[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE AND RUBBER COMPANY]

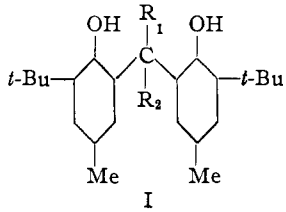
The Structure and Configuration of Dihydroxydiphenylmethanes Derived from Butylated *m*-Cresols as Evidenced by Infrared Absorption

BY JOSEPH C. AMBELANG AND JOHN L. BINDER

RECEIVED AUGUST 22, 1952

Dihydroxydiphenylmethanes were prepared from 6-*t*-butyl-3-methylphenol and aliphatic aldehydes from C_1 through C_9. Comparison by means of infrared absorption spectra with dihydroxydiphenylmethanes from 6-*t*-butyl-2-methylphenol and 2-*t*-butyl-4-methylphenol indicated that all the crystalline products from 6-*t*-butyl-3-methylphenol were 4,4′-dihydroxy compounds. Both the liquid fraction of the reaction product of the last phenol with formaldehyde and the crystalline product from 4,6-di-*t*-butyl-3-methylphenol showed intramolecular hydrogen bonding characteristic of the *cis* configuration of the 2,2′-dihydroxy structure. The dihydroxydiphenylmethane from 4-*t*-butyl-3-methylphenol was non-crystalline. The spectrum gave no evidence of intramolecular hydrogen bonding but a shift on dilution indicative of intermolecular bonding.

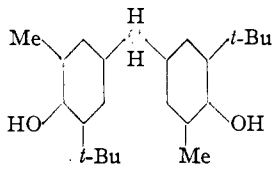
Infrared absorption measurements by Coggeshall[1] on "bisphenolalkanes" I, derived from 2-*t*-butyl-4-



I

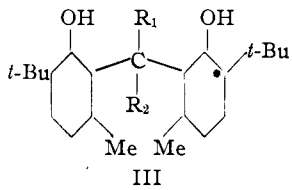
methylphenol, gave no evidence of intermolecular bonding in solutions. Intramolecular hydrogen bonding as evidenced by an absorption band close to 2.86 μ, however, was always present and was attributed to the *cis* orientation configuration. The *trans* configuration, in which the hydroxyl groups would be too far apart for intramolecular bonding, was also evidenced by a band near 2.75 μ when R_1 was hydrogen and R_2 was hydrogen, methyl, isopropyl or phenyl but not when R_2 was ethyl or when R_1 and R_2 constituted a pentamethylene. A lower homolog, from 2,4-dimethylphenol and isobutyraldehyde gave evidence of a high degree of intramolecular hydrogen bonding in an earlier publication of Sears and Kitchen.[2]

The dihydroxydiphenylmethane resulting from the condensation of 6-*t*-butyl-2-methylphenol with formaldehyde has necessarily the structure II in which the hydroxyl groups are isolated. Hence the hydroxyl absorption band in dilute solutions is to be expected only near 2.75 μ.



II

While only one classical structural formula can be written for a dihydroxydiphenylmethane derived by condensation of a carbonyl compound with a 2,4- or 2,6-dialkylphenol, three structural isomers, III, IV and V are possible when a 2,6-dialkylphenol is the starting material, *e.g.*, 6-*t*-butyl-3-methylphenol. Of these, III is sterically comparable to I and could exist in *cis* and *trans* configurations. The *cis* configuration should show intramolecular



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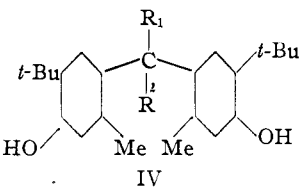
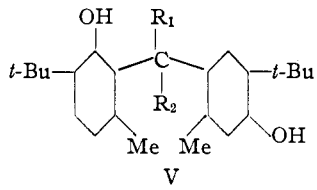


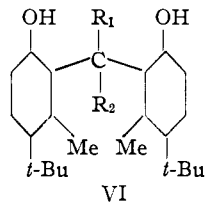
IV



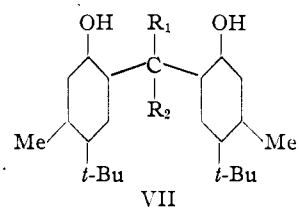
V

bonding by an absorption band near 2.85 μ. In IV and V the hydroxyl groups are isolated, no intramolecular bonding is possible and the hydroxyl absorption band should appear near 2.75 μ.

