mild oxidation, but susceptible to degradation by Hofmann's method. One application of this degradation afforded *N*-methylpavinemethine which retains the nitrogen atom of pavine. These properties, taken with the existence of optically active forms of pavine (Pope and Peachey, *J.*, 1898, **73**, 893), led Pyman (*J.*, 1915, **107**, 176) to propose the structure (II) for the base. Schöpf in a brief communication (*Experientia*, 1949, **5**, 201) rejected this formula on the grounds that the ethyleneimine ring would be opened by acid whereas *N*-methylpavine is recovered unchanged after demethylation with hydriodic acid followed by remethylation. As a result of his further finding that 1 : 2-dihydro-*N*-methylpapaverine yields *N*-methylpavine under acidic conditions, Schöpf suggested structures (IV) and (IX) for pavine, but left the choice undecided; these structures will be used below as the basis for discussion. A third structure (III) which is consistent with much of the chemistry of pavine can only be derived from papaverine by deep-seated changes; it need not be considered further, however, since it represents an internally compensated molecule.



(I)



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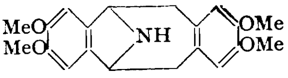

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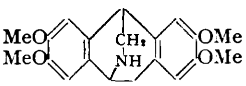

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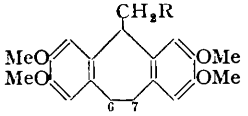
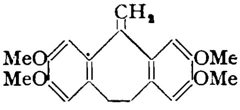
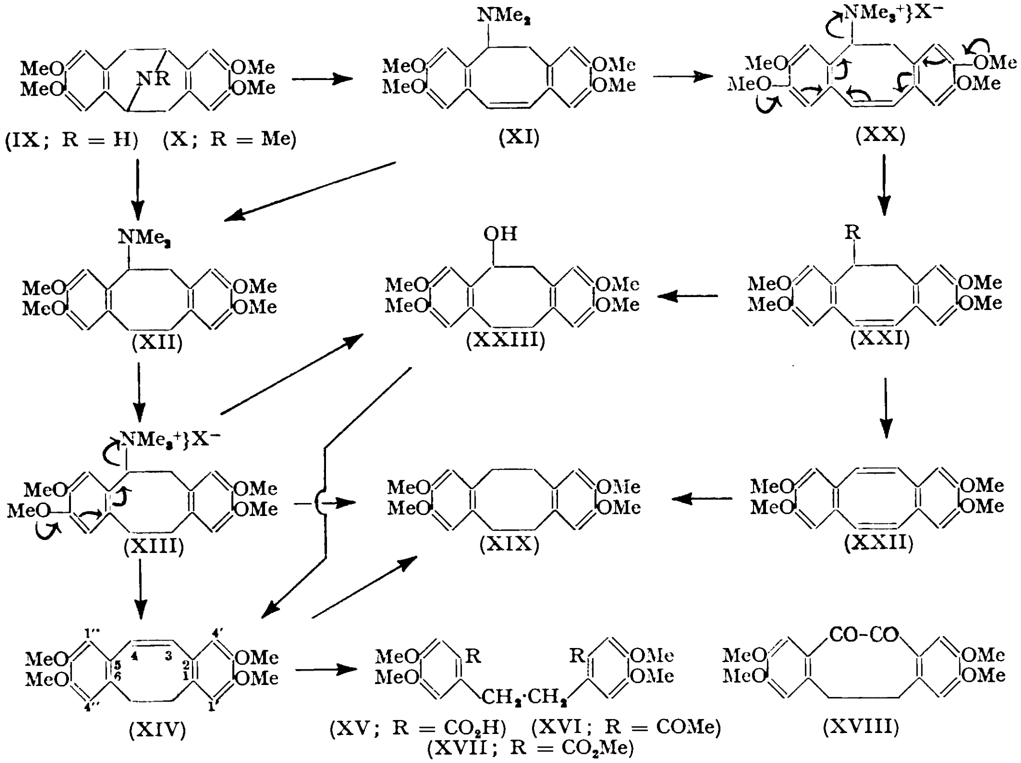


(V; R = NMe_2, 6 : 7-double bond)
(VI; R = NMe_2)
(VII; R = $NMe_3^+\}I^-$)



(VIII)

The pavine used in our work was prepared from papaverine by Pyman's chemical reduction method (*J.*, 1909, **95**, 1610), and *N*-methylpavine was obtained by cyclisation of 1 : 2-dihydro-*N*-methylpapaverine essentially as outlined by Schöpf (*loc. cit.*). Since no experimental directions have been published for the latter route, details of the two procedures we used are given in the Experimental section. One, which involved long heating of a solution of 1 : 2-dihydro-*N*-methylpapaverine in constant-boiling hydrochloric acid, gave a phenolic product. This was methylated with an excess of dimethyl sulphate, and *N*-methylpavine was isolated as its crystalline methosulphate in 89% yield. The second method employed a mixture of formic and phosphoric acid (cf. Braude and Forbes, *J.*, 1953, **2208**) and afforded 72% of *N*-methylpavine directly. Methylation of pavine from Pyman's route with formic acid and formaldehyde gave *N*-methylpavine, identical with that from the other route.



