18. *Condensation Products of Phenols and Ketones. Part VII. Molecular Complexes formed by 2'-Hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan.*

By WILSON BAKER, R. F. CURTIS, and (MISS) M. G. EDWARDS.

2'-Hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (see Part VI, preceding paper) forms crystalline 1 : 1 molecular complexes with many ethers, ketones, and amines. Although salt formation may play some part in the formation of these complexes, the size and structure of the combining molecule are of importance, particularly with the ethers and ketones. The complexes with morpholine and dioxan are abnormal and contain water.

THE dimeride of 4-*iso*propenyl-*m*-cresol has been proved to be 2'-hydroxy-2 : 4 : 4 : 7 : 4'-pentamethylflavan (formula II, Part VI). The isolation of this compound in the pure state is facilitated by the great ease with which it forms a highly crystalline complex with one molecule of diethyl ether. This complex, which has long been known (Fries and Fickewirth, *Ber.*, 1908, **41**, 371), is readily prepared by addition of ether to a light petroleum solution of the flavan, or by stirring ether into a mixture of the flavan and warm water, in which the non-crystalline flavan forms a thick oil.

In connection with other work in this laboratory on the condensation products of phenols and ketones, it was observed that the dimeride of 3-*iso*propenyl-*p*-cresol (probably 2'-hydroxy-2 : 4 : 4 : 6 : 5'-pentamethylflavan) yielded a mononitro-derivative which also crystallised with one molecule of diethyl ether, and it was recalled that a similar adduct was formed by the doubtless structurally related dimeride of 4-(*cyclo*hex-1-enyl)-*m*-cresol (Boettcher, Diss., Berlin, 1930). The persistence of this phenomenon in a group of related compounds suggested that the packing of the flavan molecules in the crystal was such as to leave spaces in the lattice in which a solvent molecule of suitable size could be accommodated. It was found that diethyl ketone and diethylamine extremely readily formed very well crystallised, 1 : 1 molecular complexes with 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan, and about ten other somewhat similar substances were also found to give crystalline adducts of the same type. In an attempt to oxidise this flavan in aqueous pyridine solution it was observed that a crystalline 1 : 1 adduct was formed with pyridine, and it was then found that many aromatic and other cyclic bases formed similar adducts. The table (p. 86) sets out the compounds with which 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan forms crystalline molecular complexes.

In Part V of this series (Baker and Besly, *J.*, 1940, 1105) it was stated that the formation of the crystalline molecular complex between 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan and diethyl ether could " be used as the basis of a delicate and specific test for diethyl ether." This test is now clearly seen to be not specific for diethyl ether.

In reviewing the list of 32 substances in the table, certain generalities are apparent. A large number and variety of substances have been investigated, but only certain ethers, ketones, and aliphatic and aromatic bases yield adducts. Of the aliphatic ethers and ketones, only seven have been found to give crystal complexes; of these, diethyl ether, di*iso*propyl ether, diethyl ketone and di*iso*propyl ketone contain the grouping $CH_3{\cdot}\overset{|}{C}H{\cdot}X{\cdot}\overset{|}{C}H{\cdot}CH_3$, where X = O or CO, methyl *n*-propyl ketone and mesityl oxide contain the grouping $CH_3{\cdot}X{\cdot}\overset{|}{C}H{\cdot}\overset{|}{\underset{|}{\ }}{\cdot}CH_3$, where X = CO, and acetylacetone is very similar in structure. It is evident that here both molecular size and chemical character are involved. Closely similar compounds which have not yet given complexes are ethyl vinyl ether, methylal, diethyl sulphide, acetone, ethyl methyl ketone, di-*n*-propyl ketone, *iso*butyl methyl ketone, di*iso*butyl ketone, *cyclo*pentanone, *cyclo*hexanone, a variety of esters with a five-atom chain, and all alcohols so far tested.

