[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Substituted Diphenylmethanes and Phenyl Benzyl Ethers Prepared from *o*- or *p*-Cresol and *o*-, *m*- or *p*- Bromobenzyl Chloride[1]

BY RALPH C. HUSTON AND HANS H. GYORGY[2]

When it was shown that a group of diphenylmethanes prepared in this Laboratory[3] showed promising specific antibacterial activity[4] a program was begun to expand the series and attempt the determination of the groups responsible for the activity. This paper describes the preparation of nine diphenylmethane derivatives and six methylphenyl bromobenzyl ethers.

The preparation of the compounds benzylated in the para position to the phenolic hydroxyl may be accomplished by aluminum chloride catalyzed condensations.[5] In the cases in which benzylation ortho to the hydroxyl group is desired the method of Claisen, *et al.*,[6] is more applicable. The aluminum chloride catalyzed condensations were carried out by the reactions of the bromobenzyl chlorides; or in one case, *p*-bromobenzyl alcohol, with *o*-cresol, using petroleum ether as solvent. The C-alkylations of *o*- and *p*-cresol by the Claisen method utilize the condensation of the bromobenzyl chlorides with the sodium cresolates in toluene solution. The necessary bromobenzyl chlorides were prepared by the peroxide catalyzed sidechain chlorination of the corresponding bromotoluenes using sulfuryl chloride.[7]

The fact that in certain cases the yield of benzylated phenol obtained by the Claisen alkylation method can be increased markedly by the addition of the corresponding benzyl phenyl ether has been shown previously.[3] As is noted in Table III this increase does not always take place. In the case of 2-hydroxy-5-methyl-4′-bromodiphenylmethane the addition of the ether has little effect; while in the reaction of sodium *o*-cresolate and *o*-bromobenzyl chloride the addition of the corresponding ether causes a decrease in the yield of 2-hydroxy-3-methyl-2′-bromodiphenylmethane.

The structures of the three groups of compounds were proved by reductive dehalogenation[8]: The 2′-, 3′- and 4′-monobromo derivatives of 2-hydroxy-3-methyldiphenylmethane, the 2′-, 3′- and 4′-monobromo derivatives of 4-hydroxy-3-methyldiphenylmethane and the 2′-, 3′- and 4′-monobromo derivatives of 2-hydroxy-5-methyldiphenylmethane were reduced to 2-hydroxy-3-methyldiphenylmethane,[9,10] 4-hydroxy-3-methyldiphenylmethane[9] and 2-hydroxy-5-methyldiphenylmethane,[11] respectively. The three compounds without halogen were prepared by the condensations of benzyl chloride and the respective cresol. Mixed melting points of these products and the corresponding compounds obtained by reductive dehalogenation showed no depression.

The ethers which were obtained as by-products in the condensations of the three bromobenzyl chlorides with sodium *o*-cresolate were rearranged by the method of Short and Stewart[12] to give diphenylmethane derivatives which were shown to be identical with those obtained by the aluminum chloride catalyzed condensation of *o*-cresol and the three bromobenzyl chlorides.

Experimental[13]

In the aluminum chloride catalyzed condensations 163 g. (1.5 moles) of the *o*- or *p*-cresol and 103 g. (0.5 mole) of the bromobenzyl chloride was dissolved in 400 ml. of petroleum ether (c. p.–b. p. range 30 to 75°). Anhydrous aluminum chloride (33.4 g., 0.25 mole) was added to this solution with stirring, over a two-hour period. The reaction was kept at 25–35° and the stirring was continued for 48 to 72 hr. The resulting reaction mixture was hydrolyzed in 500 g. of ice and 300 ml. of concentrated hydrochloric acid. The products were then extracted with ethyl ether. After removal of the solvent the remaining oil was treated with 250 ml. of Claisen alkali,[14] and the substituted phenyl benzyl ether was extracted with petroleum ether. In the condensations of *o*-cresol and the benzyl chlorides only traces of these ethers were isolated. However, in the condensation of *p*-cresol and *p*-bromobenzyl chloride a 24% yield of the 4-methylphenyl-4-bromobenzyl ether was obtained.

