[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

Preparation of the 2′-, 3′- and 4′-Chloro- and Bromo-2,4-dihydroxydiphenylmethanes[1]

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Received June 8, 1959

The preparation of the 2′-, 3′- and 4′-chloro- and bromo-2,4-dihydroxydiphenylmethanes has been carried out. Certain derivatives have also been prepared.

It is well-known that resorcinol and several of its alkyl derivatives, especially hexylresorcinol, show a remarkable improvement in germicidal action over the corresponding phenols. Klarmann[2] has shown that by the introduction of the benzyl group into the resorcinol nucleus a compound of high germicidal activity coupled with low toxicity could be obtained. Germicidal potency is also known to be increased in phenols and their alkyl derivatives by the introduction of a halogen into the nucleus. Florestano[3] has reported the testing against tubercle bacilli of a number of diphenylmethane derivatives, more than half of which contained halogen.

As part of a program in these laboratories in the synthesis of halogenated phenols and their evaluation as possible antitubercular agents, the synthesis of the 2′-, 3′- and 4′-chloro- and 2′-, 3′- and 4′-bromo-2,4-dihydroxydiphenylmethanes was undertaken. Of these compounds, two have been reported previously. Klarmann and von Wowern[4] synthesized both the 4′-chloro and 4′-bromo isomers from resorcinol and the corresponding benzonitriles by the Hoesch synthesis, the benzophenones thus obtained being converted to the diphenylmethanes by a Clemmensen reduction. These workers also prepared the 4′-chloroisomer by the Friedel-Crafts alkylation of resorcinol with *p*-chlorobenzyl chloride. The Friedel-Crafts method seemed most suitable for our work. Consequently, the compounds prepared in the course of this work were made by the latter method, using essentially the procedure of Klarmann and von Wowern. These compounds are assigned the accompanying formula since substitution in resorcinol is in the 4 position; that is, ortho to one hydroxyl group and para to the other.

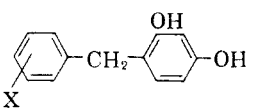

Table I shows the chloro- and bromo-dihydroxydiphenylmethanes and their derivatives prepared in the course of this work, together with pertinent physical properties and analytical data relating thereto. The 2′-, 3′- and 4′-chloro isomers were prepared satisfactorily by alkylating resorcinol with the *o*-, *m*-, and *p*-chlorobenzyl chlorides in nitrobenzene solvent. The 2′-, 3′- and 4′-bromo isomers were likewise made from the *o*-, *m*-, and *p*-bromobenzyl chlorides prepared earlier in this laboratory.[5] However, an irregularity in the melting point of the 3′-bromo isomer and our inability to raise the melting point of our 4′-bromo isomer from 92.5–93.5° to the 96° reported by Klarmann and von Wowern[4] led us to question the purity of the preparations from the bromobenzyl chlorides. As the bromobenzyl chlorides prepared by the peroxide catalyzed chlorination of the bromotoluenes with sulfuryl chloride[5] might possibly have contained traces of chlorobenzyl chlorides, the condensations with resorcinol were repeated using the bromobenzyl bromides instead of the bromobenzyl chlorides. The 2′-bromo isomer obtained from the *o*-bromobenzyl bromide possessed a slightly higher melting point (113.5–114.2° compared to 109.5–111°) than the preparation from *o*-bromobenzyl chloride; however, the melting points of the 3′- and 4′-bromo-2,4-dihydroxydiphenylmethanes prepared from either the bromobenzyl chlorides or the bromobenzyl bromides were the same.

Further attempts to purify the 3′-bromo isomer, m.p. 59–66°, involved the preparation and hydrolysis of the dibenzoate. The latter, melting sharply at 95.5–96° and possessing the correct analysis, yielded on hydrolysis the 3′-bromo isomer which again melted at 59–66°. After storing over mineral oil *in vacuo* for several days, some of the crystals were observed to melt on a block at 60–64°, whereas the remainder melted at 75–77°. After melting at 125° and cooling until crystallization, their melting point was again 59–60.5° and 77–79°. This behavior is apparently due to polymorphism. Another example of apparent polymorphism was observed with the 4′-chloro isomer. When the melting point was determined on a melting point block, some crystals were observed to melt at 76–78°, others at

(1) The material concerning the bromo-2,4-dihydroxydiphenylmethanes was abstracted from the M.S. Thesis of Richard C. Nametz, 1950. (a) Present address, Michigan Chemical Corporation, St. Louis, Michigan.

(2) E. Klarmann, *J. Am. Chem. Soc.*, **48**, 791 (1926).

(3) H. J. Florestano, *J. Pharmacol. Exp. Therap.*, **96**, 238 (1949).