Pyman (*J.*, 1915, **107**, 176) studied the oxidation of *N*-methylpavinemethine under mild conditions and isolated a dicarboxylic acid which is formed without loss of carbon. The methine therefore possesses the grouping –CH=CH– in a ring and can be represented by (V) or (XI). As briefly reported earlier (*Chem. and Ind.*, 1954, 1455), we find that the methine is reduced catalytically with the uptake of one mol. of hydrogen to yield a crystalline base, dihydro-*N*-methylpavinemethine (VI) or (XII). Methyl iodide in ethereal solution at room temperature converted the dihydromethine into its methiodide (VII) or (XIII; X = I) which was degraded by a second application of Hofmann's method. Dihydropavinebismethine (VIII) or (XIV) was formed together with trimethylamine and a little regenerated dihydro-*N*-methylpavinemethine. A decision between the structures (VIII) and (XIV) for the nitrogen-free product was sought by oxidation of the ethylenic link with potassium permanganate. The main product was a crystalline dibasic acid, $C_{20}H_{22}O_8$, isolated in 60% yield, a result in accord with the structure (XIV); the dicarboxylic acid would thus be expected to have the structure (XV). Proof was obtained by synthesis of 2 : 2′-dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV) from the related ketone (XVI) (following paper) by the haloform reaction. The synthetic acid and that from the oxidation of (XIV) were identical, as were their dimethyl esters (XVII).

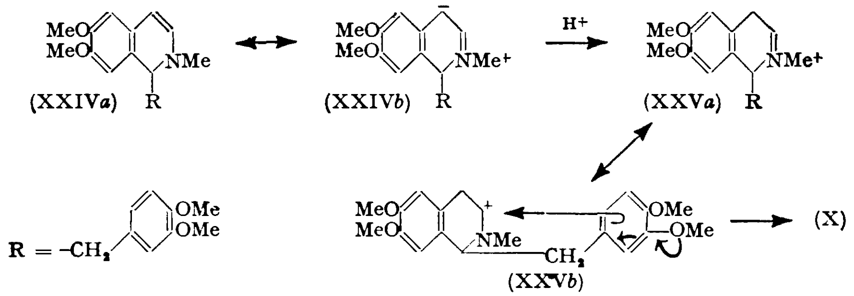
A minor product from the oxidation of the dihydrobismethine (XIV) was a neutral carbonyl compound, $C_{20}H_{20}O_6$, which gave a negative reaction in the *o*-dianisidine test for aldehydes (Feigl, " Qualitative Analysis by Spot Tests," Elsevier, New York, 3rd English Edn., p. 340). Though the small amount of material available precluded rigorous identification, the most probable structure for this product is (XVIII); a micro-test with *o*-phenylenediamine for the α-diketone residue was inconclusive.

Structure (XIV) having been proved for dihydropavinebismethine, structure (XII) follows for dihydro-*N*-methylpavinemethine in the absence of any rearrangement. There is, however, the somewhat unlikely possibility that the latter base is in fact (VI) which undergoes ring expansion during exhaustive methylation. This possibility was discounted when the base (VI) was synthesised (following paper) and found to differ from dihydro-*N*-methylpavinemethine. Additional evidence was furnished by hydrogenolysis of the benzylamine residue in dihydro-*N*-methylpavinemethine methochloride (XIII; X = Cl) to afford a small yield of the dibenzo*cyclo*octadiene (XIX). The latter also resulted in good yield by hydrogenation of the dihydrobismethine (XIV). Structures (XI) and (XII) are therefore established for *N*-methylpavinemethine and its dihydro-derivative, respectively.

A similar attempt was made to eliminate the possibility of rearrangement in the first step of the Hofmann degradation of pavine by hydrogenolysis of *N*-methylpavine methochloride (cf. X, methochloride), but no basic product was obtained. Moreover, Emde degradation of this salt, carried out in weakly alkaline solution to suppress Hofmann elimination, afforded only starting material. The quaternary chloride was smoothly cleaved, however, by sodium in liquid ammonia (Clayson, *J.*, 1949, 2016) to give the dihydromethine (XII) in good yield. Thus the first stage of the Hofmann degradation, like the second, proceeds normally.

