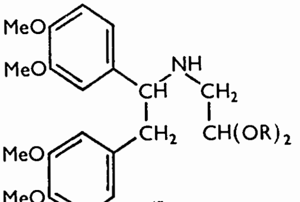
405. *Pavine. Part II.* The Structure of* iso*Pavine.*

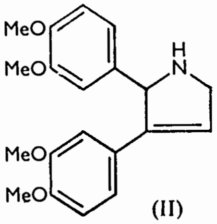
By A. R. BATTERSBY and D. A. YEOWELL.

The base obtained by acid-catalysed cyclisation of *N*-(2 : 2-dimethoxyethyl)-1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (I; R = Me) is shown to have the structure (IV) and is named *iso*pavine.

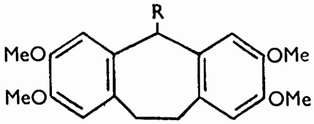
THE action of concentrated sulphuric acid on the acetal (I; R = Et) has recently been shown to yield a base, $C_{20}H_{23}O_4N$, by Guthrie, Frank, and Purves.[1] These authors assigned to it the structure (II) on the basis of its mode of formation, properties, and infrared spectrum, and the fact that it differed from the dihydropapaverines and pavine.[2,3] This structure seemed unlikely to us since the methylene group attacked in its supposed formation is not sufficiently activated toward electrophilic reagents. Moreover, we had found[4] that aldehydes and acetals condense smoothly with 3 : 4 : 3′ : 4′-tetramethoxydibenzyl in the presence of sulphuric acid to give dibenzo*cyclo*heptadiene derivatives (III). The probable structure of the base $C_{20}H_{23}O_4N$ is therefore (IV), which is practically strainless on Courtauld models. Structure (IV) was one of those considered[3,5] for pavine and therefore the elucidation of the structure of the new base bears directly on our earlier work. It is convenient to name the present base *iso*pavine.



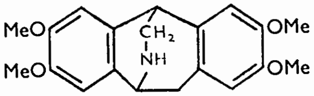
(I)



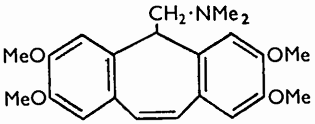
(II)



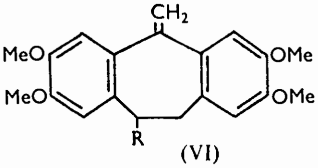
(III)



(IV)



(V)



(VI)

*iso*Pavine was prepared by a simplification of the original method;[1] as a by-product 3 : 4 : 3′ : 4′-tetramethoxybenzil was obtained, evidently derived from some basic intermediate (see p. **1990**), but we have not investigated this aspect further. The *iso*pavine base absorbed carbon dioxide readily from the atmosphere to give a carbonate or carbamate. This unstable derivative and the base itself were readily acetylated, to yield crystalline *N*-acetyl*iso*pavine whose ultraviolet absorption corresponded to the presence of two isolated veratrole residues (see Figure); also, the acetyl derivative was unaffected by hydrogenation over platinum. These observations eliminate structure (II) for *iso*pavine.

When *iso*pavine was heated with an excess of methyl iodide, the methiodide was formed, which was smoothly degraded by Hofmann's method. On the basis of structure (IV) for *iso*pavine, the resultant *N*-methyl*iso*pavinemethine must be represented by structure (V) or (VI; R = NMe_2). The ultraviolet absorption of the methine supported structure (V) since the alternative structure (VI; R = NMe_2) would undoubtedly have ultraviolet

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* Part I, *J.*, 1955, 2888.

[1] Guthrie, Frank, and Purves, *Canad. J. Chem.*, 1955, **33**, 729.

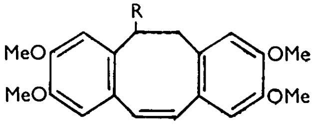
[2] Schöpf, *Angew. Chem.*, 1950, **62**, 453.