The basic aqueous fraction was acidified with hydrochloric acid and the phenolic products extracted in ethyl ether. After removal of the solvent the resultant oil was distilled at reduced pressure. The fractions containing the desired product were redistilled and recrystallized from *n*-hexane until the product reached a constant melting point. As a final step in the purification the white crystalline compounds were redistilled and again crystallized from hexane.

In the condensation using *p*-bromobenzyl alcohol,[15] 62.4 g. (0.33 mole) of this alcohol and 40 g. (0.37 mole) of *o*-cresol were dissolved in 200 ml. of petroleum ether; and 33.4 g. (0.25 mole) of aluminum chloride was added as before. The results of these aluminum chloride catalyzed reactions are given in Table II.

In the Claisen C-Alkylation of phenols 11.5 g. (0.5 mole) of sodium was refluxed in 100 ml. of toluene until it had formed small pellets. At this time 54.7 g. (0.5 mole) of the cresol, dissolved in 100 ml. of toluene, was added with

(1) From a thesis submitted by Hans H. Gyorgy to the Graduate School of Michigan State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Belle Works, E. I. du Pont de Nemours & Co., Inc., Charleston 24, West Virginia.

(3) Huston, *et al.*, THIS JOURNAL, **55**, 2146, 4639 (1933).

(4) R. G. Jones, personal communication.

(5) Huston, THIS JOURNAL, **46**, 2775 (1924).

(6) Claisen, *et al.*, *Ann.*, **442**, 210 (1925).

(7) Kharasch and Brown, THIS JOURNAL, **61**, 2142 (1939).

(8) Papa, Schwenk and Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(9) Huston, Swartout and Wardwell, THIS JOURNAL, **52**, 4484 (1930).

(10) Schorigin, *Ber.*, **58B**, 2033 (1925).

(11) Huston and Lewis, THIS JOURNAL, **53**, 2379 (1931).

(12) Short and Stewart, *J. Chem. Soc.*, 555 (1929).

(13) All boiling points and melting points are uncorrected.

(14) Claisen, *Ann.*, **418**, 96 (1919).

(15) Gilman and Blatt, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 185.

TABLE I

ALUMINUM CHLORIDE CATALYZED BENZYLATIONS

Reactants	Products	Yield, %	B. p., °C.	Mm.	M. p., °C.	Bromine, % Calcd.	Found[a]
o-Cresol, *o*-bromobenzyl chloride[b]	4-Hydroxy-3-methyl-2′-bromodiphenylmethane	21.0	173–176	2	65.4–65.8	28.83	28.94
o-Cresol, *m*-bromobenzyl chloride[b]	4-Hydroxy-3-methyl-3′-bromodiphenylmethane	5.4	172–175	3	46.4–46.8	28.83	28.85
o-Cresol, *p*-bromobenzyl chloride[b,c]	4-Hydroxy-3-methyl-4′-bromodiphenylmethane	30.4	183–185	2	75.4–76.0	28.83	28.60
o-Cresol, benzyl chloride	4-Hydroxy-3-methyldiphenylmethane	..	155–158	3	49.6–50.2		
p-Cresol, *p*-bromobenzyl chloride	2-Hydroxy-5-methyl-4′-bromodiphenylmethane[d]	4.5	165–170	2	60.0–61.0		
	4-Methylphenyl-4-bromobenzyl ether	24.0	.....	..	101.0–101.5		

[a] The bromine analyses were made by the sodium peroxide fusion method.[16] [b] *o*-Bromo, *m*-bromo- and *p*-bromobenzyl chlorides were prepared by side-chain chlorination of the corresponding bromotoluenes at initiation temperatures of 93–95, 95–97, and 93° and yields of 63, 57 and 78%, respectively. Their physical constants agreed with those recorded in the literature. [c] When *p*-bromobenzyl alcohol was used in place of the chloride, the yield of 4-hydroxy-3-methyl-4′-bromodiphenylmethane was 26%. [d] This product is prepared more easily by the Claisen method.