The foregoing degradation shows both the size of the alicyclic ring and the points at which it is fused to the aromatic nuclei and thereby establishes structure (IX) for pavine.

The most probable mechanism for the formation of *N*-methylpavine from 1 : 2-dihydro-*N*-methylpapaverine is shown in the following scheme, which by minor modification also explains the formation of pavine from papaverine by way of 1 : 2-dihydropapaverine. The dihydro-base (XXIV*a*) ◄─► (XXIV*b*) would be expected to accept a proton when dissolved in strong acid, to give (XXV*a*), a double-bond shift which has been shown to occur under acidic conditions for several αβ-unsaturated tertiary amines (Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781). Since form (XXV*a*) is stabilised by resonance with the carbonium ion (XXV*b*), cyclisation should take place with the activated *p*-position of the aromatic nucleus to afford *N*-methylpavine. A similar mechanism has been proposed to explain the dimerisation of indole (Smith, *Chem. and Ind.*, 1954, 1451).



If the above scheme is correct, it is a corollary that salts of 1 : 2-dihydro*iso*quinolines should show cationoid reactivity at position 3. The further corollary that 1 : 2-dihydro-*iso*quinolines should have anionoid reactivity at position 4 is related to the known reaction where *C*-alkylation by alkyl halides occurs at the β-position of αβ-unsaturated tertiary amines (Hamilton and Robinson, *J.*, 1916, **109**, 1029; Robinson and Saxton, *J.*, 1952, 976; Stork, Terrell, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1954, **76**, 2029). Both of these reactions offer interesting possibilities for syntheses in the *iso*quinoline series.

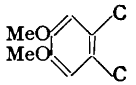
It is now possible to explain some of the reactions shown by certain derivatives of pavine. Thus, *N*-methylpavinemethine methiodide (XX; X = I) is largely decomposed in aqueous solution after 15 min. at 100° to give an alcohol, $C_{20}H_{22}O_5$ (Pyman, *loc. cit.*). We have obtained the same product, rather than the expected dibenzo*cyclo*octatetraene (XXII), from attempted Hofmann degradation of the methohydroxide (XX; X = OH) in 50% aqueous potassium hydroxide. The alcohol was also formed by boiling an aqueous solution of the hydroxide (XX; X = OH); 83% had decomposed to the alcohol after 15 min. When Pyman's decomposition of the methiodide (XX; X = I) was repeated, it was found that the alcohol was contaminated with a second product, not fully characterised, but which contained iodine and was readily hydrolysed by aqueous alkali. Structure (XX) for *N*-methylpavinemethine metho-salts is in accord with all these results since quaternary salts derived from *p*-methoxybenzylamines are known to undergo ready thermal decomposition by a unimolecular mechanism (Battersby and Openshaw, *J.*, 1949, S 59; Norcross and Openshaw, *J.*, 1949, 1174; Pailer and Bilek, *Monatsh.*, 1948, **79**, 135). In the case of *N*-methylpavinemethine methiodide or methohydroxide, the intermediate carbonium ion combines with hydroxyl ion to afford the alcohol, which can therefore be assigned the structure (XXI; R = OH). The second product from the decomposition of the methiodide is presumably the benzyl iodide (XXI; R = I) arising by combination of the intermediate carbonium ion with an iodide ion. Support for the structure assigned to the alcohol was obtained by reducing it catalytically to its crystalline dihydro-derivative (XXIII) which was dehydrated under acidic conditions to the dihydrobismethine (XIV) identical with the earlier preparation. The sample of (XIV) prepared from the alcohol (XXIII) was hydrogenated smoothly to the dibenzo*cyclo*octadiene (XIX), also identical with the material obtained above.

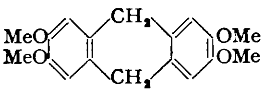
The unsaturated alcohol (XXI; R = OH) was dehydrated when heated with sulphuric acid in aqueous dioxan. Chromatography then afforded the crystalline tetramethoxydibenzo*cyclo*octatetraene (XXII) in 11% yield. This product showed the normal lack of aromatic character and could be hydrogenated under mild conditions to the related dibenzo*cyclo*octadiene (XIX).

It is interesting that under the same Hofmann conditions (hot 50% aqueous potassium hydroxide), the methohydroxide (XX; X = OH) yields the alcohol (XXI; R = OH) by replacement, whereas the corresponding dihydro-derivative (XIII; X = OH) suffers elimination to give the unsaturated compound (XIV). This can be understood if, in contrast to the rapid heterolysis which has been shown to occur with (XX), only slow S_N1 substitution takes place with (XIII), so allowing the *E*2 Hofmann elimination to predominate. In keeping with this, only 36% of (XIII; X = I) had decomposed after being boiled in water for 4 hr. and the product of the decomposition, isolated in 32% yield, was the expected dihydro-alcohol (XXIII). We ascribe this difference in the ease of separation of a carbonium ion from (XX) and (XIII) to electromeric assistance in the former from two *p*-methoxy-aromatic residues as compared with one in the latter case.

