403. *Some Derivatives of* 3 : 4 : 3′ : 4′-*Tetramethoxydiphenyl.*

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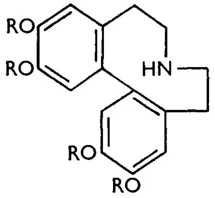
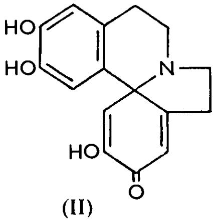
Some compounds related to 3 : 4 : 3′ : 4′-tetramethoxydiphenyl have been prepared in the course of unsuccessful attempts to obtain an azadibenzo*cyclo*nonane as potential intermediate for synthesis of Erythrina alkaloids. A new reaction involving nucleophilic displacement of aromatic halogen, leading to dihydroindole formation, is described.

A PROJECTED synthesis in the Erythrina alkaloid field envisaged oxidation of the azadibenzo*cyclo*nonane (I; R = H) to the tetracylic system (II), following a possible biogenetic route. However, we failed to obtain the starting material (I). In this paper various intermediates prepared are described.

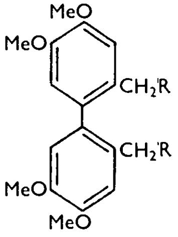
Attention was first directed to the synthesis of 4 : 5 : 4′ : 5′-tetramethoxydiphenyl-2 : 2′-diacetic acid (III; R = CO_2H) in the hope of subsequently obtaining the cyclic imide which might later be reduced. Iodination of 4 : 5-dimethoxyphenylacetic acid gave the 2-iodo-derivative whose ester was converted by the Ullmann reaction into the diphenyl derivative (III; R = CO_2Me). The free acid and diamide were readily obtained, but attempts to prepare the imide were unsuccessful. Reduction of the diester by lithium aluminium hydride gave the diol (III; R = CH_2·OH) but, unexpectedly, attempts to replace the hydroxyl groups by halogen failed. In another approach, 2-iodo-4 : 5-dimethoxytoluene, obtained by iodination of 4-methylveratrole with iodine monochloride, gave 4 : 5 : 4′ : 5′-tetramethoxy-2 : 2′-dimethyldiphenyl (III; R = H) by the Ullmann reaction, and this with *N*-bromosuccinimide gave the dibromo-derivative (III; R = Br).



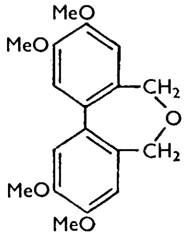
(I)



(II)

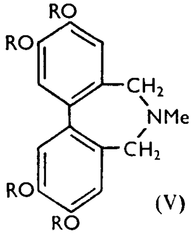


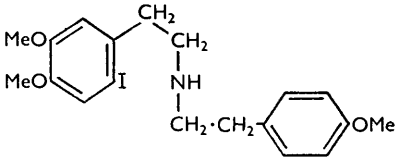
(III)

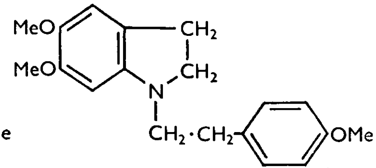


(IV)

The halogen atoms in this compound were very labile: boiling the compound with methanol rapidly gave the ether (III; R = OMe), and aqueous-alcoholic potassium cyanide the dinitrile (III; R = CN), together with a small amount of the oxepin[1] (IV).


(V)


(VI)


(VII)

The oxepin was obtained in higher yield when the dibromide was treated with sodium hydroxide. It was hoped that reduction of the dinitrile would give the amine (I; R = Me) as one of the products, but none of it was isolated even by hydrogenation over Raney nickel conducted in very dilute solutions in order to favour intramolecular reaction.

The dibromo-compound (III; R = Br) reacted readily with methylamine, giving the azepine[1] (V; R = Me), demethylated by hydrobromic acid to the tetrahydroxy-compound (V; R = H), illustrating the ease of formation of a seven-membered ring in this series in contrast to the difficulty of obtaining the desired nine-membered ring.

