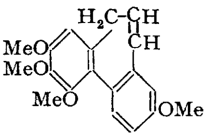
141. *Colchicine and Related Compounds. Part VI.* 3 : 4 : 5 : 6-*Dibenz*cyclo*hepta*-1 : 3 : 5-*triene.*

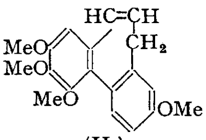
By J. W. Cook, G. T. Dickson, and J. D. Loudon.

3 : 4 : 5 : 6-Dibenz*cyclo*hepta-1 : 3 : 5-triene (IX) has been prepared, characterised and compared with deaminocolchinol methyl ether (I) which, in conformity with the structural relationship, it closely resembles in chemical properties. Evidence of the ease with which compounds of this type yield derivatives of phenanthrene on oxidation has been supplemented by isomerisation of (IX) to 9-methylphenanthrene.

Simultaneously with attempts to synthesise deaminocolchinol methyl ether, the present work was undertaken in order to ascertain whether certain properties of the compound, which led to its formulation as 9 : 12 : 13 : 14-tetramethoxy-3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-triene (I), are in fact reproduced by the unsubstituted hydrocarbon of this structure. More particularly experimental evidence was required to decide whether, as was suggested in Part V (*J.*, 1945, 176), isomerisation of a dibenz*cyclo*heptatriene accounts for the isolation by Windaus of 9-methylphenanthrene from deaminocolchinol methyl ether following demethylation and distillation with zinc (*Annalen*, 1924, **439**, 59).



(I.)



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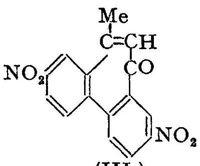

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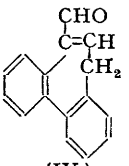
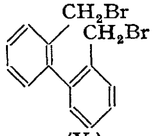


(IV.)

Comparatively little is known of the chemistry of 3 : 4 : 5 : 6-dibenz*cyclo*hepta-1 : 3 : 5-triene and its derivatives. Kenner, who prepared from ωω'-dibromo-*oo*'-ditolyl a number of compounds containing this arrangement of carbon atoms (*J.*, 1913, **103**, 613; cf. Kenner and Turner, *J.*, 1911, **99**, 2101), pointed out that the ease of forming the seven-membered ring from this particular starting material was comparable with that found in the production of indane derivatives from xylylene dibromide and on steric grounds suggested analogy between the dibenz*cyclo*heptatriene and indene series. Similarly facile ring closure is implicit in the direct formation of (III) by heating 2-bromo-5-nitroacetophenone with copper (Borsche and Herbet, *Annalen*, 1941, **546**, 293) and in the preparation of (IV), from the bisacetal of diphenyl-*oo'*-diacetaldehyde, described by Weitzenböck (*Monatsh.*, 1913, **34**, 199) who also showed that (IV) yields phenanthraquinone when oxidised in acetic acid with sodium dichromate. In all these cases a symmetrically substituted diphenyl is the actual or probable precursor of the dibenz*cyclo*heptatriene derivative in which, accordingly, a corresponding symmetry is retained. On the other hand deaminocolchinol methyl ether is not symmetrically substituted in the lateral rings and is accompanied by the isomeric compound (II) in at least two of the methods used for its preparation. Although at present no particular significance can be attached to the simultaneous formation of these two isomerides, since the structures of the compounds from which they were derived are incompletely known, yet it may be pointed out that the isomerides themselves contain a triad system and in their individual stability resemble the reluctant prototropy of αγ-diarylpropenes (Ingold and Piggott, *J.*, 1922, **121**, 2381; Ingold and Shoppee, *J.*, 1929, 447) rather than the mobility of the triad system of indene.



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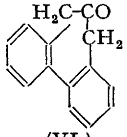

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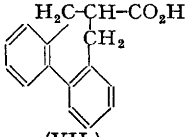
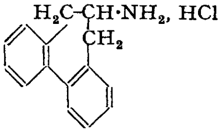
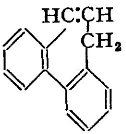


(VII.)



(VIII.)