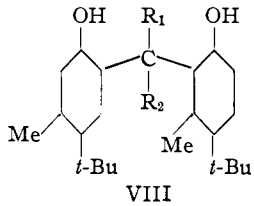
Similarly the condensation of a 3,4-dialkylphenol, *e.g.*, 4-*t*-butyl-3-methylphenol, could give rise to three structurally isomeric dihydroxydiphenylmethanes, VI, VII and VIII.



VI



VII



VIII

All of these have hydroxyl groups in the 2,2′ positions. They could exist in *cis* and *trans* configurations and hence show absorption bands in solution near 2.85 μ for the *cis* configuration and in dilute solution close to 2.75 μ for the *trans* configuration. The absence of alkyl groups in the 3,3′ positions, ortho to the hydroxyl groups, should leave the latter almost unhindered, unlike the previously discussed compounds. As unhindered phenols they might also give evidence of intermolecular bonding by the shift of the OH band from 2.75 toward 2.9 μ as Coggeshall[1] found to occur in the

(1) N. D. Coggeshall, THIS JOURNAL, **72**, 283 (1950).
(2) W. C. Sears and L. J. Kitchen, *ibid.*, **71**, 4110 (1949).

TABLE I

PREPARATION OF DIHYDROXYDIPHENYLMETHANES

	Phenol	Aldehyde	Reaction time, hr.	Yield of crystals (crude), %	Recrystallization solvent	M.p. of purified product, °C.
A	6-*t*-Butyl-3-methyl	Formaldehyde[a]	4	3.4	2:1 Heptane–benzene 120 ml.	174–175
B	6-*t*-Butyl-3-methyl	Acetaldehyde (Paraldehyde)	4	39	Benzene	195–196
C	6-*t*-Butyl-3-methyl	Propionaldehyde	3–4	13	4:1 Benzene–heptane 200 ml.	189–190
D	6-*t*-Butyl-3-methyl	Butyraldehyde	3	10	4:1 Benzene–heptane 150 ml.	207.5–208
E	6-*t*-Butyl-3-methyl	Isobutyraldehyde	3	18.4	4:1 Benzene–toluene 600 ml.	228.5–229
F	6-*t*-Butyl-3-methyl	Hexaldehyde (2-ethylbutanal)	4	9.7[b]	3:1 Cyclohexane–heptane 350 ml.	195–196.5
G	6-*t*-Butyl-3-methyl	Heptaldehyde	5.25	7.1[b]	Heptane	158.5–159
H	6-*t*-Butyl-3-methyl	Octaldehyde (2-ethylhexanal)	3.5	Negligible		
I	6-*t*-Butyl-3-methyl	Nonaldehyde (3,5,5-trimethylhexanal)	5.5	3.5	Heptane	166–167
J	4,6-Di-*t*-butyl-3-methyl	Formaldehyde[a] (0.24 mole)	3.5	24.8[c]	Benzene 150 ml.	208–209
K	6-*t*-Butyl-2-methyl[d]	Formaldehyde (0.25 mole)	72 at room temp.	47[e]	Hexane	102.5–103
L	2-*t*-Butyl-4-methyl	Formaldehyde	Product obtained from American Cyanamid Corp.		Petroleum ether	
M	4-*t*-Butyl-3-methyl[f]	Formaldehyde	24 at room temp.	(Resin)[g]		

[a] Trioxan, added gradually during heating period. [b] After dilution with hexane. [c] By extraction with benzene. [d] In 82 ml. of glacial acetic acid. [e] After dilution with water. [f] In 58 ml. of glacial acetic acid, dry HCl as catalyst. [g] Molecular weight (cryoscopic in benzene), 317.