On the above basis, the product, $C_{16}H_9(OMe)_5$, obtained by Pyman (*loc. cit.*) by the action of boiling methanol on (XX; X = I) is clearly the methyl ether (XXI; R = OMe), and his second product, $C_{20}H_{21}O_4Cl$, prepared by treating the alcohol (XXI; R = OH) with acetyl chloride, can be assigned the structure (XXI; R = Cl).

(XXVI)





(XXVII)

The ultraviolet absorption spectra recorded in Table 1 show that pavine and compounds (XII), (XIX), and (XXIII), which have no double bond in conjugation with the aromatic nuclei, have the normal absorption attributable to two isolated residues of the type (XXVI). The absorption of 9 : 10-dihydro-2 : 3 : 6 : 7-tetramethoxyanthracene (XXVII) (Robinson, *J.*, 1915, **107**, 267) was recorded for comparison. The compounds (XI), (XIV), and (XXI; R = OH), which possess a conjugated double bond, absorb more intensely and at somewhat longer wavelengths, but the shifts are only small. This is because the coplanar state of the aromatic nuclei and the double bond necessary for full interaction cannot be achieved in molecules of type (XXI) which are shaped like a partly opened hinge.

[*Added June* 30*th*, 1955.]—Professor Schöpf has kindly informed us that he and his colleagues have also established structure (IX) for pavine [work in course of publication, summarised in a lecture (*Angew. Chem.*, 1950, **62**, 453) for which no abstract was available]. Further comment is reserved for a future communication.

TABLE 1. *Ultraviolet absorption maxima and minima* (mμ) *determined in ethanol.*

	Maxima	ε	Minima	ε
Pavine (IX)	225 *	16,520	251	612
	287·5	8,700		
Dihydro-*N*-methylpavinemethine (XII)	225 *	16,600	255	614
	286	6,050		
The dibenzo*cyclo*octadiene (XIX)	225 *	15,960	253	524
	285·5	7,020		
The alcohol (XXIII)	227 *	16,290	255·5	920
	285	6,380		
The 9 : 10-dihydroanthracene (XXVII)	233	22,850	223·5	19,620
	291·5	7,430	261	1,500
N-Methylpavinemethine (XI)	290·5	9,450	272	7,690
N-Methylpavinemethine HCl	290·5	9,540	270	7,870
Dihydropavinebismethine (XIV)	296	11,040	267·5	7,200
	345 *	2,420		
The alcohol (XXI; R = OH)	292·5	11,410	267	8,700
	345 *	900		
The dibenzo*cyclo*octatetraene (XXII)	296·5	9,180	277	7,160
Oxidation product (XVIII ?)	238	28,800	222	17,300
	284·5	13,500	256	7,190
	322	11,400	303·5	10,130

* Inflexion.

EXPERIMENTAL

Analyses are by Mr. B. S. Noyes. Analytical samples were dried at 100° *in vacuo* over phosphoric oxide, unless otherwise stated.

N-*Methylpavine* (X).—(a) *From pavine.* Pavine (0·155 g.), prepared by Pyman's method (*J.*, 1909, **95**, 1610) and having m. p. 199—200° [Pyman (*loc. cit.*) records 201—202° (corr.)], was treated with formic acid (*d* 1·2; 2 ml.) and 37% aqueous formaldehyde (4 ml.). After being heated under reflux at 100—110° for 15 hr., the mixture was poured into 0·1N-hydrochloric acid (10 ml.) and extracted thrice with ether, and the ether extract shaken with 0·1N-hydrochloric acid (2 × 5 ml.). The combined aqueous layers were basified with an excess of sodium hydroxide and extracted with chloroform. Evaporation of the dried extract left *N*-methylpavine as a colourless gum (0·162 g., 100%) which was recovered quantitatively unchanged after being heated with an excess of acetic anhydride for 1·5 hr. When rubbed with anhydrous ether, *N*-methylpavine crystallised as colourless prisms. The m. p. of this base and those of its salts are given in Table 2.