[3] Battersby and Binks, *J.*, 1955, 2888.

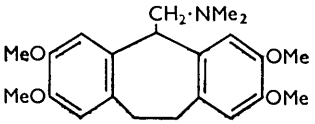
[4] *Idem*, *J.*, 1955, 2896.

[5] Schöpf, *Experientia*, 1949, **5**, 201.

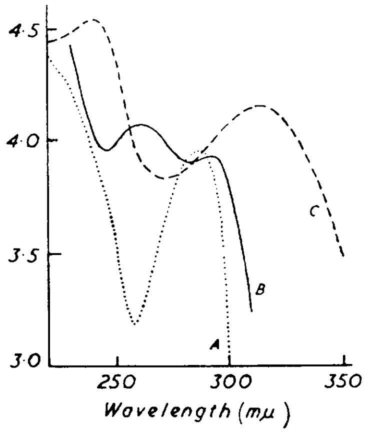
absorption characteristics very similar to those of the methylenedibenzo*cyclo*heptadiene[4] (VI; R = H). In fact, the Figure shows that *N*-methyl*iso*pavinemethine has a very different absorption curve, and it also differs from the absorption curve of *N*-methylpavinemethine (VII; R = NMe_2). Inspection of models shows that the reason for the difference between the bases (VII; R = NMe_2) and (V) is that the aromatic rings in the former are appreciably further than in the latter from the coplanar state necessary for full interaction with the double bond.



(VII)

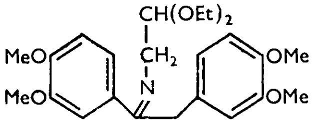


(VIII)

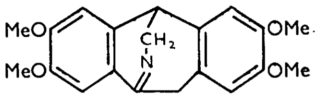


Ultraviolet absorption spectra in ethanol of (*A*) N-*acetyl*iso*pavine,* (*B*) *the methylenedibenzo*cyclo*heptadiene* (VI; R = H, *and* (*C*) N-*methyl*iso*pavinemethine* (V).

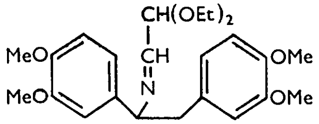
Further evidence in favour of structure (V) was that *N*-methyl*iso*pavinemethine methiodide was unchanged by water at 100° for 20 hr.: this stability would not be expected for the methiodide of the base (VI) since the closely related *N*-methylpavinemethine methiodide (VII; R = $^{+}NMe_3\}I^{-}$) is largely decomposed[3] under these conditions after 15 min.



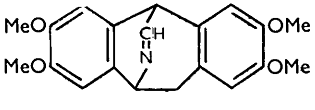
(IX)



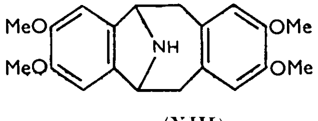
(X)



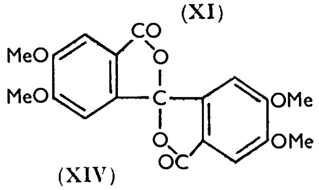
(XI)



(XII)



(XIII)



(XIV)

N-Methyl*iso*pavinemethine absorbed one mol. of hydrogen catalytically, the crystalline product being identical with the dibenzo*cyclo*heptadiene derivative (VIII) synthesised earlier and of fully established structure.[4] The structures of *iso*pavine and the corresponding methine are therefore established as (IV) and (V) respectively.

With the cyclisation of the acetal (I) now understood, one can consider the structure of the product, $C_{20}H_{21}O_4N$, obtained by Fritsch[6] from the similar cyclisation of the acetal

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[6] Fritsch, *Annalen*, 1903, **329**, 37.