(4) E. Klarmann and J. von Wowern, *J. Am. Chem. Soc.*, **51**, 605 (1929).

(5) G. L. Goerner and R. C. Nametz, *J. Am. Chem. Soc.*, **73**, 2940 (1951).

TABLE I

BROMO- AND CHLORO-2,4-DIHYDROXYDIPHENYLMETHANES

Isomer	Yield, %	B.P., °C. (mm.)	M.P., °C.	Br, %[a]	Dibenzoate M.P.	Dibenzoate Br, %[b]	Di-*p*-bromobenzoate M.P.	Di-*p*-bromobenzoate Br, %[c]
2′-Br	37[d]	202–215 (2)	109.5–111[e]	28.69	87.5–88.5	16.60	115.5–116.6	37.11
	30.5[d]	195–228 (2)						
	27.5[f]	211–212 (3)	113.5–114.2[g]					
3′-Br	36[d]	205–215 (2)	59–66.5[e,h]	28.47	95.5–96	16.69	153.5–154.5[i]	37.15
	21.5[d]	190–229 (2)						
	6[f]	190–210 (1)	59–64[h]					
4′-Br	38.5[d]	200–219 (2)	92.5–93.5[j,k]	28.48	101–102	16.37	154–155[i]	37.03
	40[d]	200–227 (5)						
	34[f]	200–218 (3)	92.5–94[e]					
2′-Cl	27.5[l]	190–200 (~1)	100–101[m]	15.62[n,o]	71–71.5[p]	8.37[n,q]	117–118[r]	20.93[n,s]
3′-Cl	20.5[t]	212–247 (3)	73–74[u]	14.59[n,o]	97.5–98[p]	8.06[n,q]	150–151[p]	20.79[n,s]
4′-Cl	27.[t]	200–205 (~1)	76–78 and 83–84[g]	[v]	114–115[p]	8.00[n,q]	139[p]	21.45[n,s]
	61[t]	193–210 (~1)						

[a] Calcd. for $C_{13}H_{11}BrO_2$: Br, 28.62. [b] Calcd. for $C_{27}H_{19}BrO_4$: Br, 16.40. [c] Calcd. for $C_{27}H_{17}Br_3O_4$: Br, 37.16. [d] Yield of crude product obtained by distillation. Based on bromobenzyl chloride. [e] Recrystallized from toluene. [f] Yield of crude product based on bromobenzyl bromide. [g] Recrystallized from water. [h] See Discussion and Experimental. Polymorphic crystalline forms melt at 59–60.5° and 77–79°. [i] Mixed melting point for the di-*p*-bromobenzoates of 3′-Br and 4′-Br isomers was 135–145°. [j] Recrystallized from 1:1 ligroin-xylene. [k] Klarmann and von Wowern (ref. 4) reported m.p. 96°. [l] Yield purified product based on chlorobenzyl chloride. [m] Extracted with Skelly Solve and recrystallized from xylene. [n] Chlorine analyses by Micro-Tech Laboratories, Skokie, Ill. [o] Calcd. for $C_{13}H_{11}ClO_2$: Cl, 15.12. [p] Recrystallized from ethanol. [q] Calcd. for $C_{27}H_{19}ClO_4$: Cl, 8.01. [r] Recrystallized first from ethanol then methanol. [s] Calcd. for $C_{27}H_{17}Cl_3O_4$: Cl, 20.80. [t] Yield of crude product based on chlorobenzyl chloride. [u] Recrystallized from water after prior extraction with ligroin. [v] Klarmann and von Wowern (ref. 4) reported m.p. 80.4°.

83–84°. When the oil from the low melting form was scratched while still on the block above its melting point, or when it was seeded with the higher melting form, it resolidified and again melted at 83–84°. Previously melted material remelted at 83–84°.

The chloro- and bromo-2,4-dihydroxydiphenylmethanes are solids which distil, usually with superheating, at 200 to 220° at 2 mm. as light yellow, viscous oils which crystallize slowly on prolonged standing or on scratching or stirring. Their solubility in oxygenated solvents, especially alcohols and esters, is so great that recovery is virtually impossible. They are insoluble in the common aliphatic hydrocarbon solvents, but can be recrystallized with difficulty from toluene, xylene-ligroin, carbon tetrachloride and large volumes of water. Although the pure solids are relatively stable, their solutions oxidize easily and the removal of traces of color is very difficult.