TABLE 2. *Melting points of* N-*methylpavine and its salts.*

	Pyman and Reynolds [a]	Preparation (*a*)	Preparation (*b*)	Mixed m. p. between (*a*) and (*b*)
N-Methylpavine	140—141° (corr.)	135—140°	135—140°	135—140°
Hydrochloride, $8H_2O$ [b]	65—81 (corr.)	72—75	80—82	75—78
Picrate	219 (corr.) [c]	119—121	118—120	118—120
Methiodide, $4H_2O$	118—119 (corr.) sinters 114	118—119 (decomp.) sinters 114	118—120 (decomp.) sinters 114	118—120 (decomp.) sinters 114
Methiodide, $2H_2O$	About 280 (corr.)	—	270—280 (decomp.)	—

[a] *J.*, 1910, **97**, 1320. [b] The m. p. varies with the conditions of drying and with the rate of heating.
[c] Probably an error; all our samples melted 100° lower.

(b) *From* 1 : 2-*dihydro*-N-*methylpapaverine.* A solution of this base (0·5 g.), m. p. 129—130° (Schöpf and Thierfelder, *Annalen*, 1932, **497**, 22; Schöpf, *Experientia*, 1949, **5**, 201), in orthophosphoric acid (*d* 1·75; 1 ml.) and 85% formic acid (2·5 ml.) was heated under reflux at 120° for 25 hr. The cooled mixture was diluted with water (10 ml.) and extracted with ether which removed a trace of non-basic material. After being made strongly alkaline with 2N-sodium hydroxide, the aqueous solution was extracted with chloroform (3 × 25 ml.), and the extracts were washed with water, dried, and distilled to leave a brown gum. This was dissolved in a slight excess of warm 2N-hydrochloric acid, crystallisation of *N*-methylpavine hydrochloride occurring (0·546 g., 72%). The free base, recovered from the hydrochloride by treatment with aqueous ammonia and extraction with chloroform, was crystallised as above. Its m. p. and those of its salts are collected in Table 2.

N-*Methylpavine Methosulphate and Methiodide*.—1 : 2-Dihydro-*N*-methylpapaverine (15·4 g.) was heated in constant-boiling hydrochloric acid (300 ml.) under nitrogen for 24 hr. The solution was evaporated to dryness under a reduced pressure of nitrogen and after dissolution of the residue in water (10 ml.) the solvent was again evaporated completely. A stirred solution of the residue in the minimum volume of methanol was treated dropwise under nitrogen with aqueous 2N-sodium hydroxide (10 equiv.) and freshly purified dimethyl sulphate (12 equiv.), added simultaneously at such a rate that the pH of the reaction mixture was kept above 10. Crystals started to separate soon after the addition was complete and were collected after 18 hr. (15·0 g.; m. p. 272—276°). The mother-liquor, adjusted to pH 3 by addition of concentrated hydrochloric acid, was concentrated *in vacuo* to one-third volume and a precipitate of inorganic salt was filtered off. A second crop of organic material (3·9 g.), m. p. 265°, slowly separated from the filtrate, and a third crop (3·0 g.), m. p. 265°, was obtained by remethylation of the final mother-liquor with dimethyl sulphate (5 ml.) and aqueous 2N-sodium hydroxide as before. A portion of the first crop, recrystallised twice from aqueous methanol, gave N-*methylpavine methosulphate* as colourless, feathery needles, m. p. 276—278° (Found, in different preparations, all dried at 110°: C, 56·1, 56·2, 56·2; H, 6·4, 6·6, 6·6; N, 2·8. $C_{23}H_{31}O_8NS,\frac{1}{2}H_2O$ requires C, 56·3; H, 6·55; N, 2·8%).

A solution of the combined crops of methosulphate (21·8 g.) in the minimum volume of boiling water was treated with an excess of potassium iodide (8·0 g.). The crystalline precipitate was collected after 15 hr. and dried in air, to afford *N*-methylpavine methiodide tetrahydrate (22 g., 89% overall yield), m. p. 118—120° after sintering at 114° (cf. Table 2).

N-*Methylpavinemethine* (XI).—Hofmann degradation of *N*-methylpavine methiodide tetrahydrate (5·2 g.) under Pyman's conditions (*J.*, 1915, **107**, 176) afforded *N*-methylpavinemethine, purified as the hydrochloride (3·2 g., 86%), m. p. 204—207°; at 210° decomposition occurred with the evolution of volatile base, presumably dimethylamine. Pyman (*loc. cit.*) records m. p. 205—206° (corr.) for the methine salt. A portion of the methine base, recovered from the hydrochloride, was converted into the picrate. This crystallised from ethanol as yellow needles, m. p. 176—180°, unchanged by repeated recrystallisation. Pyman (*loc. cit.*) reports m. p. 195—196° (corr.).