(IX), and also the nature of an isomeric base prepared by Schlitter and Müller [7] by cyclisation of the isomeric acetal (XI). The structures for these bases proposed by Guthrie *et al.*,[1] based upon (II), seem very unlikely since they are both α-pyrrolenines, the unknown tautomeric form of pyrrole. Structure (X) for Fritsch's product, based upon *iso*pavine (IV), can be rejected as sterically impossible and structure (XII) which can be considered for Schlitter and Müller's base is, when built as a model, considerably strained but probably not sufficiently so to eliminate it. Further work is required on these bases.

During the preparation of this paper, that of Waldmann and Chwala became available [8] on the structure of the base referred to here as *iso*pavine. Apparently unaware of the Canadian work,[1] they consider structures (IV) and (XIII) and select the former on the basis of the oxidation of *iso*pavine by alkaline permanganate to a crystalline product, $C_{19}H_{16}O_8$ (3—5% yield), which is assigned the structure (XIV).

EXPERIMENTAL

Analytical samples were dried at 100° *in vacuo* over phosphoric oxide, unless otherwise stated.

N-(2 : *2-Dimethoxyethyl)-*1 : *2-bis-*(3 : *4-dimethoxyphenyl)ethylamine* (I; R = Me).—A mixture of 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (4·71 g.) and 2 : 2-dimethoxyethylamine (4·69 g.) was heated under nitrogen from 105° to 125° during 40 min., the excess of amine slowly distilling, leaving a red-brown gum (5·63 g.). This crystallised partially from methanol to give 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (2·4 g.), m. p. and mixed m. p. 102—103°. The mother-liquors and washings (total 50 ml.) from this crop were shaken at 20°/760 mm. with platinic oxide (0·2 g.) and hydrogen, absorption of gas (163 ml.) being complete in 3 hr. Evaporation of the filtered solution left a gum which was mainly soluble in ether; the insoluble tar was rejected. The ethereal solution was shaken with N-hydrochloric acid (24 ml.), and the aqueous layer was quickly made alkaline; the *ethylamine derivative* (I; R = Me) then separated as colourless stout prisms (1·82 g., 62% based on unrecovered starting material), m. p. 92—95°, raised to 99° by recrystallisation from methanol (Found, in material dried at 80°: C, 65·3; H, 8·0. $C_{22}H_{31}O_6N$ requires C, 65·2; H, 7·7%). The aqueous alkaline mother-liquors from the base (I; R = Me), when exposed to the air for 24 hr., deposited a further crop of yellow crystals which, purified by recrystallisation from acetic acid, had m. p. 229° (Kubiczek [9] reports m. p. 228° for 3 : 4 : 3′ : 4′-tetramethoxybenzil) (Found: C, 65·7; H, 5·9; N, 0·0. Calc. for $C_{18}H_{18}O_6$: C, 65·45; H, 5·5%), ultraviolet absorption in ethanol, $\lambda_{min.}$ 251 and 300, $\lambda_{max.}$ 230, 284, 322 mμ (log ε 3·35, 4·17, 4·37, 4·26, 4·29, respectively).

iso*Pavine and* N-*Acetyl*iso*pavine.*—The foregoing acetal (1 g.) was cyclised essentially as described by Guthrie *et al.*[1] and the mixture was worked up for base in the usual way but with exclusion of carbon dioxide. A red gum (0·77 g.) was obtained which crystallised from ethanol, the m. p. initially being 149—151° (reported [1] m. p. 150—154°) but changing to 165—175° after contact with air. The material of higher m. p. effervesced when treated with aqueous hydrochloric acid.

The base (25 mg.) was acetylated in the usual way and the neutral product crystallised from ethanol, to give *N*-acetyl*iso*pavine (19 mg.), m. p. 202—203° (lit.,[1] m. p. 203·5—204°), $\lambda_{min.}$ 258 (log ε 3·18), $\lambda_{max.}$ 287 (log ε 3·95) in ethanol. No gas was absorbed when a solution of *N*-acetyl-*iso*pavine in ethanol was shaken with platinum and hydrogen at 20°/750 mm.