From the crude oil obtained by thermal decomposition of the amine hydrochloride (VIII), Kenner prepared a picrate of m. p. 137° which, on the basis of its analysis, he concluded was the picrate of dibenz*cyclo*heptatriene (IX). In view of the failure, recorded in Part V, to prepare a picrate from deaminocolchinol methyl ether, this result invited further inquiry. Kenner prepared (VIII) by two methods. In the first, the dibromide (V) was converted into the corresponding dinitrile which was cyclised by means of Thorpe's reaction followed by hydrolysis to the ketone (VI) and reduction of the ketoxime with sodium and alcohol. In the second, the dibromide was condensed with malonic ester, followed by hydrolysis and removal of carbon dioxide to form the acid (VII) which was then converted *via* the hydrazide, azide, and urethane into the required amine. Repetition of each of these methods, with an improved preparation of the dibromide and employing pressure-hydrogenation with Raney nickel as catalyst for reducing the ketoxime, gave in our hands consistent results which, however, differed slightly from Kenner's in respect of the m. ps. found for the amine hydrochloride and the corresponding acetylated base. Thermal decomposition of our hydrochloride gave an oil which was separated by distillation into a solid and a liquid fraction. The solid was identified as 9-methylphenanthrene by direct comparison and by formation of the picrate. The liquid was shown to contain dibenz*cyclo*heptatriene (IX) (cf. Experimental), but this compound was much more satisfactorily prepared by heating the acetylated base with phosphorus pentoxide in xylene following the procedure discovered by Cook and Graham (Part III; *J.*, 1944, 322) for deaminating *N*-acetylcolchinol methyl ether. The purified triene yielded a crystalline *dibromide* and absorbed approximately the correct amount of hydrogen for one double bond when hydrogenated in presence of palladium. We have not, however, been able to obtain from it a picrate, and this negative result is in accord with our experience with deaminocolchinol methyl ether. On the other hand it is by no means certain that Kenner's picrate (m. p. 137°) is to be explained by the presnce of 9-methylphenanthrene in the crude decomposition products of (VIII). Indeed, the m. p. of 9-methylphenanthrene picrate (152—153°) is in better agreement with that of a second picrate (m. p. 147—149°)—which depresses the m. p. of the first and was prepared by Kenner from the oily residue formed when the barium salt of (VII) was heated under diminished pressure. Repetition of this last experiment by us gave in fact some 9-methylphenanthrene.



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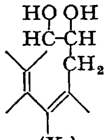

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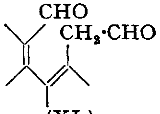

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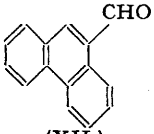

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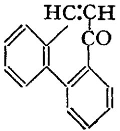

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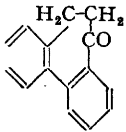

(XIV.)

Oxidation of dibenz*cyclo*heptatriene (IX) reproduced in all essential respects the behaviour of deaminocolchinol methyl ether with corresponding oxidising agents (Part V). With osmium tetroxide in ether the triene formed the *diol* (X) which by fission with lead tetra-acetate in benzene gave a gum, converted into 9-phenanthraldehyde (XII) on warming with a trace of sodium carbonate in ethanol. The presumed intermediate, namely the dialdehyde (XI), was not isolated. Oxidation of the triene with sodium dichromate in acetic acid gave phenanthrene-9-carboxylic acid and phenanthraquinone—products which may well represent successive stages of an oxidation course proceeding through the above diol and phenanthraldehyde. In addition a ketonic *by-product*, $C_{15}H_{10}O$, was also obtained, corresponding with a similar by-product, $C_{15}H_6O(OMe)_4$, isolated from deaminocolchinol methyl ether and regarded in Part V as an αβ-unsaturated ketone. In the present instance the structure (XIII) for this by-product was confirmed by its preparation from (IX) through the action of selenium dioxide and also by its quantitative hydrogenation with palladium as catalyst to the *ketone* (XIV). Oxidation of (XIV) and of its isomer (VI) afforded further examples of the ease with which the central seven-membered ring in this series of compounds undergoes oxidative degradation to a six-membered ring: in each case with sodium dichromate in acetic acid phenanthraquinone and some diphenic acid were produced.

The simultaneous production of the triene (IX) and 9-methylphenanthrene from (VIII) as described above, is not proof that the former product can be converted into the latter. Apart from some resinification the triene was unaffected by direct heating or by distillation from sodium ethoxide, while distillation under reduced pressure from anhydrous zinc chloride yielded only high-boiling products, presumably polymerides. On the other hand, when subjected to the treatment used by Windaus to remove the methoxyl groups from deaminocolchinol methyl ether—namely, heating with hydriodic acid and subsequent distillation from zinc dust—the triene first gave an iodinated product which at the second stage, or by distillation from sodium ethoxide, yielded 9-methylphenanthrene. Accordingly, dibenz*cyclo*heptatriene (IX) in the method of its preparation from the *N*-acetylated base, in its behaviour towards oxidation and reduction, in non-formation of a picrate and in its conversion into 9-methylphenanthrene, closely reflects the behaviour of deaminocolchinol methyl ether, which was formulated in Part V as the tetramethoxy-derivative.