The bases which yield crystalline complexes are of a much wider variety, ranging from diethylamine and di-*n*-butylamine to quinoline and *iso*quinoline, including aniline and halogenated pyridines. The complexes are all of the 1 : 1 type, with the two exceptions mentioned below. It seems probable that salt formation is playing a prominent, though not an exclusive, part in the formation of these flavan–base complexes. Trimethylenediamine, di*iso*butylamine, mono- and di-alkylanilines, *p*-toluidine, piperidine, 2-aminopyridine, 2-iodoquinoline, and nicotine have not yielded crystalline adducts.

Two complexes only, those with dioxan and morpholine, have been found which are not of the 1 : 1 type. These particularly well crystallised products separated very slowly from light petroleum only after many days, and the explanation of this abnormal behaviour was found to be that, not only dioxan and morpholine, but also water of crystallisation was taken up. Analysis showed the presence of two molecules of the flavan, one of dioxan or morpholine, and two of water. Crystalline material could not be obtained in the absence of water. Crystallisation with two different solvents at the same time must be a very rare phenomenon. It is significant that with dioxan and morpholine, both of which are bifunctional molecules, the complex contains two molecules of the flavan to each molecule of organic solvent.

The behaviour of 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan with 2-iodopyridine requires special mention; similar behaviour has not been encountered with other adducts, but has not been deliberately sought. The 1 : 1 molecular complex was prepared by crystallisation from light petroleum in presence of excess of 2-iodopyridine. When this complex was recrystallised, *i.e.*, when it separated from a solution containing equimolecular quantities of the components, the complex had an iodine content (20·6%) corresponding to a ratio of flavan to 2-iodopyridine of approximately 1·5 : 1; and a solution containing the flavan and 2-iodopyridine in the molecular ratio of 4 : 1 deposited crystals having an iodine content (10·6%) corresponding to a ratio of approximately 3·5 : 1, respectively. No significant difference was observed between the melting points of these three specimens. This is clearly an unusual case of a molecule, the flavan, incorporating into its crystal lattice a second substance, 2-iodopyridine, in whatever proportion may be available up to a maximum of the equimolecular ratio when all the spaces in the lattice are filled. The only other comparable cases are the quinol–formic acid and quinol–acetylene complexes (Palin and Powell, *J.*, 1948, 815) in which there is incomplete filling of the spaces in the crystal lattice by organic molecules, even though the second components were present in excess; variations in the amount of the lattice filling were not recorded.

A further point of interest about these 2-iodopyridine complexes is that they are completely stable on exposure to light, whereas 2-iodopyridine, like most organic iodine compounds, becomes brown during the course of a few days. It appears that the molecules of 2-iodopyridine enclosed in the lattice are protected from oxidative attack.

X-Ray investigation of these complexes is being carried out by Dr. H. M. Powell, of the

Department of Chemical Crystallography, Oxford, and the halogen compounds listed in the table were prepared for this work. It is clear that the complexes with bases are not solely lattice compounds, but with the ethers and ketones the general form of the molecule is capable of little variation. Even here, however, it is probable that chemical or polar interaction plays a part in complex formation, since both ethers and ketones are weak proton acceptors, and salt formation or hydrogen bonding may occur between the ether or ketone on the one hand, and the phenolic hydroxyl group of the flavan on the other.

The complexes all melt with partial loss of solvent over a range of about 2°, varying from below 50° in the case of the flavan–mesityl oxide compound to over 105° in the cases of di*iso*propylamine and dioxan–water; the free crystalline flavan melts at 82—84°. The flavan–diethyl ether and flavan–diethylamine complexes have melting points some 42° above the boiling points of the solvents of crystallisation. On exposure to the air, the complexes usually begin to turn opaque within a few days, owing to loss of solvent and formation of microscopic crystals of the free flavan, though some are considerably more stable than others. Only the flavan–dioxan–water and the flavan–morpholine–water complexes are quite stable under ordinary laboratory conditions.

It is probable that 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan is unique amongst organic compounds in the great number, which could undoubtedly be increased, of substances with which it forms crystalline adducts. These adducts may find use for isolation and identification purposes and for the preparation of certain solvents in a state of very high purity.