TABLE II

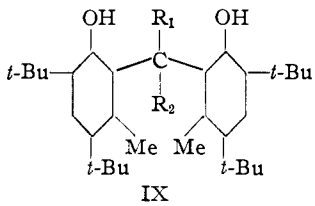
ANALYTICAL DATA FOR CONDENSATION PRODUCTS OF 6-*t*-BUTYL-*m*-CRESOL WITH ALDEHYDES

Aldehyde	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Mol. wt. Calcd.	Mol. wt. Found (cryoscopic)
Ar–CHR–Ar							
Formaldehyde	$C_{23}H_{32}O_2$	81.1	81.69	9.4	9.54	340	299 (Solid fraction)
							315 (Solid fraction)
							300 (Liquid fraction)
							336 (Liquid fraction)
Acetaldehyde	$C_{24}H_{34}O_2$	81.3	81.34	9.6	9.54	354	335[a]
			81.17		9.50		340[a]
Propionaldehyde	$C_{25}H_{36}O_2$	81.5	82.01	9.8	9.40	368	345[a]
			82.05		9.41		
Butyraldehyde	$C_{26}H_{38}O_2$	81.6	81.47	9.9	9.77	382	370[a]
			81.39		9.68		
Isobutyraldehyde	$C_{26}H_{38}O_2$	81.6	81.66	9.9	9.65	382	344[b]
			81.99		9.70		
Hexaldehyde (2-ethylbutanal)	$C_{28}H_{42}O_2$	81.7	81.76	10.3	9.76	411	422
Heptaldehyde	$C_{29}H_{44}O_2$	81.8	81.97	10.4	10.36	425	400
Nonaldehyde (3,5,5-trimethylhexanal)	$C_{31}H_{48}O_2$	82.1	82.52	10.7	10.46	453	473

[a] Salol used as solvent. [b] Rast.

case of 2,2′-dihydroxy-3,3′-dimethyl-5,5′-di-*t*-octyldiphenylmethane.

Dihydroxydiphenylmethanes from 4,6-di-*t*-butyl-3-methylphenol can have only one Structure IX since the alkylphenol has only one reactive position



IX

as does 2-*t*-butyl-4-methylphenol. Whether the hydroxyl band occurs at 2.75 μ and/or 2.85 μ depends on the configuration, *viz.*, *cis*, *trans* or a mixture.

Experimental

Preparation of Dihydroxydiphenylmethanes.—One-half mole of the phenol was stirred and heated on a steam-bath with 0.33 mole of aldehyde and 15 ml. of concentrated hydrochloric acid. When no further separation of solid appeared to be taking place, the mixture was diluted, usually with 100 ml. of heptane. The aqueous layer was drawn off in a separatory funnel. The oil and solid layer were washed with water, then aqueous sodium carbonate. The solid product was obtained by filtration. Variations of this general procedure are shown in Table I along with details of individual preparations.

A number of the same products have been made by the following modified procedure utilizing a lower temperature, of which the following is an example.

Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-hexylmethane.[3]—Twelve hundredths mole of 6-*t*-butyl-3-methylphenol (19.8 g.) was dissolved in 14 ml. of glacial acetic acid, 0.06 mole (6.8 g.) of *n*-heptaldehyde was added, then 3.4 ml. of concentrated hydrochloric acid. After standing 48 hr., the mixture was stirred into a large volume of water. The oil crystallized slowly. After several hours, it was filtered and the residue washed with water, lastly with petroleum ether. The air-dried yield weighed 8 g., 24% of the theoretical. The product was colorless and melted at 157–157.5°.

Infrared Absorption Spectra.—The infrared absorption was recorded between 2.5 and 3.4 μ with a Beckman IR-2 spectrophotometer. Wave lengths of the bands were found by linear interpolation between fiduciary marks, the positions of which were determined by comparison with CO_2 and H_2O bands. The resolution was sufficient to show the same bands for the same compounds reported by Coggeshall.[1] The dilute solutions were 0.07 molar; the concentrated solutions were 0.5 molar where possible, otherwise saturated. The crystalline derivatives of butylated *m*-cresol had too

(3) We are indebted to F. J. Webb of this Laboratory for the details of the procedure; *cf.* J. B. Niederl and J. S. McCoy, THIS JOURNAL, **65**, 629 (1943); D. R. Stevens and A. C. Dubbs, U. S. Patents 2,515,906–7 (1950); T. Zincke, *Ann.*, **343**, 85 (1905).

