The Synthesis of 2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*dienes and Related Compounds.*

By Alan R. Battersby and R. Binks.

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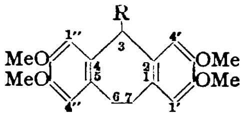
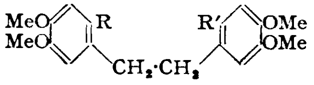
3 : 4 : 3′ : 4′-Tetramethoxydibenzyl reacts with aldehydes under strongly acidic conditions to give derivatives of 2′ : 3′ : 2″ : 3″-tetramethoxy-1 : 2-4 : 5-dibenzo*cyclo*hepta-1 : 4-diene (I ; R = H) in good yield. An alternative route to these compounds involves the preparation and cyclisation of 2-carboxy-4 : 5 : 3′ : 4′-tetramethoxydibenzyl. The products from the two routes have been correlated. A new reaction of sodium bismuthate is recorded briefly.

Our interest in the degradation products from pavine (Battersby and Binks, preceding paper) led us to prepare certain derivatives of the tetramethoxydibenzo*cyclo*heptadiene (I ; R = H). The analogous compound lacking the methoxyl groups and some derivatives of it have been prepared from 1 : 2-4 : 5-dibenzo*cyclo*hepta-1 : 4-dien-3-one, which is available by cyclisation of 2-carboxydibenzyl (Cope and Fenton, *J. Amer. Chem. Soc.*, 1951, **73**, 1673 ; Treibs and Klinkhammer, *Ber.*, 1951, **84**, 671).

In the methoxylated series, one synthesis of compounds of type (I) takes advantage of the activated state of the aromatic nuclei in 3 : 4 : 3′ : 4′-tetramethoxydibenzyl (II ; R = R′ = H) towards electrophilic reagents. Thus, acetaldehyde and the ether (II ; R = R′ = H) condensed at room temperature in the presence of concentrated sulphuric acid, giving the methyldibenzo*cyclo*heptadiene (I ; R = Me) in 60% yield. The molecular weight of this material eliminated possible structures for it which involve macrocyclic rings (cf. Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75**, 4281). 2 : 2-Dimethoxyethylamine and 2 : 2-dimethoxyethyl-*NN*-dimethylamine with the tetramethoxydibenzyl (II ; R = R′ = H) similarly gave good yields of basic products which were



(I)



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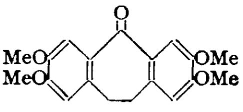
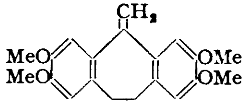
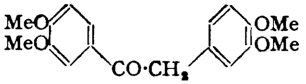


(III)

(IV)





(V)

assigned the structures (I; R = $CH_2 \cdot NH_2$ and $CH_2 \cdot NMe_2$ respectively). This method can clearly be extended to afford 1 : 2-4 : 5-dibenzo*cyclo*hepta-1 : 4-dienes from those derivatives of dibenzyl which carry 3- and 3′-alkoxyl groups and have the 6- and the 6′-position available.

In a second route to the tricyclic series the last step follows the work of Cope and Fenton and of Treibs and Klinkhammer (*locc. cit.*). 3 : 4 : 3′ : 4′-Tetramethoxydibenzyl and acetyl chloride in the presence of aluminium chloride gave smoothly a mixture of 2-acetyl-4 : 5 : 3′ : 4′-tetramethoxydibenzyl (II; R = Ac, R′ = H) and 2 : 2′-diacetyl-4 : 5 : 4′ : 5′-tetramethoxydibenzyl (II; R = R′ = Ac) which were separated by virtue of their different solubilities in ethanol. These structures can be assigned with confidence, since the 3 : 4-dimethoxy-derivatives of toluene and ethylbenzene are acylated at the 6-position under the conditions of the Friedel–Crafts reaction (Fargher and Perkin, *J.*, 1921, **119**, 1724; Shinoda and Sato, *J. Pharm. Soc. Japan*, 1927, **548**, 860). Oxidation of the monoketone with alkaline sodium hypochlorite yielded 2-carboxy-4 : 5 : 3′ : 4′-tetramethoxydibenzyl (II; R = CO_2H, R′ = H) which with phosphorus pentachloride gave the corresponding acid chloride. This was cyclised at room temperature with aluminium chloride in nitrobenzene to give the *cyclo*heptadienone (III); two crystalline forms of this ketone were isolated and found to be readily interconvertible. An attempt to prepare it from 3 : 4 : 3′ : 4′-tetramethoxydibenzyl and carbon tetrachloride by the procedure used for benzophenone (*Org. Synth.*, **8**, 26) gave a high recovery of starting material.