2′-Hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan should be capable of existing in enantiomorphous forms owing to the presence of an asymmetric carbon atom in position 2. The complex with (−)-coniine was prepared in order to see if resolution could be effected, but decomposition of the apparently homogeneous, crystalline adduct gave the unchanged racemic flavan.

It may finally be mentioned that the closely related dimeride of 3-*iso*propenyl-*p*-cresol (probably 2′-hydroxy-2 : 4 : 4 : 6 : 5′-pentamethylflavan) has also been found to give molecular complexes with a large number of organic solvents, particularly bases.

EXPERIMENTAL.

(M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.)

2-*Iodopyridine.*—Considerable difficulty was experienced in attempts to repeat the preparation of 2-iodopyridine by diazotisation of 2-aminopyridine (Tschitschibabin and Rjasanzew, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1571; see *Zentr.*, 1915, I, 1065; Craig, *J. Amer. Chem. Soc.*, 1924, **46**, 232). No reaction occurred when 2-bromopyridine was heated with a neutral solution of sodium iodide in acetone or ethyl methyl ketone (cf. preparation of 6-iodo- from 6-chloro-nicotinic acid, Klingsberg, *ibid.*, 1950, **72**, 1031), but reaction occurred in presence of acid. The method finally adopted was as follows. 2-Bromopyridine (20 g.) was boiled under reflux for 6 hours with hydriodic acid (100 c.c.; *d* 1·7), and the mixture was poured into aqueous sodium hydroxide (100 c.c.; 40%) and ice (100 g.), and extracted with ether (3 × 50 c.c.). The extracts were washed successively with water, aqueous sodium sulphite, and water, dried ($MgSO_4$), and fractionated through a 12-inch column, giving 2-bromopyridine, b. p. 75°/13 mm. (6·1 g.), and 2-iodopyridine, b. p. 93—95°/13 mm. (9·1 g., 35%) (Found: C, 29·5; H, 2·2; I, 62·3. Calc. for C_5H_4NI: C, 29·3; H, 2·0; I, 62·0%). The picrate obtained by treatment with saturated ethanolic picric acid formed thin, yellow prisms, m. p. 119—120°, from ethanol (Found: C, 30·2; H, 1·1; N, 12·4; I, 28·8. Calc. for $C_{11}H_7O_7N_4I$: C, 30·4; H, 1·6; N, 12·9; I, 29·3%).

2-*Iodoquinoline.*—2-Chloroquinoline (Friedländer and Ostermaier, *Ber.*, 1882, **15**, 333) (3 g.) was treated with a mixture of ethyl methyl ketone (70 c.c.) and water (1 c.c.) which had been saturated at the b. p. with sodium iodide. Hydriodic acid (1 c.c.; *d* 1·57) and water (2 c.c.) were added, and the mixture was refluxed for 30 hours. The ketone was then removed under reduced pressure, water was added and sodium hydroxide (2N.) until alkaline, and after cooling to 0° the solid was collected (3·85 g.). Recrystallisation from aqueous ethanol gave fine, very pale yellow needles, m. p. 52° (3·35 g.; 72%), raised by recrystallisation to 53° (Found: C, 42·5; H, 2·3; N, 5·5; I, 49·8. Calc. for C_9H_6NI: C, 42·4; H, 2·3; N, 5·5; I, 49·8%) (Friedländer and Weinberg, *Ber.*, 1885, **18**, 1531, give m. p. 53°).

General Method of Preparation of Complexes.—The following method has been used for the preparation of the majority of the complexes. 2′-Hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan (for preparation see Part VI) (2 g.) is dissolved in light petroleum (b. p. 40—60°) (20 c.c.), and the other component (*ca.* 1 g.) added. In many cases the complexes begin to separate almost immediately, and if the mixture is stirred the separation of fine crystals is complete in a few minutes. Large crystals are usually obtained if the mixture is not disturbed. The solid is collected, washed with a little cold light petroleum, and dried by short exposure to the air. The yields vary from about 1·5 to 2·0 g. In other cases crystalline material may only separate after one or more days, owing to lack of crystal nuclei. We have not observed the crystallisation of the free flavan from light petroleum solutions containing a solvent with which a complex is formed, but it frequently separates from such solutions containing another solvent with which complexes are not formed, particularly if the crystalline flavan itself (see Part VI) has been handled in the laboratory. Many of the complexes may be recrystallised with some loss from light petroleum without alteration of the molecular ratio of the components.