Other synthetic approaches to dibenz*cyclo*heptatriene derivatives are under investigation in these laboratories. One route, on which some exploratory experiments had been carried out, was abandoned following the publication of a paper by Drake and Sweeney (*J. Org. Chem.*, 1946, **11**, 67) who showed that the acid, which we had also obtained, formed by hydrolysis of the product of the action of ethyl diazoacetate on phenanthrene, is not a dibenz*cyclo*heptatriene-carboxylic acid, but the alkali-stable dibenznorcaradienecarboxylic acid.

EXPERIMENTAL.

ωω'-Dibromo-oo'-*ditolyl*.—A gently boiling solution of *oo'*-ditolyl (46 g.) in carbon tetrachloride (400 c.c.), containing a small crystal of iodine and covered by a layer of water (100 c.c.), was exposed to the light of three 40-watt bulbs while a solution of bromine (84·5 g.) in carbon tetrachloride (150 c.c.) was slowly added (2 hours). After further heating (½ hour) the cooled solution was washed with dilute sodium hydroxide, dried, and concentrated. The product, which solidified on rubbing with ligroin, formed small colourless rhombs, m. p. 89—90°, yield 54% (Kenner *loc. cit.*, gives m. p. 87·5°).

1-*Amino*-3 : 4 : 5 : 6-*dibenz*cyclo*hepta*-3 : 5-*diene Hydrochloride* (VIII).—(*a*) The corresponding urethane (Kenner, *loc. cit.*) was heated with concentrated hydrochloric acid in a sealed tube at 150° for 6 hours.

(*b*) The corresponding 1-ketoxime (0·82 g.; Kenner, *loc. cit.*) in ethanol (100 c.c.) was hydrogenated in presence of Raney nickel at 85°/64 atm. The base, precipitated as the picrate from an ether solution of the filtered concentrates, was recovered in ether and, after removal of the solvent, was treated with concentrated hydrochloric acid. In each case the hydrochloride was obtained as needles, m. p. 256—258°, from dilute hydrochloric acid (Kenner gives m. p. 287°) (Found : C, 73·4; H, 6·7. Calc. for $C_{15}H_{16}NCl$: C, 73·3; H, 6·5%). By shaking with dilute sodium hydroxide and acetic anhydride it yielded the *N*-acetyl derivative, colourless needles, m. p. 157—158° from aqueous ethanol (Kenner gives m. p. 147°) (Found : C, 81·1; H, 6·7. Calc. for $C_{17}H_{17}ON$: C, 81·3; H, 6·8%).

3 : 4 : 5 : 6-*Dibenz*cyclo*hepta*-1 : 3 : 5-*triene* (IX).—(*a*) The aforesaid *N*-acetyl compound (3·1 g.) in pure xylene (75 c.c.) was heated under reflux (½ hour) with phosphorus pentoxide (10 g.). Fractional distillation of the filtered solution gave the *triene* (68% yield) as a colourless mobile oil, b. p. 100—110° (air bath)/10 mm. (Found : C, 93·6; H, 6·4. $C_{15}H_{12}$ requires C, 93·8; H, 6·3%. Microhydrogenation with palladium black gave 0·85 double bond). The triene displayed no evidence of picrate formation when treated with picric acid in ethanol, but with bromine in acetic acid, followed by dilution and extraction with ether, it gave a *dibromide*, m. p. 90—91° from methanol (Found : C, 51·1; H, 3·5. $C_{15}H_{12}Br_2$ requires C, 51·2; H, 3·4%).

(*b*) In a similar experiment using the urethane in place of the *N*-acetyl compound, some unchanged urethane was recovered as the solid produced when the xylene concentrates were rubbed with ligroin. Evaporation of the ligroin solution gave a semi-solid which was washed with ethanol, giving an unidentified material, needles m. p. 322—325° (with sublimation) from 2-ethoxyethanol (Found : C, 83·2; H, 6·2; N, 5·8%). The concentrated ethanol washings from this material gave on distillation a small quantity of the triene, identified as the above dibromide, m. p. and mixed m. p. 89—90°.