The overall yield of the ketone (III) from the second series of reactions was low and in order to relate the products from the two routes, it was decided to degrade the materials from the aldehyde condensation to the ketone (III) rather than attempt the synthesis of the former from the latter.

The methiodide derived from the tertiary base (I; R = $CH_2 \cdot NMe_2$) was degraded by Hofmann's method to give a homogeneous nitrogen-free product (IV). This was readily hydrogenated to a crystalline dihydro-derivative, identical with the product (I; R = Me) obtained from acetaldehyde with 3 : 4 : 3′ : 4′-tetramethoxydibenzyl. Warm potassium permanganate in acetone slowly oxidised the Hofmann product (IV), and the neutral fraction afforded the same dibenzo*cyclo*heptadienone (III) which had been obtained as above. This ketone did not react with 2 : 4-dinitrophenylhydrazine, in agreement with Buchanan's finding on the related dibenzo*cyclo*heptadienone lacking the methoxyl groups (*Chem. and Ind.*, 1952, 855).

Before the nature of the oxidation product from the ether (IV) was known, it was treated with sodium bismuthate in glacial acetic acid as a test for a glycol residue (Rigby, *J.*, 1950, 1907). One mol. of the reagent was consumed at room temperature in 2 hr., a result of some interest now that the structure of the starting material is known. Sodium bismuthate also attacked 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (V) and *o*-dimethoxybenzene at room temperature, and the neutral products from the latter, after hydrogenation and alkaline hydrolysis, gave a very small yield of adipic acid. Anisole was attacked slowly under the conditions used above. A careful study of this reaction is desirable, but these preliminary results are presented in view of the use of sodium bismuthate as a diagnostic test for glycol and related groupings.

Ultraviolet absorption maxima (mμ) *in ethanol* (ε *in parentheses*).

3 : 4 : 3′ : 4′-Tetramethoxydibenzyl (II; R = R′ = H)	230 (17,620)	280 (6470)	
2-Acetyl-4 : 5 : 3′ : 4′-Tetramethoxydibenzyl (II; R = Ac, R′ = H)	231 (30,690)	276 (11,220)	304 (5120)
2 : 2′-Diacetyl-4 : 5 : 4′ : 5′-Tetramethoxydibenzyl (II; R = R′ = Ac)	234 (43,700)	273 (17,060)	306 (10,100)
3 : 4 : 3′ : 4′-Tetramethoxydeoxybenzoin (V)	230 (24,150)	276 (14,000)	305 (9620)
The dibenzo*cyclo*heptadiene (II; R = $CH_2 \cdot NMe_2$)	285 (7870)		
The dibenzo*cyclo*heptadienone (III)	245 (13,500)	292 (11,500)	346 (11,800)
The methylenedibenzo*cyclo*heptadiene (IV)	261 (11,780)	291 (8630)	

The ultraviolet absorption spectra of our materials (see Table) are in agreement with the structures presented above.

EXPERIMENTAL

Analyses are by Mr. B. S. Noyes of Bristol.

3 : 4 : 3′ : 4′-*Tetramethoxydibenzyl* (II; R = R′ = H).—3 : 4 : 3′ : 4′-Tetramethoxydeoxybenzoin (V) (Kubiczek, *Monatsh.*, 1946, **76**, 55) was reduced by the method Erdtman employed with 3 : 4 : 3′ : 4′-tetramethoxybenzil (*Annalen*, 1933, **505**, 198), save that the reduction period was increased to 1·5 hr. The product (62%) had m. p. 108—110°; Erdtman (*loc. cit.*) records 109—110°.

