222. *Molecular Configuration and Isomorphism in the* meso-αβ-*Divinyldibenzyl Series.*

By G. A. Jeffrey, H. P. Koch, and S. C. Nyburg.

X-Ray crystallographic studies of molecular symmetry have been combined with a consideration of scale models, ultra-violet absorption data, and the steric requirements of resonance theory in order to determine details of molecular configuration in the *meso*-*αβ*-divinyldibenzyl series. *αβ*-Diethylidenedibenzyl of m. p. 101° is shown to be the *trans-trans*-isomer of 3 : 4-diphenylhexa-2 : 4-diene. The *meso*-*αβ*-divinyldibenzyl, *meso*-*αβ*-diethyldibenzyl, *αβ*-diethylidenedibenzyl, and *trans*-*αβ*-diethylstilbene structures are all centrosymmetrical, with parallel non-coplanar aromatic ring planes. The isomorphous relationships in this series are discussed with reference to crystal geometry, miscibility, and physiological activity, and some comments are made on the spatial conformation of the corresponding phenolic molecules which belong to the class of the highly active synthetic oestrogens.

In the foregoing paper an account has been given of the isolation and chemical properties of *meso*-αβ-divinyldibenzyl. The present communication is primarily concerned with the presentation of some crystallographic data and a discussion of the molecular configuration of this new hydrocarbon together with that of the isomeric αβ-diethylidenedibenzyl of which only a bare mention exists in the literature (Stern, *Monatsh.*, 1905, **26**, 1565). The results are compared with those similarly derived for the two structural analogues *meso*-αβ-diethyldibenzyl and *trans*-αβ-diethylstilbene which have already been examined crystallographically by Carlisle and Crowfoot (*J.*, 1941, 6) and with regard to their isomorphous relationship by Wessely and Welleba (*Ber.*, 1941, **74**, 777, 785). Although no attempt has as yet been made at a detailed *X*-ray analysis of crystal structure in this series, yet the present study illustrates the application of preliminary *X*-ray and ultra-violet absorption data to the elucidation of complex organic structures, and consideration is also given in this paper to such diverse but probably interrelated phenomena as isomorphism and oestrogenic activity in relation to variations of spatial configuration.

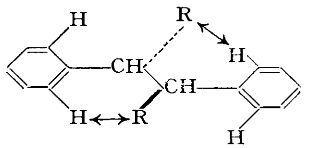
The hitherto unrecorded crystallographic properties of *meso*-αβ-divinyldibenzyl and αβ-diethylidenedibenzyl are given in the table, together with those obtained by Carlisle and Crowfoot (*loc. cit.*) for which the axes have been rearranged so as to refer all four crystal structures to the same space-group description $P2_1/n$.

Hydrocarbon.	Symbol.	M.p.	Unit cell dimensions (A.). *a*.	*b*.	*c*.	*β*.	No. of mols. in cell.	Space-group.	Molr. symmetry.	Oestrogen. activity, E.D.50.[3]
meso-*αβ*-Divinyldibenzyl ...	*A*	87°	6·71	18·76	5·85	110½°	2	$P2_1/n$	Centre	> 1 Mg. < 10 mg.
meso-*αβ*-Diethyldibenzyl [1]...	*B*	89	7·00	19·27	5·75	110½	2	$P2_1/n$	Centre	< 1 Mg.
αβ-Diethylidenedibenzyl [2]...	*C*	101	6·47	18·70	6·16	110½	2	$P2_1/n$	Centre	> 1 Mg. < 10 mg.
trans-*αβ*-Diethylstilbene [1]...	*D*	71	12·38	20·18	7·66	131	4	$P2_1/n$	Centre or asymm.	~50 Mg.

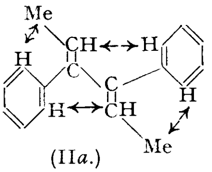
[1] Crystallographic data from Carlisle and Crowfoot (*loc. cit.*).
[2] Hydrocarbon of Stern (*loc. cit.*) and Lawson *et al.* (unpublished).
[3] Data obtained at the Courtauld Institute of Biochemistry, E.D.50 being defined as the dose necessary to effect 50% response in spayed rats after injection by a standard procedure (cf. this vol., p. 1116).