(*c*) The hydrochloride (VIII; 0·35 g.) was heated in a sublimation tube at 320° (bath temp.; at 300° the compound slowly sublimes unchanged). The sublimate, dissolved in ether, was washed with dilute hydrochloric acid (which removes some unchanged hydrochloride) and recovered from the solvent. It distilled mainly between 80° and 115° (air bath)/0·1 mm., the later portion solidifying and giving 9-methylphenanthrene, m. p. and mixed m. p. 91°; picrate, m. p. and mixed m. p. 152—153°. The earlier oily fraction contained the triene as was shown by formation of the dibromide, m. p. and mixed m. p. 87—90°. A third small fraction, b. p. 175—185°/0·2 mm., was not investigated further beyond noting that it did not yield a picrate in ethanol.

Thermal decomposition of the barium salt of (VII). The barium salt, containing some un-neutralised barium hydroxide, was heated under reduced pressure. A yellow viscous oil slowly distilled [170—200° (bath temp.)/10 mm.] and solidified in the receiver. After purification by chromatography this furnished colourless needles, m. p. and mixed m. p. with 9-methylphenanthrene, 90—91°; the picrate had m. p. and mixed m. p. 153—154°.

Oxidation of the Triene (IX).—(a) *With sodium dichromate.* The triene (0·3 g.) in acetic acid (1·6 c.c.) was treated with sodium dichromate (0·98 g.) in acetic acid (2·3 c.c.), and the solution was heated for 1¼ hours at 100°. After dilution, a chloroform extract of the mixture was washed with dilute sodium carbonate, dried, and concentrated. The residue, dissolved in benzene–ligroin (1 : 1), was separated on a column of alumina into a feebly adsorbed pale-pink band and a more strongly adsorbed orange band. The eluate of the former gave, on evaporation, a gum which solidified when rubbed with ligroin, yielding 3 : 4 : 5 : 6-*dibenz*cyclo*hepta*-1 : 3 : 5-*trien*-7-*one* (XIII), m. p. 83—84° from benzene–ligroin (Found: C, 87·4; H, 4·9. $C_{15}H_{10}O$ requires C, 87·4; H, 4·9%. Microhydrogenation with palladium black gave 0·98 double bond). The compound gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 231—232° (Found: C, 65·3; H, 3·6. $C_{21}H_{14}O_4N_4$ requires C, 65·3; H, 3·6%), and dissolved in strong sulphuric acid to a bright yellow solution.

The orange band was eluted with benzene–ethanol from which was recovered phenanthraquinone, m. p. and mixed m. p. 200—202° from benzene (diazine, from *o*-phenylenediamine, m. p. and mixed m. p. 218°). The carbonate washings of the chloroform solution gave, on acidification, phenanthrene-9-carboxylic acid, m. p. and mixed m. p. 249—251° after purification.

(b) *With selenium dioxide.* A solution of the triene (0·19 g.) in xylene (1 c.c.) was heated under reflux with selenium dioxide (0·125 g.) for 6 hours. The gum obtained from the filtered and concentrated solution was dissolved in ether, washed with dilute sodium hydroxide, then with water, dried, recovered, and distilled. Dibenz*cyclo*heptatrien-7-one was obtained as a yellow oil, b. p. 115° (bath-temp.)/0·2 mm., which solidified in the receiver, m. p. and mixed m. p. with the above sample 83—84°.

(c) *With osmium tetroxide.* A solution of the triene (0·5 g.) in dry ether (25 c.c.) was treated with osmium tetroxide (0·75 g.) in dry ether (25 c.c.). After 3 days, the residue obtained by removing the solvent was heated under reflux with a solution of hydrated sodium sulphite (8 g.) in water (75 c.c.) and methanol (100 c.c.) for 3 hours. Undissolved solid was collected and well washed with methanol, filtrate and washings being combined and concentrated. The concentrates were diluted with water and extracted with ether from which, after further washings with water and drying, the product was recovered. cis-1 : 2-*Dihydroxy*-3 : 4 : 5 : 6-*dibenz*cyclo*hepta*-3 : 5-*diene* (X) formed colourless prisms, m. p. 121° from methanol (Found: C, 79·8; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·7; H, 6·2%).

Scission with lead tetra-acetate. Lead tetra-acetate (120 mg.) was added, portionwise and with shaking, to a solution of the above diol (60 mg.) in pure dry benzene (18 c.c.) maintained at 40°. The mixture was heated to boiling and then left at room temperature for 1 hour. After filtration the benzene solution was washed with water, dried, and evaporated. The resulting gum, which did not crystallise from ethanol, slowly deposited pale yellow needles of 9-phenanthraldehyde after being warmed with a little sodium carbonate in ethanol. The aldehyde had micro-m. p. 99—100° (positive test with 2 : 4-dinitrophenylhydrazine), and was oxidised by dropwise addition of 6% potassium permanganate (0·3 c.c.) to its solution (11 mg.) in pure acetone (1 c.c.). After clarification with sulphurous acid, the solution was extracted with chloroform from which phenanthrene-9-carboxylic acid, m. p. and mixed m. p. 245—248°, was recovered by means of aqueous sodium carbonate and was purified by vacuum sublimation. The chloroform residues contained some unchanged aldehyde.