TABLE III

INFRARED ABSORPTION BANDS OF HYDROXYL RADICALS IN DIPHENYLMETHANES PREPARED FROM BUTYLATED CRESOLS AND ALIPHATIC ALDEHYDES

Methylphenol	Aldehyde	Product, -methane	Infrared absorption, hydroxyl band, μ: Crystal. mull	Concn.[a] soln.	Dilute[b] solution
		Crystalline products			
6-*t*-Butyl-2-	Formaldehyde	Di-(4-hydroxy-3-methyl-5-*t*-butylphenyl)-	2.75	2.75	2.74
2-*t*-Butyl-4-	.....	2-*t*-Butyl-4-methylphenol	2.72 2.78	2.76	2.75
6-*t*-Butyl-3-	Formaldehyde	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-	2.86		2.77
6-*t*-Butyl-3-	Acetaldehyde	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-methyl-	2.85		2.75
6-*t*-Butyl-3-	Propionaldehyde	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-ethyl-	2.86		2.78
6-*t*-Butyl-3-	*n*-Butyraldehyde	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-propyl-	2.85		2.76
6-*t*-Butyl-3-	Isobutyraldehyde	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-isopropyl-	2.85		..
6-*t*-Butyl-3-	Hexaldehyde (2-ethylbutanal)	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-3-pentyl-	2.85		2.76
6-*t*-Butyl-3-	Heptaldehyde	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-hexyl-	2.84		2.76
6-*t*-Butyl-3-	Nonaldehyde (3,5,5-trimethylhexanal)	Di-(4-hydroxy-2-methyl-5-*t*-butylphenyl)-octyl-	2.83		2.77
4,6-Di-*t*-butyl-3-	Formaldehyde	Di-(2-hydroxy-3,5-di-*t*-butyl-6-methylphenyl)-	2.81		2.86
2-*t*-Butyl-4-	Formaldehyde	Di-(2-hydroxy-5-*t*-butyl-5-methylphenyl)-	2.82 2.75 2.92	2.87 2.72	2.88 2.72
		Non-crystalline products			
4-*t*-Butyl-3-	Formaldehyde	Possible mixture of: 2,2′-Dihydroxy-6,6′-dimethyl-5,5′-di-*t*-butyldiphenyl- 2,2′-Dihydroxy-4,4′-dimethyl-5,5′-di-*t*-butyldiphenyl- 2,2′-Dihydroxy-4,6′-dimethyl-5,5′-di-*t*-butyldiphenyl-		3.07	3.07 2.75 .
6-*t*-Butyl-3-	Formaldehyde	2,2′-Dihydroxy-6,6′-dimethyl-3,3′-di-*t*-butyldiphenyl- 2,4′-Dihydroxy-6,2′-dimethyl-3,5′-di-*t*-butyldiphenyl- 4,4′-Dihydroxy-2,2′-dimethyl-5,5′-di-*t*-butyldiphenyl-		2.85	2.85 2.75

[a] 0.5 molar or saturated. [b] 0.07 molar.

low solubility in usable solvents to permit an infrared absorption measurement in concentrated solution. Data are shown in Table III.

Discussion

As expected for a diphenol with isolated hydroxyl groups (structure II) the formaldehyde derivative of 6-*t*-butyl-2-methylphenol gave only one hydroxyl band, at 2.74 μ. The crystalline products from 6-*t*-butyl-3-methylphenol and the homologous series of aldehydes from C_1 to C_9 showed a single band at nearly the same wave length, 2.75–2.78 μ. Hence all of them can be assigned the structure IV or V. The more symmetrical structure IV is favored in view of the high melting points of the series.[4] The derivative of 2-*t*-butyl-4-methylphenol and formaldehyde checks Coggeshall's results[1] and is included for comparison.