The crystalline modification of αβ-divinyldibenzyl of m. p. 87° must be assigned the *meso*-structure, since the crystal data require that each of the two molecules in the unit cell should possess a centre of symmetry. As might therefore be expected, the unit cell dimensions closely resemble those of *meso*-αβ-diethyldibenzyl, and it appears likely from the absence of any depression of mixed melting points that the two hydrocarbons form mixed crystals. Isomorphous replacement of vinyl by ethyl groups is evidently permitted in the *meso*-αβ-dialkyldibenzyl structure, and in fact the two molecules must possess almost identical shape. The presence of a centre of symmetry implies that the two benzene rings are parallel and that the three single bonds connecting the rings are all in one plane which may or may not contain the benzene rings. Coplanarity of these rings may, however, be excluded by inspection of Stuart models on account of the close approach of the substituent ethyl or vinyl groups to the *o*-hydrogen atoms of the benzene rings [cf. (I), where steric interference with a coplanar dibenzyl skeleton is indicated by double-headed arrows]. It seems certain therefore that both *meso*-αβ-divinyldibenzyl and *meso*-αβ-diethyldibenzyl exist in the " staggered " configuration characteristic of dibenzyl itself

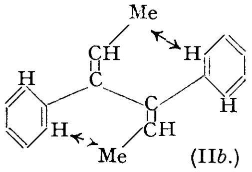
(Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 348; Jeffrey, *ibid.*, 1947, *A*, **188**, 222), in which the plane of the central bonds is approximately perpendicular to the planes of the benzene rings. In the crystal structure of dibenzyl this angle was measured accurately to be 70°, instead of the right angle which is to be expected in the isolated molecule. It has been suggested (Jeffrey, *loc. cit.*) that in the crystal the dibenzyl molecules can pack together with minimal lattice energy if the angle is 70° rather than 90°, and similar considerations may also be involved in the dialkyldibenzyl structures. The ethyl or vinyl substituents must be symmetrically disposed about the centre of the molecule at some orientation governed by the balance of steric requirements of atoms in the same and adjacent molecules.



(I; R = $CH{:}CH_2$ or C_2H_5.)



(II*a*.)

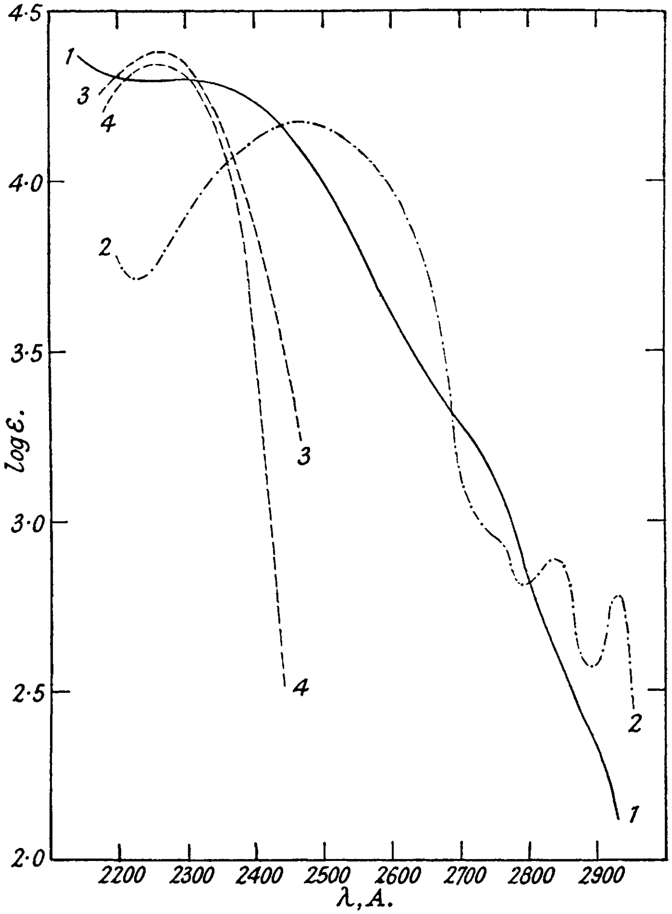


(II*b*.)

The spatial configuration of αβ-diethylidenedibenzyl of m. p. 101°, the conjugated double bond isomer of αβ-divinyldibenzyl, provides a more complicated problem. Although the crystallographic data reveal that the molecule possesses a centre of symmetry, two distinct forms both fulfilling this requirement are theoretically possible because of *cis-trans*-isomerism of the aliphatic hexadiene chain. These are the *trans-trans* form (II*a*) and the *cis-cis* form (II*b*).