Dihydro-N-*methylpavinemethine* (XII).—A solution of *N*-methylpavinemethine hydrochloride (1 g.) and hydrated sodium acetate (1·1 g.; *ca.* 3 equiv.) in ethanol (45 ml.) was shaken with hydrogen and platinic oxide (50 mg.). Uptake of hydrogen (1·0 mol.) was complete in 1·25 hr. After removal of the catalyst, the solution was evaporated to dryness under reduced pressure and the residue was dissolved in water (20 ml.). This solution was acidified to Congo-red, thoroughly extracted with ether, and then made strongly alkaline. The precipitated base was extracted into ether (3 × 50 ml.) and recovered as a colourless glass (0·743 g.) by evaporation of the dried extract. It crystallised from ether to afford *dihydro*-N-*methylpavinemethine* (XII) as colourless prisms, m. p. 117—119°. A sample was distilled at 130—140°(bath)/0·05 mm., crystallised from ether, and dried at 56° for 2 hr. (Found: C, 71·0; H, 7·6; N, 3·8. $C_{22}H_{29}O_4N$ requires C, 71·1; H, 7·85; N, 3·8%).

Dihydro-N-*methylpavinemethine Methiodide* (XIII; X = I).—A solution of the foregoing base (3·3 g.) in anhydrous ether (100 ml.) and an excess of methyl iodide (1 ml.) was kept overnight in the dark. The precipitated *methiodide* (XIII; X = I) was collected (4·2 g., 92%) and was recrystallised by dissolving the finely powdered salt in hot methanol then immediately cooling the solution. Pale yellow rods were obtained, having m. p. 188—200° (decomp.), raised by recrystallisation from methanol in the same way to 194—200° (decomp.) (Found, in material dried at 20°: C, 54·1; H, 6·4; I, 24·8. $C_{23}H_{32}O_4NI$ requires C, 53·8; H, 6·3; I, 24·7%).

Dihydropavinebismethine (2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-5 : 6-*dibenzo*cyclo*octa*-1 : 3 : 5-*triene*) (XIV).—A solution of the foregoing methiodide (4·2 g.) in 50% aqueous methanol (200 ml.) was shaken with moist silver oxide (from 10 g. silver nitrate) for 45 min. and then filtered. The clear filtrate and washings, now free from iodide ion, were concentrated below

40° under reduced pressure to *ca.* 80 ml. Potassium hydroxide (80 g.) was added; a colourless oil separated which increased in amount as the solution was heated under reflux for 5 hr. The volatile base evolved during this period was collected in dilute hydrochloric acid and identified as trimethylamine by conversion into the picrate, m. p. and mixed m. p. 217°.

The oil present in the main reaction mixture was extracted with ether (3 × 150 ml.), and the extract was washed with water, twice with dilute hydrochloric acid, and finally with water. Evaporation of the dried ethereal solution left a crystalline residue of *dihydropavinebismethine* (XIV) (2·26 g., 86%), m. p. 152—154°. It formed glistening plates, m. p. 154—156°, from ethanol (Found, in material dried at 110°: C, 73·5; H, 7·0. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

The basic fraction (0·15 g.) separated when the acidic extracts above were made alkaline, and was isolated by ether extraction as usual. Recrystallised from ether, it had m. p. 113—119° raised to 114—120° in admixture with an authentic sample of dihydro-*N*-methylpavinemethine (XII).

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-5 : 6-*dibenzo*cyclo*octa*-1 : 5-*diene* (XIX).—The foregoing product, previously dried at 110° *in vacuo*, was shaken in ethanol (10 ml.) with platinic oxide (10 mg.) and hydrogen at room temperature and atmospheric pressure. The uptake of hydrogen (0·97 mol.) was complete in 3 hr. After removal of the catalyst, the solution was concentrated. The *dibenzo*cyclo*octadiene* separated as colourless plates, m. p. 198—200° raised by recrystallisation from ethanol and sublimation at 145—160° (bath)/0·01 mm. to 201—203° (Found: C, 73·1; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%).

2 : 2′-*Dicarboxy*-4 : 5 : 4′ : 5′-*tetramethoxydibenzyl* (XV).—A solution of 2 : 2′-diacetyl-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (0·266 g.) (Battersby and Binks, following paper) in dioxan (20 ml.) was oxidised with alkaline sodium hypochlorite (6 ml.) as described for the preparation of 2-carboxy-4 : 5 : 3′ : 4′-tetramethoxydibenzyl (Battersby and Binks, *loc. cit.*). The acidic fraction crystallised from glacial acetic acid, to afford the *dicarboxylic acid* (XV) as colourless needles (0·231 g., 93%), m. p. 310—312° (decomp.) unchanged by further recrystallisation (Found: C, 61·3; H, 5·6%; equiv. 185. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·7%; equiv. 195).