TABLE II

CLAISEN C-BENZYLATION OF PHENOLS

Reactants	Products	Yield, %	B. p., °C.	Mm.	M. p., °C.	Bromine, % Calcd.	Found
o-Cresol, *o*-bromobenzyl chloride	2-Hydroxy-3-methyl-2′-bromodiphenylmethane	13.0	157–160	2	41.4–42.0	28.83	28.85
	2-Methylphenyl-2-bromobenzyl ether	18.0	136–140	2	46.6	28.83	28.90
o-Cresol, *m*-bromobenzyl chloride	2-Hydroxy-3-methyl-3′-bromodiphenylmethane	12.0	162–167	2	48.8–49.4	28.83	28.86
	2-Methylphenyl-3-bromobenzyl ether	18.0	157–162	3	Liquid	28.83	28.80
o-Cresol, *p*-bromobenzyl chloride	2-Hydroxy-3-methyl-4′-bromodiphenylmethane	8.7	162–164	3	50.6–51.0	28.83	28.89
	2-Methylphenyl-4-bromobenzyl ether	18.0	152–155	2	70.8–71.2	28.83	28.62
o-Cresol, benzyl chloride	2-Hydroxy-3-methyldiphenylmethane[9]	..	148–152	2	50.2–50.6		
	2-Methylphenylbenzyl ether[9]	..	118–124	3	Liquid		
p-Cresol, *o*-bromobenzyl chloride	2-Hydroxy-5-methyl-2′-bromodiphenylmethane	20.0	158–161	2	47.5–48.1	28.83	28.79
	4-Methylphenyl-2-bromobenzyl ether	14.0	142–146	2	25.0–26.0	28.83	29.04
p-Cresol, *m*-bromobenzyl chloride	2-Hydroxy-5-methyl-3′-bromidiphenylmethane	16.0	174–176	2	58.8–59.2	28.83	28.82
	4-Methylphenyl-3-bromobenzyl ether	10.6	157–161	2	53.0–53.6	28.83	28.87
p-Cresol, *p*-bromobenzyl chloride	2-Hydroxy-5-methyl-4′-bromodiphenylmethane	41.9	172–175	2	61.6–62.2	28.83	28.82
	4-Methylphenyl-4-bromobenzyl ether	10.0	161–165	2	101.5–102.0	28.83	28.79
p-Cresol, benzyl chloride	2-Hydroxy-5-methyldiphenylmethane[11]	..	144–147	3	36.2–36.8		
	4-Methylphenylbenzyl ether[11]	..	.....	..	40.0–41.2		

TABLE III

DERIVATIVES

Compound, bromo-diphenylmethane	Benzoate M. p., °C.	Benzoate Bromine, % Calcd.	Benzoate Bromine, % Found	*p*-Toluenesulfonate M. p., °C.	*p*-Toluenesulfonate Bromine, % Calcd.	*p*-Toluenesulfonate Bromine, % Found
4-Hydroxy-3-methyl-2′-	50.0–51.0	20.96	20.97	82.4–83.0	18.53	18.56
4-Hydroxy-3-methyl-3′-	74.4–75.4	20.96	20.91	[a]	...	...
4-Hydroxy-3-methyl-4′-	74.2–74.8	20.96	20.84	58.8–59.2	18.53	18.49
2-Hydroxy-3-methyl-2′-	87.3–88.2	20.96	20.98	60.2–60.6	18.53	18.62
2-Hydroxy-3-methyl-3′-	50.0–50.6	20.96	21.10	39.4–40.6	18.53	18.64
2-Hydroxy-3-methyl-4′-	50.5–51.2	20.96	20.89	63.5–64.5	18.53	18.62
2-Hydroxy-5-methyl-2′-	66.8–67.6	20.96	21.07	74.0–74.8	18.53	18.50
2-Hydroxy-5-methyl-3′-	75.5–75.9	20.96	20.80	[a]	...	...
2-Hydroxy-5-methyl-4′-	63.5–64.0	20.96	20.94	69.5–71.0	18.53	18.63

[a] These *p*-toluenesulfonates could not be crystallized.

caution. After 1.5 hr. of reflux 103 g. (0.5 mole) of the bromobenzyl chloride, dissolved in 100 ml. of toluene, was added over a one-hour period. The reaction was refluxed and stirred vigorously for 48–72 hr. The mixture was then acidified with 6 *N* hydrochloric acid and the toluene layer separated. After complete removal of the toluene by distillation the resulting oil was treated with Claisen alkali and the ether and phenolic products separated. The latter were purified as in the case of the condensation products of the aluminum chloride catalyzed reactions.