The similarity in cell dimensions to the diethyl and the divinyl compound suggests that this molecule also has a staggered dibenzyl type of structure. On the other hand, the butadiene-type conjugation between the two double bonds, and the styrene-type conjugation of each double bond with a benzene ring, would induce the molecule to attain a completely coplanar configuration in order to gain the maximum resonance energy, in so far as such an arrangement is compatible with the van der Waals radii of atoms indicated by the double arrows in (II*a*) and (II*b*). That the structure cannot be entirely planar is immediately apparent from Stuart models (cf. also Zechmeister and LeRosen, *J. Amer. Chem. Soc.*, 1942, **64**, 2755). A further inference from the presence of a centre of symmetry in the molecule is that the two double bonds of the hexadiene chain and the three single bonds connecting the benzene rings must all lie in one plane, as also must the carbon atoms of the methyl groups if the ethylenic substituents are to retain their customary planar trigonal valency distribution. The aliphatic hexadiene chain is therefore completely planar, and the relief of the steric hindrance involved in a fully coplanar molecule must be brought about solely by rotation of the benzene rings out of the plane of the double bonds. The molecule thus retains the full butadiene-type resonance unimpaired, while the conjugation energy of each of the two styrene systems is to some degree reduced. This condition is reflected also in the ultra-violet absorption spectrum of the molecule which is recorded in the figure. The spectrum differs from that of a typical sterically unhindered styrene derivative but shows a main region of selective absorption similar to that observed for simple conjugated hexadienes. Considerable general absorption occurs at greater wave-lengths (including a shoulder near 2750 A.), and this is presumably associated with the reduced additional conjugation of the double bonds with the non-coplanar benzene rings. Similarly, the reported addition of *two* atoms of bromine to the doubly unsaturated compound (Stern, *loc. cit.*) may be cited as evidence for the presence of a typical aliphatic conjugated diene system in the molecule, while the coloration produced on mixing the hydrocarbon with *s*-trinitrobenzene in chloroform solution recalls the behaviour of substituted styrenes generally.

In arriving at a decision between the *trans-trans-* and the *cis-cis*-configurations for the molecule, the following considerations are involved. In the fully planar *trans-trans* model (II*a*) the steric hindrance affects all four *ortho*-positions and could be conveniently reduced by rotating the benzene rings about the single bonds to which they are attached. If one half of the molecule is rotated about the central single bond instead, steric interference with one of the two *ortho*-positions of each benzene ring would still occur, and the latter rotation is therefore regarded as an unlikely alternative. These conclusions are in accord with the observed symmetry properties of the molecule, which exclude the possibility of rotation about the central bond. On the other hand, it is found on examination of the *cis-cis* model that rotation of the benzene rings alone is hardly sufficient to remove all steric hindrance, for in the extreme perpendicular arrangement (III*b*) the carbon atoms of the methyl groups would still approach the benzene rings to a distance of only about 2·5 A. Moreover, such rotation would in any case appear to be the more unlikely concession to steric requirements in the *cis-cis* structure, involving as it does the sacrifice of some resonance energy in the *two* fully planar styrene systems in favour of *one* butadiene conjugation kept intact. An unhindered and energetically stable molecule of the *cis-cis*-configuration could therefore only be obtained by rotation about the central single bond, resulting in asymmetry contrary to the experimental facts.

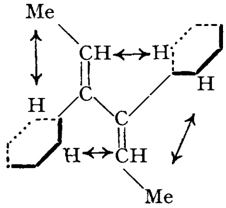


Absorption spectra in n-*hexane solution.*

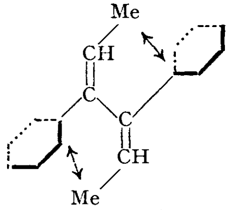
1, 3 : 4-*Diphenylhexa*-2 : 4-*diene* (*αβ-diethylidenedibenzyl*).
2, 1-*Phenylpropylene.*
3, *Hexa*-2 : 4-*diene* (*in ethanol*; *after Booker, Evans, and Gillam,* J., 1940, 1453).
4, 2 : 3-*Dimethylbuta*-1 : 3-*diene* (*in methyl*cyclo*hexane*; *after Scheibe and Pummerer,* Ber., 1927, **60**, 2163).

It appears reasonable therefore to conclude that the αβ-diethylidenedibenzyl of m. p. 101° has the *trans-trans*-configuration, which is presumably associated with greater stability than the hypothetical *cis-cis*-. In the *trans-trans* model (III*a*), rotation of the benzene rings by some 50° out of the plane of the double bonds would be sufficient to remove most of the steric interference (cf. Zechmeister and LeRosen, *loc. cit.*), giving rise to a centrosymmetric molecule which has the full resonance energy of a coplanar butadiene derivative and some appreciable fraction of the styrene conjugation. The shape of the dibenzyl skeleton may therefore be expected to be intermediate between the hypothetical coplanar and the staggered arrangements of the divinyl and diethyl compounds.