Crystal Complexes with 2-Iodopyridine.—(*a*) The 1 : 1 *complex* was prepared from the flavan (2 g.), light petroleum (20 c.c.), and 2-iodopyridine (2 c.c.); it separated as thick prisms (2·8 g.) (for m. p. and analyses, see table). (*b*) The approximately 1·5 : 1 (flavan : 2-iodopyridine) *complex* separated, on recrystallising the 1 : 1 complex, in aggregates of very small crystals, m. p. 73—75° (Found : C, 64·6; H, 6·2; N, 2·2; I, 20·6. $1{\cdot}5C_{20}H_{24}O_2,C_5H_4NI$ requires C, 64·7; H, 6·2; N, 2·2; I, 19·6%). (*c*) The approximately 3·5 : 1 (flavan : 2-iodopyridine) *complex* separated (1·2 g.) when the flavan (2 g., 4 mols.) and 2-iodopyridine (0·35 g., 1 mol.) were mixed in light petroleum; it formed clusters of small, very thin prisms, m. p. 73—75° (Found : I, 10·6. $3{\cdot}5C_{20}H_{24}O_2,C_5H_4NI$ requires I, 10·2%). There is no evidence to suggest that the last two complexes are mixtures of the crystalline flavan and the 1 : 1 complex.

Crystalline complexes formed by 2′-*hydroxy*-2 : 4 : 4 : 7 : 4′-*pentamethylflavan.*

Component.	M. p. (dissociation).	Analyses : Found, % (required, %, in parentheses).		
		Carbon.	Hydrogen.	Nitrogen.
1 : 1 Complexes.				
Diethyl ether	76—77°	77·8 (77·8)	9·2 (9·2)	—
Di*iso*propyl ether	79—81	78·8 (78·4)	9·5 (9·6)	—
Diethyl ketone	79—81	78·7 (78·5)	8·9 (8·9)	—
Di*iso*propyl ketone	58—60	78·7 (79·0)	9·3 (9·3)	—
Methyl *n*-propyl ketone	71—73	78·4 (78·5)	8·4 (8·9)	—
Mesityl oxide	45—47	79·1 (79·2)	8·8 (8·6)	—
Acetylacetone	62—64	76·0 (75·8)	8·3 (8·1)	—
Diethylamine	97—99	78·4 (78·1)	9·4 (9·5)	3·8 (3·8)
Diethylmethylamine	75—77	78·3 (78·3)	9·7 (9·7)	3·9 (3·7)
Triethylamine	54—56	78·7 (78·6)	9·6 (9·8)	3·6 (3·5)
Di-*n*-propylamine	49—52	79·0 (78·6)	9·9 (9·8)	3·7 (3·5)
Di*iso*propylamine	105—107	78·3 (78·6)	9·8 (9·8)	3·9 (3·5)
Di-*n*-butylamine	54—56	79·2 (79·1)	10·5 (10·1)	3·2 (3·3)
Di-*sec.*-butylamine	50—52	79·0 (79·1)	9·7 (10·1)	2·8 (3·3)
*cyclo*Hexylamine	73—75	79·0 (79·0)	9·2 (9·4)	3·5 (3·5)
Benzylamine	91—93	80·5 (80·4)	8·1 (8·2)	3·7 (3·5)
Aniline	56—58	80·4 (80·2)	8·0 (8·0)	3·9 (3·6)
Pyridine	75—77	79·9 (80·0)	7·8 (7·7)	3·7 (3·7)
N-Ethylpiperidine	88—90	79·0 (79·2)	9·3 (9·5)	3·5 (3·4)
2-Methylpyridine	64—66	80·1 (80·2)	7·7 (8·0)	3·8 (3·6)
3-Methylpyridine	55—57	80·7 (80·2)	8·0 (8·0)	3·4 (3·6)
4-Methylpyridine	80—82	80·2 (80·2)	8·0 (8·0)	3·6 (3·6)
2 : 4-Dimethylpyridine	84—86	80·5 (80·4)	8·4 (8·2)	3·8 (3·5)
2 : 6-Dimethylpyridine	87—89	80·1 (80·4)	8·4 (8·2)	3·2 (3·5)
Quinoline	75—77	81·9 (81·9)	7·2 (7·3)	3·0 (3·3)
*iso*Quinoline	97—99	81·4 (81·9)	7·5 (7·3)	3·6 (3·3)
2-Methylquinoline	96—98	81·9 (82·0)	7·3 (7·5)	2·9 (3·2)
2-Bromopyridine	59—62	65·8 (66·1)	6·2 (6·2)	3·0 (3·1) *
3-Bromopyridine	50—52	66·1 (66·1)	6·2 (6·2)	3·0 (3·1) †
2-Iodopyridine	75—77	59·3 (59·9)	5·2 (5·6)	— ‡
2-Chloroquinoline	89—91	75·5 (75·7)	6·2 (6·5)	3·1 (3·1) §
(—)-Coniine	102—104	79·6 (79·4)	9·5 (9·7)	3·0 (3·3)
Other complexes, $C_{20}H_{24}O_2 : H_2O$: Component = 2 : 2 : 1.				
Dioxan	106—108	73·6 (73·7)	8·5 (8·4)	— ‖
Morpholine	94—96	73·9 (73·8)	8·5 (8·5)	2·0 (2·0) ¶