The substituted phenyl benzyl ethers extracted from the Claisen alkali were purified in the same fashion as the C-bromobenzylated products. However, 95% ethanol, rather than *n*-hexane was used as crystallization solvent.

The results of these Claisen method benzylations are given in Table II.

The rearrangement of the bromobenzyl ethers of *o*-cresol was accomplished by the use of zinc chloride and anhydrous hydrogen chloride.[12] In a typical reaction 50 g. of 2-methylphenyl-2-bromobenzyl ether (m. p. 46.6–47.2°), was combined with 2.5 g. of $ZnCl_2$ and heated to 100°. This temperature was maintained while anhydrous hydrogen chloride was bubbled through the reaction mixture. Two hours was sufficient time for the completion of the reaction. The hot mixture was then poured into 200 ml. of water, and the product extracted with ethyl ether. After removal of the solvent, treatment with Claisen alkali showed no trace of the original oxygen alkylated compound. The phenolic fraction, obtained from the acidified Claisen alkali, was distilled. A small amount of *o*-cresol was isolated and identified by its aryloxyacetic acid derivative. The 4-hydroxy-2-methyl-2′-bromodiphenylmethane was purified as in the previous cases and was shown to be identical to the compound obtained by the aluminum chloride catalyzed condensation of *o*-cresol and *o*-bromobenzyl chloride (m. p. 65.4–65.8°). A mixed melting point showed no depression. The same procedure was used in the cases of 2-methylphenyl-3-

(16) Lemp and Brodersen, this journal, **39**, 2060 (1917).

bromobenzyl ether and 2-methylphenyl-4-bromobenzyl ether to give 4-hydroxy-3-methyl-3′-bromodiphenylmethane (m. p. 46.4–46.8°) and 4-hydroxy-3-methyl-4′-bromodiphenylmethane (m. p. 75.4–76.0°), respectively. These, too, were shown to be identical to the products of the respective aluminum chloride catalyzed condensations.

Summary

Nine diphenylmethane derivatives were prepared from ortho and para cresols and the three monobromobenzyl chlorides.

The structures of these compounds have been proved by reductive dehalogenation.

The six methylphenylbromobenzyl ethers obtainable from ortho and para cresols were isolated.

The monobromobenzyl-2-methylphenyl ethers obtained from *o*-cresol were rearranged in the presence of zinc chloride and hydrogen chloride to give diphenylmethane derivatives in which the hydroxyl group is in the 4-position.

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The Reaction of Tribenzoyl-β-D-arabinopyranosyl Bromide and Tribenzoyl-α-D-xylopyranosyl Bromide with Methanol

BY HEWITT G. FLETCHER, JR., AND C. S. HUDSON

It has recently been shown that tribenzoyl-β-D-ribopyranosyl bromide[1] reacts with anhydrous methanol to give methyl β-D-ribopyranoside tribenzoate in 88% yield. Similarly tetrabenzoyl-α-D-glucopyranosyl bromide was found to give methyl β-D-glucopyranoside tetrabenzoate (90% yield)[2] while tetrabenzoyl-α-D-mannopyranosyl bromide gave methyl α-D-mannopyranoside tetrabenzoate (69% yield).[2] Attention was drawn to the fact that these reactions involved a net reversal of the configuration of carbon 1 in the D-glucose series and retention of configuration at carbon 1 in the D-ribose and D-mannose series. An extension of this investigation to the D-arabinose and D-xylose series will now be described.