2-*Acetyl*-4 : 5 : 3′ : 4′-*tetramethoxydibenzyl* (II; R = Ac, R′ = H) *and* 2 : 2′-*Diacetyl*-4 : 5 : 4′ : 5′-*tetramethoxydibenzyl* (II; R = R′ = Ac).—The foregoing product (5 g.) in anhydrous benzene (150 ml.) was stirred at room temperature with powdered anhydrous aluminium chloride (4·4 g.) whilst acetyl chloride (2·6 ml., 2 equiv.) in benzene (70 ml.) was added during 1 hr. After being stirred for a further 1 hr., the mixture was heated to the b. p. during 0·5 hr. and then for 2 hr. under reflux. The cooled suspension was poured on ice, and the complex was decomposed as usual with hydrochloric acid. The insoluble matter (*A*) (0·835 g.), m. p. 171—175°, was collected and the clear filtrate was extracted thrice with benzene. The combined extracts were washed with water, dilute sodium hydroxide, and water, then dried (Na_2SO_4) and evaporated to a semi-crystalline gum (6·25 g.). When the alkaline extract was acidified, only a trace of phenolic material (*ca.* 0·2 g.) separated. The main gummy fraction partly crystallised from ethanol to yield a mother-liquor (*B*) and a crop of crystals (1·25 g.), m. p. 169—170°. The latter was combined with the insoluble matter *A* and recrystallised from ethanol; 2 : 2′-*diacetyl*-4 : 5 : 4′ : 5′-*tetramethoxydibenzyl* (II; R = R′ = Ac) was obtained as colourless rods (1·83 g., 28%), m. p. 173—175°, after slight sintering at 166° (Found, in material dried at 100°: C, 68·7; H, 6·9. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%). It afforded a dark red 2 : 4-dinitrophenylhydrazone. A sample (3·2 mg.) in ethanol (12·5 ml.) was shaken with 10% palladium–charcoal (50 mg.) and hydrogen at room temperature and pressure; the uptake (0·86 ml.; 4 mol. = 0·79 ml.) was complete in 1 hr.

When the alcoholic mother-liquor *B* was concentrated, impure starting material separated (1·02 g.; m. p. 90—103°, raised to 105—109° on admixture with an authentic sample). Evaporation of the final mother-liquor left a gum which was fractionated in a short-path still. A colourless oil distilled at 120—130° (bath)/20 mm. and was identified as acetophenone by its 2 : 4-dinitrophenylhydrazone. The second fraction distilled at 160—180° (bath)/0·01 mm. as a yellow oil which crystallised on addition of ether. This solid was adsorbed from benzene–light petroleum on to a column of alumina and then was eluted with ether–benzene (1 : 1). After a first fraction consisting of 3 : 4 : 3′ : 4′-tetramethoxydibenzyl, 2-*acetyl*-4 : 5 : 3′ : 4′ *amethoxydibenzyl* (II; R = Ac, R′ = H) was obtained (0·76 g., 13%). It crystallised from aqueous ethanol as colourless needles, m. p. 96—98° (Found, in material dried at 65°: C, 69·7; H, 6·8. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0%). This product gave a dark red 2 : 4-dinitrophenylhydrazone.

2-*Carboxy*-4 : 5 : 3′ : 4′-*tetramethoxydibenzyl* (II; R = CO_2H, R′ = H).—A solution of sodium hypochlorite was prepared by passing chlorine (3·2 g.) into a solution of sodium hydroxide (4·4 g.) in water (30 ml.) at 0°. A portion (3·5 ml.) was warmed to 55° and added to a solution of the monoketone (0·157 g.) in rigorously purified dioxan (10 ml.). Addition of water (10 ml.) gave a clear solution which was warmed at 60—70° for 1·5 hr. After the dioxan had been evaporated under reduced pressure, the mixture was freed from hypochlorite ion by the addition of aqueous sodium metabisulphite and was then acidified to Congo-red with concentrated hydrochloric acid. The crystalline precipitate was collected and redissolved in dilute aqueous sodium hydroxide, and the filtered solution was acidified once more to afford the *carboxylic acid* as colourless compact prisms (0·12 g., 76%), m. p. 159—160°, raised to 161—164° by recrystallisation from ethanol (Found, in material dried at 100°: C, 65·4; H, 6·2%; equiv., 350. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%; equiv., 346).