Hydrogenation of 3 : 4-dimethoxyphenylacetonitrile over Raney nickel gave a mixture of about equal amounts of 3 : 4-dimethoxyphenethylamine and bis-3 : 4-dimethoxyphenethylamine, easily separated by distillation. Iodination of the secondary amine was examined with a view to subsequent intramolecular Ullmann reaction. A mono- and a di-iodo-derivative were obtained by treatment with iodine monochloride. The free bases were unstable, rapidly liberating iodide on storage. When the monoiodo-compound (VI) was liberated from its stable hydrochloride and taken up in benzene, the solution soon deposited crystals of the hydriodide of an iodine-free base, further characterised as picrate. Evidently cyclisation had occurred, giving the dihydroindole (VII). This ready displacement of nuclear halogen is noteworthy.

To obviate this cyclisation, the stable *N*-benzenesulphonyl derivative of the di-iodo-amine was prepared, but attempted Ullmann reactions under a variety of conditions gave none of the desired product.

EXPERIMENTAL

2-*Iodo*-4 : 5-*dimethoxyphenylacetic Acid*.—A solution of 3 : 4-dimethoxyphenylacetic acid (75 g.) and iodine monochloride (75 g.) in acetic acid (900 ml.) was kept at room temperature for a week. Addition of water (1·5 l.) precipitated the product (90 g.) which was collected and washed with sodium thiosulphate solution. Recrystallised from aqueous ethanol, the *iodo-acid* formed colourless needles, m. p. 164—165° (Found: C, 37·8; H, 3·8. $C_{10}H_{11}O_4I$ requires C, 37·3; H, 3·4%). With refluxing, absolute methanol containing a little concentrated sulphuric acid, it gave the *methyl ester*, needles, m. p. 72—73° (from aqueous methanol) (Found: C, 39·3; H, 4·3. $C_{11}H_{13}O_4I$ requires C, 39·3; H, 3·9%).

Dimethyl 4 : 5 : 4′ : 5′-*Tetramethoxydiphenyl*-2 : 2′-*diacetate*.—The above ester (5 g.) and copper bronze (30 g.) were slowly heated to 200—220° and kept at that temperature for 2 hr. with occasional stirring, then cooled and extracted (Soxhlet) for 24 hr. with boiling benzene. Removal of the benzene left a dark oil, which on two recrystallisations from ethanol (charcoal) gave *dimethyl* 4 : 5 : 4′ : 5′-*tetramethoxydiphenyl*-2 : 2′-*diacetate* (1·2 g.) as rods, m. p. 145° (Found: C, 63·6; H, 6·3. $C_{22}H_{26}O_8$ requires C, 63·2; H, 6·1%). Hydrolysis with boiling aqueous sodium hydroxide gave the corresponding *acid* which formed needles, m. p. 228—230°, from aqueous ethanol (Found: C, 61·8; H, 6·2. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·7%).

The acid (3 g.) was refluxed with thionyl chloride (5 ml.) until all was dissolved (10—15 min.), and the excess of thionyl chloride was then removed under reduced pressure, leaving

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[1] Cf. Beaven, Hall, Lesslie, Turner, and Bird, *J.*, 1954, 131.

crystalline acid chloride. This was triturated in small portions with ammonia solution (50 ml.; *d* 0·88) in a mortar. The resulting *diamide* was collected, washed, and recrystallised from ethanol as prisms, m. p. 233—234° (Found: C, 61·7; H, 6·7; N, 6·8. $C_{20}H_{24}O_6N_2$ requires C, 61·9; H, 6·2; N, 7·2%).