N-*Methyl*iso*pavine Methiodide.*—A solution of the foregoing base (0·77 g.) in water (5 ml.) containing hydrochloric acid (1 equiv.) was treated with anhydrous sodium carbonate (0·98 g.), methanol (15 ml.), and methyl iodide (7 ml.). After the mixture had been heated under reflux for 9 hr., the methanol and excess of methyl iodide were evaporated, and the aqueous solution was acidified with hydrochloric acid and treated with potassium iodide (1 g.). The precipitated quaternary iodide was collected and that remaining in solution was extracted into chloroform and recovered from the dried solution by evaporation. The combined crude iodide was recrystallised (charcoal) from water by precipitation of the salt (0·85 g., 71%) with potassium iodide (3·5 g.). Recrystallisation of this *salt* twice from water and twice from methanol gave

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[7] Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 914.

[8] Waldmann and Chwala, *Annalen*, 1957, **609**, 125.

[9] Kubiczek, *Monatsh.*, 1946, **76**, 54.

colourless prisms, m. p. 230° (decomp.) after sintering at 169° (Found: C, 52·2; H, 5·8; N, 2·8. $C_{22}H_{28}O_4NI,CH_4O$ requires C, 52·2; H, 6·1; N, 2·65%).

N-*Methyl*iso*pavinemethine* (V).—A solution of *N*-methyl*iso*pavine methiodide (0·25 g.) in warm water (10 ml.) was shaken with moist silver oxide (from 0·5 g. of silver nitrate) for 3 hr. and then filtered. The clear filtrate and washings (now 30 ml.) were treated with potassium hydroxide (30 g.) and heated under reflux for 3 hr., a crystalline precipitate being formed. This was extracted into ether and separated in the usual way into a neutral (3 mg.) and a basic fraction (0·15 g.), m. p. 157—158°. Crystallisation of the latter from ethanol gave the *methine base*, m. p. 158—159° (Found: C, 71·9; H, 7·6; N, 3·8. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·4; N, 3·8%), ultraviolet absorption in ethanol, $\lambda_{max.}$ 239, 314; $\lambda_{min.}$ 272 (log ε 4·54, 4·15, 3·83, respectively).

N-*Methyl*iso*pavinemethine Methiodide*.—A solution of the methine (20 mg.) in ether (3 ml.) and methyl iodide (0·3 ml.) was kept overnight. Crystals separated (23 mg.), having m. p. 269° after some decomp. at 170°. These crystals were washed thoroughly with ether.

All this product was heated under reflux in water (3·5 ml.) for 20 hr. without the smell of trimethylamine being detected. The solution was then diluted to 10 ml. and extracted thrice with ether which removed a trace of brown gum. Concentration of the aqueous layer gave starting material (23 mg.) which was recrystallised several times from water to afford the pure *methine methiodide* (Found: C, 54·1; H, 5·9. $C_{23}H_{30}O_4NI$ requires C, 54·0; H, 5·9%).

Dihydro-N-*methyl*iso*pavinemethine* (3-*Dimethylaminomethyl*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (VIII).—The methine (V) (20 mg.) was shaken with pre-reduced platinum catalyst (10 mg.) in glacial acetic acid (10 ml.) under hydrogen at 17°/761 mm. Absorption of gas (1·02 mol.) was complete in 8·5 hr. After filtration, the solution was evaporated to dryness and the residue was dissolved in aqueous hydrochloric acid. This solution was extracted thrice with ether and then basified; crystals separated (20 mg.), having m. p. 134—136°, raised to 136—138° by recrystallisation from aqueous methanol, unchanged in admixture with an authentic sample [4] of the base (VIII). The two samples of the base (VIII) had identical infrared spectra.

THE UNIVERSITY, BRISTOL. [*Received, January* 30*th*, 1958.]