The crystalline condensation product of 4,6-di-*t*-butyl-3-methylphenol with formaldehyde appears to exist solely in the *cis* configuration since it shows the band at 2.86 μ indicative of hydrogen bonding and no band at 2.75 μ which would be expected if the isolated hydroxyl groups of the *trans* configuration were present.

The rotation is apparently restricted by the methyl groups ortho to the methylene bridge between the benzene rings. Coggeshall's compounds[1] which exist only in the *cis* form had only hydrogen ortho to the bridge but had bulkier groups on the bridge, *viz.*, ethyl or pentamethylene.

Yields of crystalline material from aldehydes and 6-*t*-butyl-3-methylphenol were rather small, particularly in the case of formaldehyde as shown in Table I. The non-crystalline fraction of the product was examined in this case. This fraction showed bands at both 2.75 μ and at 2.85 μ, indicating both isolated hydroxyl groups and hydrogen bonding. Hence, the structure III must be present in the *cis* configuration. The isolated hydroxyl groups can be attributed either to the *trans* configuration of III or to structures IV or V. From the reaction of 4-*t*-butyl-3-methylphenol and formaldehyde or acetaldehyde no crystalline product was obtained. The absorption bands of the first product were found at 2.75 and 3.07 μ. The former band can be attributed to *trans* configurations of VI, VII, or VIII. The latter band, whose wave length is longer than that of the band for intramolecular bonds observed in an isomeric *cis* structure, indicates intermolecular hydrogen bonding. Also, this is the only band present in concentrated solution. The absence of any group larger than a hydrogen atom ortho to the hydroxyl groups, in the 3,3′ positions, should be favorable to intermolecular bonding. The shift here is 0.32 μ, comparable to 0.30 μ for 2,6-di-methyl-4-*t*-butylphenol.[5] The absence of a band near 2.85 μ indicates no intramolecular bonding is present. Although Fisher–Hirschfelder molecular models indicate that the benzene rings are free to rotate around the methylene bridge, the *trans* configuration is the only one apparent in the spectrum.

(4) *Cf.* D. J. Beaver and P. J. Stoffel, THIS JOURNAL, **74**, 3410 (1952).

(5) N. D. Coggeshall, *ibid.*, **69**, 1620 (1947).

Acknowledgment.—The writers gratefully acknowledge the interest, encouragement and assistance of F. W. Stavely, J. W. Liska and G. E. P. Smith, Jr., in this investigation. The authors' gratitude is hereby expressed to the Management of the Firestone Tire and Rubber Company for permission to publish these results.

AKRON, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

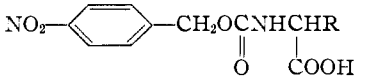
p-Nitrobenzyloxycarbonyl Derivatives of Amino Acids

BY DUANE T. GISH[1] AND FREDERICK H. CARPENTER

RECEIVED SEPTEMBER 27, 1952

The preparation of crystalline *p*-nitrobenzyloxycarbonyl derivatives of fifteen amino acids is described.

The introduction of the use of *p*-nitrobenzyl chloroformate in the preparation of derivatives of amino acids and in peptide synthesis was reported in an earlier paper.[2] The preparation of crystalline *p*-nitrobenzyloxycarbonyl derivatives (I) of the nineteen commonly occurring amino acids has now



been completed. These derivatives include the monosubstituted derivatives of glycine, L-proline, hydroxy-L-proline, L-leucine, L- and D,L-isoleucine, previously reported,[2] D,L-methionine, D,L-valine, L-glutamic acid, D,L-aspartic acid, D,L-tryptophan, D,L-serine, D,L-threonine, D,L-phenylalanine, D,L-alanine, 3,5-diiodo-L-tyrosine and D,L-histidine and the disubstituted derivatives of L-lysine, L-cystine, D,L-tyrosine and L-arginine.