* Found : Br, 17·5. $C_{20}H_{24}O_2,C_5H_4NBr$ requires Br, 17·6%.
† Found : Br, 17·4%.
‡ Found : I, 25·1. $C_{20}H_{24}O_2,C_5H_4NI$ requires I, 25·3%.
§ Found : Cl, 7·9. $C_{20}H_{24}O_2,C_9H_6NCl$ requires Cl, 7·7%.
‖ Loss in weight, 17·1. $2C_{20}H_{24}O_2,2H_2O,C_4H_8O_2$ requires loss, 17·3%.
¶ Loss in weight, 17·5. $2C_{20}H_{24}O_2,2H_2O,C_4H_9ON$ requires loss, 17·2%.

Complex with (—)-*Coniine.*—A crude, dark brown specimen of (—)-coniine (86%, 0·257 g.) was dissolved in light petroleum (b. p. 40—60°; 7 c.c.), filtered, and added to a solution of the flavan (0·888 g.) in light petroleum (10 c.c.). After treatment with charcoal, filtration, and concentration to *ca.* 7 c.c., the *complex* separated as colourless prisms [0·454 g.; m. p. *ca.* 100° (decomp.)], which, after recrystallisation from light petroleum, had m. p. 102—104° (decomp.).

Crystal Complexes with Dioxan and Water, and with Morpholine and Water.—Repeated attempts to prepare complexes in the absence of water from 2′-hydroxy-2 : 4 : 4 : 7 : 4′-pentamethylflavan and anhydrous dioxan or morpholine in light petroleum were unsuccessful. As with many other cases, complexes containing dioxan and morpholine are readily prepared in small crystals by shaking at about 50—60° a mixture of the then-fluid dimeride and water with the organic solvent.

The well-crystallised complexes were obtained as follows. The dimeride (6 g.) was dissolved in light petroleum (30 c.c.; b. p. 40—60°), and dioxan or morpholine (2 c.c.) and water (0·5 c.c.) were added, followed by enough ethyl alcohol (6 c.c.) to give a homogeneous solution. The complexes separated rapidly, preferably after seeding, in the form of large, highly refracting, rhombic crystals (yields: of dioxan–water complex, 5·7 g., collected at room temperature; of morpholine–water complex, 5·7 g., collected after final cooling to 0°). These substances give turbid solutions in warm toluene owing to the separation of water.

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