Heating the acid (0·1 g.) in methanol (60 ml.) and concentrated sulphuric acid (1 ml.) for 24 hr., concentration to one-third volume under reduced pressure, filtration whilst hot, and cooling gave the *dimethyl ester* (XVII) as long, colourless needles (40 mg.), m. p. 176—178°, raised to 182—185° by recrystallisation from methanol (Found: C, 63·4; H, 6·3. $C_{22}H_{26}O_8$ requires C, 63·1; H, 6·3%).

Oxidation of Dihydropavinebismethine (XIV).—Potassium permanganate (1·174 g.; equiv. to 6 O) in acetone (160 ml.) and water (80 ml.) was added during 2 hr. to a stirred solution of dihydropavinebismethine (0·599 g.) in acetone (100 ml.) at 50°. The oxidising agent had been largely consumed by the end of the addition. Next morning the slight excess of permanganate was destroyed with aqueous hydrogen peroxide and the manganese dioxide removed. The filter pad was extracted with boiling acetone (2 × 50 ml.) and boiling 0·01N-sodium hydroxide (2 × 50 ml.), and the washings were combined with the main aqueous solution. This was concentrated under reduced pressure until free from acetone and then extracted with ether (3 × 100 ml.) to afford the neutral fraction (*A*) (0·15 g.) which was recovered from the dried ethereal solution by evaporation. The aqueous layer was acidified to Congo-red, a gel forming which was coagulated by heat. The solid was collected, dried *in vacuo*, and recrystallised twice from glacial acetic acid. 2 : 2′-Dicarboxy-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (XV) separated as colourless needles (0·43 g., 60%), m. p. 310—312° (decomp.) unchanged in admixture with the sample prepared as above. A portion was converted into the dimethyl ester, identical with authentic (XVII) in crystal form, m. p., and mixed m. p.

The neutral fraction *A* crystallised from a large volume of ethanol to give colourless needles (85 mg.), m. p. 242—244° raised to 252—254° by repeated recrystallisation from the same solvent (Found, in material dried at 110°: C, 66·9, 67·1; H, 5·3, 5·8. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%). This *substance* gave (*a*) a deep red 2 : 4-dinitrophenylhydrazone, (*b*) no colour reaction with *o*-dianisidine under conditions which gave a strong yellow colour with veratraldehyde, and (*c*) a brownish-yellow colour when a portion (9·7 mg.) was heated under reflux with *o*-phenylenediamine (6 mg.) in ethanol (6 ml.), and glacial acetic acid (1 drop) for 4 hr. (no phenazine derivative could be isolated).

Hydrogenolysis of Dihydro-N-*methylpavinemethine Methochloride* (XIII; X = Cl).—A solution of the methiodide (XIII; X = I) (0·406 g.) in 50% aqueous ethanol (140 ml.) was shaken for 2 hr. with freshly prepared silver chloride (from 0·41 g. of silver nitrate). The silver salts were then filtered off and washed with ethanol. The filtrate and washings, now free from iodide ion, were shaken with 10% palladium–charcoal (0·5 g.) and hydrogen for 1·5 hr. After removal of the catalyst, the solution was concentrated under reduced pressure, the dibenzo*cyclo*octadiene (XIX) separating (40 mg.; m. p. 200—203°, raised to 202—203° in admixture with the earlier preparation).

Reductive Fission of N-*Methylpavine Methochloride*.—The methochloride of *N*-methylpavine (X), prepared from the related methiodide by Pyman's method (*J.*, 1910, **97**, 1320), was dried at 100°/0·05 mm. for 1·5 hr. and a portion (0·130 g.) was suspended in anhydrous liquid ammonia (15 ml.). Sodium was added until a blue colour was obtained which faded only slowly. After cautious addition of water (20 ml.), the mixture was poured into water (100 ml.) and extracted with ether (3 × 50 ml.). Evaporation of the dried extract left a colourless gum (0·109 g.) which crystallised completely on being seeded with dihydro-*N*-methylpavinemethine (XII). The m. p. of the product, 117—119°, was unchanged by further recrystallisation or by admixture with the earlier preparation of (XII).

Hofmann Degradation of N-*Methylpavinemethine Methiodide* (XX; X = I).—A suspension of the methiodide (2·58 g.), prepared from *N*-methylpavinemethine as described by Pyman (*J.*, 1915, **107**, 176), in water (180 ml.) was shaken with moist silver oxide from 4 g. of silver nitrate until the solution was free from iodide ion. Potassium hydroxide (200 g.) was added to the filtered solution (200 ml.), which was then heated under reflux for 5 hr. The volatile base evolved was collected in dilute hydrochloric acid and identified as trimethylamine by conversion into the picrate, m. p. and mixed m. p. 217°. The neutral fraction (1·49 g.) from the main aqueous solution was isolated as in the preparation of dihydropavinebismethine. A portion of it, recrystallised twice from benzene, afforded the alcohol (XXI; R = OH) as nodules, m. p. 145—146°. The analytical sample was sublimed at 180°(bath)/5 × 10^{-4} mm. (Found: C, 70·3; H, 6·4; active H, 0·37. Calc. for $C_{20}H_{22}O_5$: C, 70·2; H, 6·5; active H, 0·29%). Pyman (*loc. cit.*) records m. p. 147—148° (corr.).