The preparation of dicarbobenzoxy-L-arginine has not yet been reported in the literature. Fruton[3] reported that he was unable to prepare dicarbobenzoxy-L-arginine by the methods which yield other disubstituted products of arginine, such as dibenzoyl-L-arginine[4] or dibenzenesulfonyl-L-arginine.[5] However, when L-arginine was treated with either one or two moles of *p*-nitrobenzyl chloroformate in the usual manner di-*p*-nitrobenzyloxycarbonyl-L-arginine was the only crystalline product isolated. Since the disubstituted derivative does not give a color in the ninhydrin reaction,[6] one of the *p*-nitrobenzyloxycarbonyl groups must be attached to the α-amino nitrogen of arginine. The other group is presumably attached to the guanido group of arginine.

Bergmann and Zervas[7] reported only a very modest yield in the preparation of carbobenzoxy-L-histidine. A yield of almost 60% was obtained in the preparation of *p*-nitrobenzyloxycarbonyl-D,L-histidine. Since this derivative gives a negative ninhydrin color test and a positive Folin color test[8] it is considered to be substituted on the α-amino group of histidine.

When the derivatives of D,L-serine, D,L-threonine and D,L-tyrosine were prepared in a strongly alkaline solution in the usual manner the yields ranged from 30–40% and a large amount of di-*p*-nitrobenzyl carbonate was found in the reaction mixture. In the cases of serine and threonine this result is believed to be due to hydrolysis of the N-*p*-nitrobenzyloxycarbonyl derivatives in the strong alkali during the course of the reaction since these derivatives were quantitatively hydrolyzed with the liberation of *p*-nitrobenzyl alcohol in less than a minute when dissolved in 4 *N* alkali at room temperature. The low yield in case of the disubstituted tyrosine derivative may have been due to the hydrolysis of the O-substituted group in the strongly alkaline solution. It was found that in the case of these three derivatives the yield could be increased several fold by performing the coupling reaction in a mixture which was buffered at *p*H 9–10.

The derivative of D,L-tryptophan was the only compound in the entire series exhibiting any appreciable visible color (a bright orange-yellow). It possessed absorption maxima at 222 and 273 mμ with molecular extinction coefficients of 32,400 and 14,100, respectively, in 95% ethanol. The derivatives of the other amino acids showed an absorption maximum at about 268 mμ with molecular extinction coefficients of 9,500 for the monosubstituted derivatives and of 19,200 for the disubstituted derivatives.

Experimental[9]

N-*p*-Nitrobenzyloxycarbonyl Derivatives.—Essentially two procedures were used in the preparation of the derivatives whose properties are described in Table I. In procedure A the reaction mixture was strongly alkaline, while in procedure B the reaction mixture was buffered to about *p*H 9–10. The derivatives of several of the amino acids, not described in Table I, were prepared by modified procedures.

Procedure A.—The amino acid was dissolved in 1.25 equivalents of 4 *N* sodium hydroxide and the resulting solution was placed in a reaction vessel so designed as to allow vigorous shaking on a mechanical shaker with simultaneous cooling in an ice-bath. The reaction vessel was constructed

(1) Public Health Service Research Fellow of the National Institutes of Health.

(2) F. H. Carpenter and D. T. Gish, THIS JOURNAL, **74**, 3818 (1952).

(3) J. S. Fruton, "Advances in Protein Chemistry," Vol. 5, ed. by M. Anson, J. Edsall and K. Bailey, Academic Press, Inc., New York, N. Y., 1949, p. 1.

(4) K. Felix and K. Dirr, *Z. physiol. Chem.*, **176**, 29 (1928).

(5) H. T. Clarke and H. B. Gillespie, THIS JOURNAL, **54**, 1964 (1932).

(6) S. Moore and W. H. Stein, *J. Biol. Chem.*, **176**, 367 (1948).

(7) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(8) O. Folin and U. Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).

(9) All melting points were taken on the hot-stage. The analyses were performed by the Microchemical Laboratory, Department of Chemistry, University of California, Berkeley. The water analysis was by the method of Karl Fischer as modified by E. Almy, W. Griffin and C. Wilcox, *Anal. Chem.*, **12**, 392 (1940).