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*dien*-3-*one* (III).—(a) *By cyclisation of the acid* (II; R = CO_2H, R′ = H). A suspension of the foregoing acid (0·108 g.) and phosphorus pentachloride (78 mg., 1·2 equiv.) in dry nitrobenzene (12 ml.) was stirred at room temperature for 1 hr. Powdered anhydrous aluminium chloride (85 mg., 2 equiv.) was then added and the deep red solution was kept for 2 days. After addition of 2N-hydrochloric acid (5 ml.), the solvent was distilled in steam, to leave a suspension of gum in water. This was made alkaline with 2N-sodium hydroxide (10 ml.), and the gum was dissolved by addition of acetone. When the acetone was removed under reduced pressure, the neutral fraction separated as pale yellow needles which were recrystallised twice from ethanol, to give the *dibenzo*cyclo*heptadienone* (III) (48 g., 47%) (Found, in material dried at 100° : C, 69·5; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·15%). The first preparation of this ketone had m. p. 128·5—129°, but later samples melted consistently at 142—143° with a transition at 128—129°. When the needles were kept in contact with ethanol for several days, they changed to compact prisms, m. p. 141—143°. Recrystallisation of the latter from ethanol afforded needles with m. p. behaviour as above.

Slightly impure starting material (55 mg.), m. p. 154—156°, raised to 158—160° on admixture with an authentic sample, was recovered by acidification of the aqueous alkaline filtrate.

Attempted preparations of the ketone (III) in which thionyl chloride was used under a variety of conditions to convert the acid into its chloride were unsuccessful, as was direct cyclisation of the acid with concentrated sulphuric acid (cf. Haworth and Mavin, *J.*, 1931, 1363).

(b) *By oxidation of the methylene derivative* (IV). A stirred solution of this derivative (0·178 g.) in acetone (100 ml.) was unaffected at room temperature by part of a solution of potassium permanganate (0·35 g.; equiv. to 6 O) in acetone (52 ml.) and water (26 ml.). Oxidation occurred under reflux and all the remaining oxidising agent was added dropwise during 1·5 hr. After being heated and stirred for a further 1·5 hr., the solution, now colourless, was filtered and the filter pad was washed with hot water and boiling acetone. The clear filtrate was freed from acetone under reduced pressure and the precipitated solid was collected (0·134 g.). This crystallised from ethanol to give the ketone (III) as pale yellow needles (77 mg.), m. p. 142—143° with a transition at 126°, unchanged on admixture with the foregoing product. The prismatic modification was obtained as before and was identical with that prepared as above.

Ozonolysis of a solution of the derivative (IV) in ethyl chloide at −78° gave a brown neutral fraction from which the ketone (III) could not be isolated.

2 : 2-*Dimethoxyethyl*-NN-*dimethylamine.*—Dimethylamine, prepared from the hydrochloride (300 g.), was carried in nitrogen through a column of barium oxide and into a solution of 2 : 2-dimethoxyethyl chloride (31 g.) in absolute methanol (400 ml.). The mixture was heated at 140° for 12 hr. in an autoclave and was worked up as described by Woodward and Doering (*J. Amer. Chem. Soc.*, 1945, **67**, 860). The acetal (5·5 g., 17%) had b. p. 80—8.°/112 mm. With methyl iodide in ether it gave the methiodide as rods (from acetone), m. p. 126—127° to a resin which flowed at 133—134°. Fourneau and Chantalou (*Bull. Soc. chim. France*, 1945, **12**, 845) record m. p. 126°.

2′ : 3′ : 2″ : 3″-*Tetramethoxy*-3-*methyl*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (I; R = Me).—(*a*) Paraldehyde (0·192 g.) in glacial acetic acid (3 ml.) was added during 0·5 hr. to a stirred solution of 3 : 4 : 3′ : 4′-tetramethoxydibenzyl (1·3 g.) in glacial acetic acid (25 ml.) and concentrated sulphuric acid (15 ml.) at room temperature. After being stirred for a further 2 hr., the solution was poured on ice, and the insoluble matter was crystallised from ethanol. The *dibenzo*cyclo*heptadiene* (I; R = Me) separated as colourless blades (0·845 g., 60%), m. p. 126—128° unchanged by further recrystallisation or by sublimation at 100—135° (bath)/0·05 mm. [Found, for sublimed material: C, 73·0; H, 7·3%; *M* (in camphor), 281. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%; *M*, 328].

(*b*) A solution of the Hofmann degradation product (IV) (38·8 mg.) in ethanol (10 ml.) was shaken with hydrogen and platinic oxide (10 mg.). Hydrogen (1 mol.) was absorbed during 9 hr. After removal of the catalyst, the solution was concentrated. The diene (I; R = Me) crystallised and had m. p. 127—129° unchanged on admixture with the foregoing product.