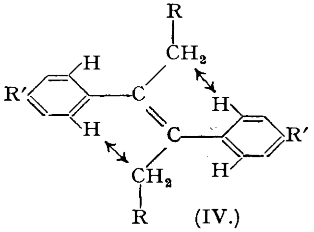
In contrast to diethyldibenzyl, diethylidenedibenzyl was observed to depress the m. p. of the divinyl derivative, although there are marked similarities in unit-cell dimensions. The lengths of the long *b*-axes in particular, which must be closely related geometrically to twice the length of the long axes of the molecules, are almost identical in the two isomers. It would seem a tempting speculation to attribute the lengthening of the *c*-axis in the conjugated compound to the greater spatial extension of the fully coplanar six-carbon zigzag chain in its molecule, and again to suspect a connection between the shortening of the *a*-axis and the general flattening of the structure which is demanded by resonance theory.



(III*a*.)



(III*b*.)

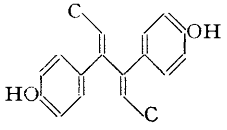


(IV.)

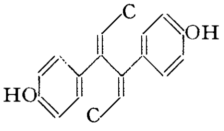
The molecular shape of *trans*-αβ-diethylstilbene (IV; R = Me, R′ = H) must finally be considered as the remaining structure of the series under discussion. Except for the two methyl carbons R, the whole molecule will again seek to attain coplanarity so as to gain the full resonance energy of stilbene-type conjugation, but some rotation of the benzene rings out of the plane of the ethylenic centre is required by the steric interferences indicated by double-headed arrows in the diagram. The reality of this steric hindrance (geometrically similar to those discussed above) and its inhibitory effect on electronic resonance have already been inferred from the observed ultra-violet absorption spectrum of the corresponding dimethylstilbene (IV; R = R′ = H) by Lewis and Calvin (*Chem. Reviews*, 1939, **25**, 302) and by Jones (*J. Amer. Chem. Soc.*, 1943, **65**, 1818). The benzene rings are presumably rotated symmetrically and kept parallel, by analogy with the centrosymmetrical character of the related *trans-pp′*-dihydroxy-αβ-diethylstilbene dipropionate structure (IV; R = Me, R′ = $CH_3{\cdot}CH_2{\cdot}CO_2$) (Carlisle and Crowfoot, *loc. cit.*). The existence or otherwise of a centre of symmetry in *trans*-αβ-diethylstilbene itself is not revealed by the available preliminary *X*-ray data alone. The space-group still requires the presence of four asymmetric units in the cell, but the hydrocarbon crystallises with four molecules in a doubled unit cell which differs from that of *meso*-αβ-diethyldibenzyl in much the same way in which stilbene differs from dibenzyl (cf. Prasad, Robertson, and Woodward, *Proc. Roy. Soc.*, 1935, *A*, **154**, 187). The molecular shapes of *trans*-diethylstilbene and *meso*-diethyldibenzyl, both necessarily non-coplanar on steric grounds, correspond more closely, however, than those of stilbene and dibenzyl which are characterised by planar and staggered configurations, respectively. These spatial relationships are apparently illustrated by the properties of the mixed solid systems. Wessely and Welleba (*loc. cit.*) found that *trans*-αβ-dimethylstilbene (IV; R = R′ = H) and *meso*-αβ-dimethyldibenzyl (I; R = Me), and also *trans-pp′*-dimethoxy-αβ-diethylstilbene (IV; R = Me, R′ = OMe) and *meso-pp′*-dimethoxy-αβ-diethyldibenzyl gave rise to continuous series of mixed crystals, and analogous isomorphous behaviour may therefore be reasonably predicted for *trans*-αβ-diethylstilbene and *meso*-αβ-diethyldibenzyl as well. On the other hand, the planar stilbene and the non-planar dibenzyl molecules have recently been reported to be truly miscible only over a very small range in the crystalline state (Kofler and Brandstaetter, *Z. physikal. Chem.*, 1942, *A*, **190**, 341).