2 : 2′-*Di*-(2-*hydroxyethyl*)-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl.*—The foregoing ester (3·35 g.) was extracted from a Soxhlet thimble into a solution of lithium aluminium hydride (1·5 g.) in ether (200 ml.). When the extraction was complete (about 10 hr.), the excess of hydride was destroyed by moist ether, and dilute sulphuric acid was added to dissolve inorganic material, leaving the product (which was very sparingly soluble in ether) as a white suspension. Ethyl acetate was added until all had dissolved, the aqueous layer was separated and discarded, the organic layer dried (Na_2SO_4), and the solvent removed. 2 : 2′-*Di*-(2-*hydroxyethyl*)-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* formed rhombs, m. p. 148—149·5°, from ethyl acetate–light petroleum (Found: C, 66·3; H, 7·6. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%).

4 : 5 : 4′ : 5′-*Tetramethoxy*-2 : 2′-*dimethyldiphenyl.*—3 : 4-Dimethoxytoluene (35 g.) in acetic acid (110 ml.) was treated with iodine monochloride (50 g.) in acetic acid (110 ml.). Next morning the mixture was poured into water (1·5 l.) and sulphur dioxide passed into it. The dark solid was collected and recrystallised from aqueous methanol. 2-*Iodo*-4 : 5-*dimethoxytoluene* (54 g., 85%) formed plates, m. p. 64° (Found: C, 39·1; H, 4·1. $C_9H_{11}O_2I$ requires C, 38·9; H, 4·0%). The iodo-compound (4 g.) and copper bronze (4 g.) were heated at 200—210° for 1·5 hr. The product was sublimed out of the resulting mass at 200°/1 mm., giving 4 : 5 : 4′ : 5′-*tetramethoxy*-2 : 2′-*dimethyldiphenyl* (1·2 g.), white plates, m. p. 115—116° (from aqueous methanol) (Found: C, 71·4; H, 7·2. $C_{18}H_{22}O_5$ requires C, 71·5; H, 7·3%).

2 : 2′-*Bisbromomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl.*—To a solution of the foregoing diphenyl (1·2 g.) in dry carbon tetrachloride (20 ml.), *N*-bromosuccinimide (1·4 g.) and benzoyl peroxide (0·05 g.) were added, and the mixture refluxed for 4 hr. After filtration from succinimide, the solvent was removed, leaving brown crystals. Recrystallisation from ethyl acetate gave 2 : 2′-*bisbromomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* (1·2 g., 65%) as hexagonal plates, m. p. 179—180° (Found: C, 47·1; H, 4·6. $C_{18}H_{20}O_4Br_2$ requires C, 47·0; H, 4·4%). An alcoholic solution gave an immediate precipitate of silver bromide on treatment with silver nitrate. When a methanol solution of the dibromo-compound was refluxed for 1 hr. and then concentrated, 2 : 2′-*dimethoxymethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* separated as needles, m. p. 110° (Found: C, 66·6; H, 7·4. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%).

The dibromo-compound (1·8 g.) was refluxed for 2 hr. with sodium hydroxide (3 g.) in water (15 ml.) and ethanol (5 ml.). After cooling and dilution with water, the pale orange solid was filtered off and recrystallised from benzene, giving 2 : 7-*dihydro*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-3 : 4-5 : 6-*dibenzoxepin* (IV) as plates m. p. 249° (Found: C, 68·2; H, 6·0. $C_{18}H_{20}O_5$ requires C, 68·6; H, 6·3%).

2 : 7-*Dihydro*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine.*—To a solution of the foregoing dibromo-compound (14·8 g.) in dry benzene (100 ml.) a solution of methylamine (3 g.) in dry benzene (100 ml.) was added and the mixture set aside overnight. The methylamine hydrobromide which had separated was filtered off and the filtrate washed with water (to remove methylamine) and extracted with dilute hydrochloric acid. The acid extract was basified by ammonia and extracted with benzene. After separation and drying (Na_2SO_4), the benzene was removed, leaving the crude solid amine (5·3 g., 53%). Sublimation at 120—125°/0·02 mm. gave 2 : 7-*dihydro*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine* (V; R = Me) as needles, m. p. 160—162° (Found: N, 4·2. $C_{19}H_{23}O_4N$ requires N, 4·3%). The *picrate* formed yellow needles, m. p. 211—213°, from ethanol (Found: C, 54·0; H, 4·5; N, 10·2. $C_{19}H_{23}O_4N,C_6H_3O_7N_3$ requires C, 54·0; H, 4·7; N, 10·0%). The *methiodide* formed needles, m. p. 277—278° (decomp.), from ethanol (Found: C, 51·1; H, 5·5. $C_{19}H_{23}O_4N,CH_3I$ requires C, 51·0; H, 5·5%).