3-*Dimethylaminomethyl- and* 3-*Aminomethyl*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (I; R = CH_2·NMe_2) *and* (I; R = CH_2·NH_2).—A solution of 3 : 4 : 3′ : 4′-tetramethoxydibenzyl (0·5 g.) and 2 : 2-dimethoxyethyl-*NN*-dimethylamine (0·25 g.) in glacial acetic acid (10 ml.) was treated with concentrated sulphuric acid (3 ml.), kept for 15 hr., and then poured on ice. Extraction of the aqueous solution with benzene removed only a trace of neutral matter. The aqueous layer was made strongly alkaline with sodium hydroxide, and the precipitated crystalline base (0·506 g.) was collected and washed with water. It recrystallised from aqueous methanol, to afford the 3-*dimethylaminomethyl compound* (I; R = CH_2·NMe_2) as colourless plates (0·385 g., 62%), m. p. 136—138° [Found, in material dried at 100° : C, 71·5; H, 7·7; N, 4·0%; *M* (in benzene), 368. $C_{22}H_{29}O_4N$ requires C, 71·1; H, 7·9; N, 3·8%; *M*, 371].

(With P. S. UZZELL.) By replacing the *NN*-dimethyl-acetal above with 2 : 2-dimethoxyethylamine (Woodward and Doering, *loc. cit.*), the 3-*aminomethyl analogue* (I; R = CH_2·NH_2) was prepared. It crystallised from aqueous ethanol as colourless plates, m. p. 129—130°

(Found, in material dried at 78° : C, 66·6; H, 7·5; N, 3·9; H_2O, 4·8. $C_{20}H_{25}O_4N,H_2O$ requires C, 66·5; H, 7·5; N, 3·9; H_2O, 5·0%).

Hofmann Degradation of the Base (I; R = $CH_2{\cdot}NMe_2$).—A suspension of this base (0·38 g.) in anhydrous ether (20 ml.) was treated with sufficient methanol to give a clear solution and then with methyl iodide (1 ml.). After 2 days, the precipitated *methiodide* (0·503 g., 95%), m. p. 280—282° (decomp.), was collected. It crystallised from methanol as feathery needles of the same m. p. (Found, in material dried at 100° : C, 53·5; H, 6·2. $C_{23}H_{32}O_4NI$ requires C, 53·8; H, 6·3%).

Moist silver oxide (from 2 g. of silver nitrate) was shaken with a solution of the methiodide (0·46 g.) in 50% aqueous methanol (170 ml.) until the precipitation of iodide was complete (45 min.). The filtered solution and washings were concentrated at room temperature under reduced pressure to remove the methanol. Potassium hydroxide (90 g.) was added to the aqueous solution which was then heated under reflux for 2·5 hr. Trimethylamine was rapidly evolved and an oil separated. The latter was extracted into ether, and the extract washed with water, dilute hydrochloric acid, and water. Evaporation of the dried ether solution left a crystalline residue (0·271 g., 91%), m. p. 182—187°, which, recrystallised thrice from ethanol, gave the 2′ : 3′ : 2″ : 3″-*tetramethoxy*-3-*methylene*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (IV) as plates, m. p. 184—187° (Found, in material dried at 100° : C, 73·3; H, 6·5. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

Action of Sodium Bismuthate on o-*Dimethoxybenzene.*—A solution of *o*-dimethoxybenzene (5 g.) in glacial acetic acid (50 ml.) was shaken at room temperature with sodium bismuthate (15 g.) until the latter had been reduced (10 hr.). A second portion of sodium bismuthate (total 26 g., 2 mol. based on 80% purity) was consumed in the same way during a further 24 hr. The dark mixture was treated with phosphoric acid (*d* 1·75; 5·2 ml.), and the products were extracted into ether. After being shaken with an excess of aqueous potassium carbonate, the extract was dried and evaporated, to leave a brown oil (2·5 g.). This was hydrogenated at room temperature and pressure in ethanol, in the presence of platinum; uptake of hydrogen (220 ml.) ceased after 2 hr. The recovered reduced material was heated under reflux for 3 hr. with methanolic N-potassium hydroxide (100 ml.), and the methanol was removed under reduced pressure. A solution of the residue in water was acidified, made alkaline with potassium carbonate, extracted with ether, and finally acidified to Congo-red. Continuous extraction of this solution with ether afforded adipic acid (*ca.* 100 mg.) which was purified by sublimation at 110°/0·05 mm. and had m. p. and mixed m. p. 149—153°.

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