3 : 4 : 5 : 6-*Dibenz*cyclo*hepta*-3 : 5-*dien*-2-*one* (XIV.)—The unsaturated ketone (XIII; 170 mg.), hydrogenated in acetic acid (7 c.c.) with palladium black as catalyst (50 mg.), absorbed the calculated quantity of hydrogen in 45 minutes at room temperature. After removal of the solvent from the filtered solution, the product was obtained as pale yellow hexagonal prisms, m. p. 85—86° from benzene–ligroin (m. p. depressed to 55—75° by admixture with starting material) (Found: C, 86·5; H, 5·7. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%); the 2 : 4-*dinitrophenylhydrazone* had m. p. 240° (decomp.) (Found: C, 65·1; H, 4·1. $C_{21}H_{16}O_4N_4$ requires C, 65·0; H, 4·1%). The ketone was oxidised by adding a solution of sodium dichromate (0·5 g.) in acetic acid (1·5 c.c.) to its solution (115 mg.) in acetic acid (1 c.c.) and subsequent heating under reflux for 1 hour. After dilution with water, extraction with chloroform, and washing the extract with aqueous sodium carbonate, the recovered neutral fraction was identified as phenanthraquinone, m. p. and mixed m. p. 204—205° from benzene (diazine, m. p. and mixed m. p. 218—219°). Acidification of the carbonate washings gave diphenic acid, m. p. and mixed m. p. 220—223° from ethanol.

The same products were obtained from similar oxidation of 3 : 4 : 5 : 6-dibenz*cyclo*hepta-3 : 5-dien-1-one (VI).

Conversion of the Triene (IX) *into* 9-*Methylphenanthrene.*—A solution of the triene (0·16 g.) in acetic acid (4·2 c.c.) and hydriodic acid (1·5 c.c.; *d* 1·7) was heated under reflux for 4 hours. The oil obtained by evaporation was saturated towards bromine and contained (non-ionic) iodine. Since attempted purification by distillation in a vacuum caused liberation of iodine, the crude material was used in two portions: (*a*) Chromatography gave no evidence of the presence of 9-methylphenanthrene at this stage, but, when the eluted and recovered material was distilled from sodium ethoxide, the distillate consisted of almost pure 9-methylphenanthrene, m. p. and mixed m. p. 90—92°. (*b*) When the oil was mixed with zinc dust and distilled at atmospheric pressure, much charring ensued; the distillate, which contained only a little solid, was again mixed with zinc dust, heated at 260° for several hours, and re-distilled. The product was a pale yellow oil, b. p. 90—100° (air bath)/10 mm., of which the later portion solidified and was separately crystallised from methanol giving 9-methylphenanthrene, m. p. and mixed m. p. 89—90° (picrate, m. p. and mixed m. p. 153—154°). The earlier oily portion of the distillate was saturated towards bromine and was analysed after renewed distillation in which only the first runnings were taken (Found: C, 92·9; H, 6·8. Calc. for $C_{15}H_{14}$: C, 92·8; H, 7·2%). It was possibly dibenz*cyclo*heptadiene.

Action of Ethyl Diazoacetate on Phenanthrene.—This was carried out by a procedure based on that use by Buchner and Schottenhammer (*Ber.*, 1920, **53**, 868) for a similar reaction with mesitylene. The higher-boiling fractions, after reaction, were hydrolysed with alcoholic potash and gave an acid which, after vacuum sublimation and then crystallisation from ethanol, formed colourless needles, m. p. 259° (Found : C, 81·1; H, 5·15. Calc. for $C_{16}H_{12}O_2$: C, 81·3; H, 5·1%). This was obviously the acid, m. p. 257·4—258°, obtained in better yield by Drake and Sweeney (*loc. cit.*) and shown by them to be dibenznorcaradienecarboxylic acid. In agreement with these authors, we found the acid to be moderately resistant to oxidation by alkaline permanganate and by chromic acid in acetic acid. The ***methyl*** ester, obtained with ethereal diazomethane, formed colourless elongated plates, m. p. 144—145° (from methanol) (Found : C, 81·3; H, 5·7. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

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