Decomposition of N-*Methylpavinemethine Methohydroxide* (XX; X = OH).—The corresponding methiodide (0·25 g.) was converted into the methohydroxide as in the preceding experiment, and the solution (15 ml.) was heated under reflux. A gum separated rapidly on the sides of the flask and after 15 min. the cooled solution was decanted from the gum which was washed with water and dried *in vacuo* (138 mg., 83%). The decanted solution was heated under reflux for a further 1 hr., cooled, and extracted with ether. Evaporation of the dried ethereal solution left a gum (19 mg., 11%). When the final aqueous solution was evaporated to dryness, only 4 mg. of residue remained. Crystallisation of the combined gummy fractions from benzene afforded the alcohol (XXI; R = OH) (128 mg.), m. p. 145—146° alone or in admixture with the foregoing product.

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-5 : 6-*dibenzo*cyclo*octatetraene* (XXII).—A solution of the alcohol (0·34 g.) obtained in the foregoing experiment, in rigorously purified dioxan (10 ml.) and aqueous 4N-sulphuric acid (10 ml.), was heated under reflux for 6 hr. After removal of the dioxan under reduced pressure, the solution was extracted with ether (3 × 50 ml.), and the combined extracts were washed with aqueous sodium hydroxide and water. Evaporation of the ether left a gum (0·235 g.) which was dissolved in benzene and run on to a column of alumina. Elution with benzene (80 ml.) followed by ether–benzene (1 : 9; 60 ml.) gave the *dibenzo*cyclo*octatetraene* (XXII) as colourless needles (37 mg., 11%), m. p. 159—164°, as the first fraction; later fractions were only semi-crystalline. The crystalline material was recrystallised from benzene for analysis (Found: C, 73·7; H, 6·5. $C_{20}H_{20}O_4$ requires C, 74·0; H, 6·2%). A solution of the dibenzo*cyclo*octatetraene (14·05 mg.) in ethanol (12·5 ml.) was shaken with hydrogen and platinum. Uptake of hydrogen proceeded smoothly, but ceased abruptly when crystallisation of the reduction product occurred on the catalyst. At this point, 1·54 ml. had been absorbed (theory for 2 mols., 2·08 ml.). The catalyst was filtered off from the hot solution and, on cooling, crystallisation again occurred to afford the dibenzo*cyclo*octadiene (XIX), m. p. and mixed m. p. 197—201°.

Decomposition of Dihydro-N-*methylpavinemethine Methiodide* (XIII; X = I).—A solution of the methiodide (207 mg.) in water (9 ml.) was heated under reflux for 4 hr., diluted with water (15 ml.), cooled, and extracted several times with ether, each extract being washed once with water. The combined aqueous solutions were concentrated under reduced pressure to 8 ml. and the crystals which separated were collected (132 mg., 64%). This material contained ionic iodine and had m. p. 190° alone or in admixture with the starting material. The ethereal extracts, after being dried and evaporated, afforded a gum (44 mg., 32%) which crystallised from ethanol to give the *alcohol* (XXIII) as colourless compact prisms, m. p. 177—179° (Found: C, 69·3; H, 6·8; I, 0. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%).

Hydrogenation of the Alcohol (XXI; R = OH).—This alcohol (118 mg.) was shaken in ethanol

(30 ml.) with hydrogen and platinic oxide until the uptake was complete. After removal of the catalyst, the solution was concentrated to low volume. The dihydro-alcohol (XXIII) crystallised, m. p. 172—176° raised to 174—177° in admixture with the foregoing product.

Dehydration of the Dihydro-alcohol (XXIII).—A solution of the dihydro-alcohol (0·25 g.) in purified dioxan (10 ml.) and aqueous 4N-sulphuric acid (10 ml.) was heated under reflux for 3 hr. Crystals of dihydropavinebismethine (XIV) (96 mg., 40%) separated from the cooled solution. These recrystallised from ethanol as colourless plates, m. p. 152—154° alone or in admixture with the sample of (XIV) prepared earlier (m. p. 152—154° in the same bath). A portion (52·6 mg.) of this product was reduced in alcohol with hydrogen and platinum, and the product, isolated in the usual way, was the dibenzo*cyclo*octadiene (XIX), m. p. and mixed m. p. 196—200°.

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