The azepine (4 g.) was refluxed for 1·5 hr. with hydrobromic acid (*d* 1·49; 20 ml.). The resulting solution was evaporated to dryness under reduced pressure and the residual solid recrystallised from acetone (charcoal), giving 2 : 7-*dihydro*-2′ : 3′ : 2″ : 3″-*tetrahydroxy*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine hydrobromide* as prisms, m. p. 170—172° (Found: C, 48·8; H, 5·1; N, 4·1. $C_{15}H_{15}O_4N,HBr,H_2O$ requires C, 48·5; H, 4·7; N, 3·8%).

2 : 2′-*Biscyanomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl.*—A solution of the foregoing dibromo-compound (4·2 g.) and potassium cyanide (16 g.) in ethanol (80 ml.) and water (20 ml.) was boiled under reflux for 1·5 hr. After evaporation of the ethanol the brown tarry residue

was taken up in ethyl acetate, washed with dilute hydrochloric acid and then with water, and dried ($CaCl_2$). The solvent was removed, leaving a brown gum which crystallised on addition of methanol. Two recrystallisations from methanol gave 2 : *2-biscyanomethyl-*4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* (1·5 g.) as needles, m. p. 163° (Found: C, 67·9; H, 5·9; N, 8·0. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%).

During the recrystallisation a sparingly soluble by-product was obtained in small amount. This was shown (mixed m. p.) to be the oxepin.

Bis-3 : 4-*dimethoxyphenethylamine*.—A solution of 3 : 4-dimethoxyphenylacetonitrile (50 g.) in ethanol (500 ml.) was hydrogenated over Raney nickel at 80 atm. at 90° for 5 hr. After filtration the solvent was removed and then 3 : 4-dimethoxyphenethylamine (23 g.) was distilled off at 118—120°/1·5 mm. The residual oil was dissolved in ether (50 ml.) and dry hydrogen chloride passed in. The precipitated hydrochloride was collected and recrystallised from ethanol, giving bis-3 : 4-dimethoxyphenethylamine hydrochloride (23 g.) as plates, m. p. 195—196°.

The foregoing hydrochloride (13 g.) in acetic acid (20 ml.) was treated with a solution of iodine monochloride (11 g.) in acetic acid (10 ml.). After 1 hr. the yellow crystalline precipitate was collected and twice recrystallised from ethanol, giving *di*-(6-*iodo*-3 : 4-*dimethoxyphenethyl*)-*amine hydrochloride* (15·5 g.) as yellow needles, m. p. 176—177° (Found: C, 37·2; H, 4·3. $C_{20}H_{26}O_4NClI_2$ requires C, 37·9; H, 4·2%).

2 : 3-*Dihydro*-5 : 6-*dimethoxy*-1-(3 : 4-*dimethoxyphenethyl*)*indole* (VII).—The foregoing experiment was repeated but with half of the quantity of iodine monochloride. The crude monoiodo-compound (VI) was shaken with aqueous sodium hydroxide and benzene. The benzene layer was separated and when kept for a week deposited dark crystals. On two recrystallisations from ethanol these yielded the *indole hydriodide* as pale brown needles, m. p. 194° (Found: C, 49·7; H, 5·6. $C_{20}H_{25}O_4N,HI,0{\cdot}5H_2O$ requires C, 50·0; H, 5·6%). The *picrate* formed yellow prisms, m. p. 155—156° (Found: C, 53·5; H, 5·3; N, 9·5. $C_{20}H_{25}O_4N,C_6H_3O_7N_3$ requires C, 54·5; H, 4·9; N, 9·8%).

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