Unfortunately, no complete phase-diagrams could be obtained in the present work owing to the minute amounts of the diethyl- and diethylidene-dibenzyls at our disposal, and the non-availability of a specimen of diethylstilbene, but despite this shortcoming some interesting facts relating to the isomorphous relationships in the *meso*-αβ-divinyldibenzyl series emerge from the table. True isomorphism is obviously exhibited by the hydrocarbons *A* and *B*, a random mixture of which does not produce any depression of m. p. The compounds *A* and *C* possess extremely similar crystal geometry and physiological potency and are therefore probably isomorphous, too, in which case the depression of their mixed m. p. must be ascribed to the formation of a continuous mixed-crystal system of type III of the Bakhuis Roozeboom classification. On the other hand, *D* is crystallographically distinct from the other three members of the series but may nevertheless be presumed to give rise to an isomorphous phase-diagram in admixture with *B* in view of Wessely and Welleba's corresponding results on two pairs of homologous compounds (cf. above). Continuous mixed-crystal formation is evidently not a function of strictly analogous lattice geometry alone. It may well be that in the mixtures of *B* with *D* there is only a small energy gradient opposing the configurational adjustments required in the shape of either or both molecules for the formation of a mixed-crystal lattice, the resulting intra-molecular instability being more than compensated for by a gain in lattice energy. Correns and others (*Chemie*, 1944, **57**, 29) have recently suggested on more general gounds that the idealised concept of isomorphism should be abandoned or qualified by reference to the several specific criteria such as miscibility, crystal geometry, and physiological activity. On this view, all four hydrocarbons of the table constitute an isomorphous series with respect to physiological activity and probably also miscibility, but only the first three appear to satisfy the criterion of analogous crystal structure.

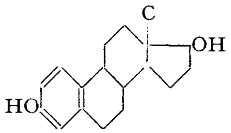
In conclusion, it may be pointed out that the arguments relating to the spatial configuration of the hydrocarbons are equally applicable to their *pp'*-dihydroxy-derivatives, the highly active synthetic oestrogens. This circumstance is of some interest in connection with the marked dependence of high oestrogenic activity on stereochemical factors (cf. Dodds *et al.*, *Proc. Roy. Soc.*, 1944, *B*, **132**, 83; Shoppee, *Nature*, 1947, **160**, 64). In particular, it is now revealed that the true structure of dienoestrol, the centrosymmetrical *pp'*-dihydroxy-derivative of αβ-diethylidenedibenzyl (cf. Carlisle and Crowfoot, *loc. cit.*), must be *trans-trans* (V), and not the conventionally depicted *cis-cis* of the structure (VI) which has been designed to afford a superficial resemblance on paper to the space-arrangement of the nuclear carbon atoms in the natural oestrogenic hormone oestradiol (VII). Similarly, the conformation of the single bonds contained in the two ethyl groups of stilboestrol must be expected to approximate to a regular zigzag rather than to the S-shaped configuration of the " corresponding " atoms in the tetracyclic oestradiol structure, in order to offer the least possible steric opposition to a coplanar arrangement of the stilbene skeleton. Again, the principle of maximum resonance energy demands that the highly active *oo'*-αβ-tetramethylstilboestrol molecule (Bretschneider *et al.*, *Ber.*, 1941, **74**, 571; Hudson and Walton, *J.*, 1946, 85) should be near-planar with the ring configuration (VIII), offering no close analogy to the skeletal arrangement of the natural hormone. Scale models suggest, however, that the thickness of the highly active synthetic molecules is in every case similar to that of oestradiol itself, whereas some reported cases of feeble activity appear to differ in this respect (cf. Dodds, *loc. cit.*, and *ibid.*, 1939, *B*, **127**, 141).



(V.)



(VI.)



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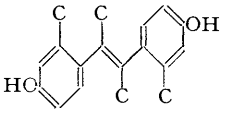

(VIII.)

EXPERIMENTAL.

meso-*αβ-Divinyldibenzyl.*—From petrol were obtained well-formed crystals of the monoclinic system, tabular on {010} with {101} and {001}. Careful indexing of single-crystal oscillation phtographs about the principal axes, in revealing the systematic extinctions characteristic of the space-group $P2_1/n$, showed that the two molecules in the unit cell were centrosymmetric.

meso-*αβ-Diethylidenedibenzyl* (trans-trans-3 : 4-*Diphenylhexa*-2 : 4-*diene*).—An almost pure sample of the hydrocarbon (small leaflets, m. p. 99—100°; cf. Stern, *loc. cit.*, who described shiny leaflets of m. p. 99°) was provided by Mr. W. Lawson of the Courtauld Institute of Biochemistry (Middlesex Hospital Medical School). After recrystallisation from ethanol, needles of m. p. 101—102° were obtained which depressed the m. p. of *meso-αβ*-divinyldibenzyl below 80°. The crystals, which were poorly formed, were tabular on {001} and elongated along [$10\bar{1}$]. As with the previous compound, the indexing of oscillation photographs identified the space-group as $P2_1/n$ with two centrosymmetric molecules in the unit cell. The ultra-violet absorption spectrum, except for the disappearance of a small shoulder near 2825 A., did not change after one further crystallisation. A yellow colour but no compound crystals were obtained on mixing with 2 mols. of *s*-trinitrobenzene in concentrated chloroform solution.

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