Tribenzoyl-β-D-arabinopyranosyl bromide (I) which may readily be prepared from either of the anomeric D-arabinopyranose tetrabenzoates[3] reacts rapidly with anhydrous methanol even at room temperature, methyl α-D-arabinopyranoside tribenzoate (II) being isolated in 72% yield and identified through comparison with the tribenzoate of authentic methyl α-D-arabinopyranoside.[4] In order to ascertain the nature of this reaction and whether its course is as simple as would appear from these facts, a brief polarimetric study was carried out. Since the solubility of both the bromide and the glycoside in methanol at 20° is slight, the rate of the reaction was measured after diluting with methanol a solution of the bromide in pure dioxane. The changing rotation of the resulting reaction mixture is given in Table I together with the rate values derived therefrom; these latter indicate the approximately pseudo-unimolecular nature of the reaction. The initial rotation corresponds closely to that which may be calculated from the rotation of the bromide in chloroform, while the final rotation attained in one hundred and twenty minutes agrees with that derived from the specific rotation of methyl α-D-arabinopyranoside tribenzoate (II) in the same mixture of dioxane and methanol.

Tribenzoyl-α-D-xylopyranosyl bromide (III) was likewise found to react readily with methanol, the product in this case being methyl β-D-xylopyranoside tribenzoate (IV), isolated in 83%

(1) R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 4055 (1948).

(2) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 2200 (1950).

(3) Tribenzoyl-β-D-arabinopyranosyl bromide has been reported by M. L. Wolfrom and C. C. Christman [THIS JOURNAL, **58**, 39 (1936)] and by the present authors [*ibid.*, **69**, 1145 (1947)] as a substance crystallizing from methanol in the form of needles melting at 146° and showing, for the D-isomer, $[\alpha]^{20}D$ −202° (*c*, 1.27) in chloroform. While simple aliphatic alcohols have frequently been employed for the crystallization of acylohalogen sugars [E. Fischer, M. Bergmann and A. Rabe, *Ber.*, **53**, 2362 (1920); E. Fischer, *ibid.*, **49**, 584 (1916); K. Freudenberg, A. Noë and E. Knopf, *ibid.*, **60**, 238 (1927); L. Gattermann and H. Wieland, "Laboratory Methods of Organic Chemistry," Macmillan Co., New York, N. Y., 1937, p. 391] it appeared wise, in view of recent work in this laboratory, to avoid hydroxylic solvents entirely in the repreparation of tribenzoyl-β-D-arabinopyranosyl bromide. The product obtained from a mixture of ether and pentane consisted of prismatic crystals which melted at 147–148°, showed in chloroform $[\alpha]^{20}D$ −353.3° (*c*, 1.4), and gave analytical data for carbon, hydrogen and bromine conforming with that expected for tribenzoyl-β-D-arabinopyranosyl bromide. On recrystallization from warm methanol the product was converted to needle-shaped crystals, free of halogen and showing $[\alpha]^{20}D$ −202° in chloroform; that these are in reality methyl α-D-arabinopyranoside tribenzoate is evident from the present research and we wish to join with Drs. Wolfrom and Christman in pointing out that the physical constants of tribenzoyl-β-D-arabinopyranosyl bromide recorded previously by us are in fact those of methyl α-D-arabinopyranoside tribenzoate. While tribenzoyl-β-D-arabinopyranosyl bromide is here described for the first time it should be noted that the isolation in the earlier researches of methyl α-D-arabinopyranoside tribenzoate where tribenzoyl-β-D-arabinopyranosyl bromide was expected does not in any way invalidate the conclusions resulting from those studies.

(4) The preparation of methyl α-D-arabinopyranoside through the reaction of D-arabinose with acidic methanol has been well investigated [C. S. Hudson, THIS JOURNAL, **47**, 267 (1925); F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," U. S. Govt. Printing Office, Washington, D. C., 1942, p. 520]. However, the separation of this compound from its less soluble anomer which is formed at the same time and in higher yield is laborious. We therefore report here a more satisfactory method of preparation which, starting with the readily preparable triacetyl-β-D-arabinopyranosyl bromide, gives methyl α-D-arabinopyranoside in 77% yield.