Attempts were made to prepare five different types of derivatives from the bromo isomers. Of these only the dibenzoates and di-*p*-bromobenzoates were satisfactory. The diacetates were apparently oils, the *p*-tosylates failed to form, and the diaryloxyacetic acids were obtained in insufficient quantities for purification and subsequent analysis. The chloro isomers formed both the dibenzoates and the di-*p*-chlorobenzoates. However, the latter could not be made entirely satisfactorily using *p*-chlorobenzoyl chloride and pyridine in the customary manner. Under these conditions the predominant product was *p*-chlorobenzoic acid anhydride. A preparation for the latter from the acid chloride and pyridine is described in *Organic Syntheses*.[6] Heating *p*-chlorobenzoyl chloride directly with the chloro isomers above 130° easily produced in excellent yield the *p*-chlorobenzoates, uncontaminated with the acid anhydride.

All of the chloro and bromo isomers were submitted for testing for antitubercular activity.[7] All were very toxic but were without activity against tuberculosis. All except the 2′-bromo isomer were submitted to the Cancer Chemotherapy Section of the National Institutes of Health for testing in the cancer screening program. None possessed activity when tested against the S-180, Ca-755 and L-1210 tumor systems.

EXPERIMENTAL

Materials used. The *bromobenzyl chlorides* and *bromobenzyl bromides* were prepared from the bromotoluenes as described previously,[5] the former by the peroxide-catalyzed chlorination with sulfuryl chloride[8] and the latter by bromination in bright light. The physical properties of the benzyl halides are listed in a prior communication.[5]

o-Chlorobenzyl chloride was Eastman white label grade. *m-Chlorobenzyl chloride*, prepared by the chlorination of *m*-chlorotoluene with sulfuryl chloride and benzoyl peroxide,[8]

(6) C. F. H. Allen, C. J. Kibler, D. M. McLachlin and C. V. Wilson, *Org. Syntheses*, **26**, 1 (1946).

(7) We wish to express our thanks to Eli Lilly and Company, Indianapolis, Indiana, and to the Michigan Department of Health, Lansing, Michigan, for carrying out these tests.

(8) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2142 (1939).

distilled at 98° (14 mm.), n_D^{20} 1.5563–1.5576, reported b.p. 104° (17 mm.).[9] *p-Chlorobenzyl chloride* was redistilled Eastman practical grade, b.p. 100.5–101° (15 mm.), reported b.p. 94–96° (14 mm.).[10]

p-Bromobenzoyl chloride, obtained in 82% yield from *p*-bromobenzoic acid and phosphorus pentachloride, distilled at 220–225°. *p-Chlorobenzoyl chloride*, obtained by treating the acid with thionyl chloride, distilled at 107–108° (17 mm.).

The *chloro- and bromo-2,4-dihydroxydiphenylmethanes* were all obtained by the same general procedure. Typically, *4'-bromo-2,4-dihydroxydiphenylmethane* was prepared from 70 g. (0.636 mole) resorcinol, 64.7 g. (0.31 mole) *p*-bromobenzyl chloride and 50 g. (0.378 mole) anhydrous aluminum chloride in nitrobenzene solvent (400 g.) by the procedure of Klarmann and von Wowern.[4] Distillation of the resulting heavy red oil from an Allihn flask, the column of which was wrapped with asbestos tape and heated by a nichrome wire winding, gave 33.7 g. (38.4%) of a light colored viscous oil distilling at 200–219° (2 mm.). After standing several days or after repeated stirring the crude product solidified. Recrystallization from 1:1 ligroin-xylene gave colored needles of m.p. 90–92°. A product of slight gray color, m.p. 92.5–93.5°, was obtained after treatment with charcoal and repeated recrystallization from ligroin-xylene.

Derivatives. The *dibenzoates* and the *di-p-bromobenzoates* were made in the customary manner[11] by heating the dihydroxy compound and the appropriate acid chloride in pyridine. Attempts to prepare the *di-p-chlorobenzoates* of the 2'-chloro and 3'-chloro isomers in a similar fashion yielded small amounts of the impure derivative plus large quantities of a difficulty soluble crystalline material, m.p. 194–197°, which was identified as *p*-chlorobenzoic acid anhydride. The desired derivatives could be purified only with considerable difficulty because of their like solubility with the acid anhydride. Larger quantities of an initially purer di-*p*-chlorobenzoate could be made more conveniently by heating the dihydroxy compound with about 2.5 times its weight of *p*-chlorobenzoyl chloride at temperatures approximating 130° for about 4 hr.[12] The solid which resulted on cooling was broken up and dissolved in ether and the acidic materials were extracted with sodium bicarbonate solution. After evaporation of the ether, the residual solid or oil was dissolved in ethanol and permitted to crystallize. Recrystallization was from ethanol.

The *aryloxydiacetic acid* of the 3'-bromo isomer resulted in minute amounts when the 3'-bromo isomer was heated for one hour with chloroacetic acid in the presence of base.[13] The resulting solid, after crystallization from aqueous acetic acid melted at 172.5–174°. This derivative was not further investigated.

The attempted *purification* of the *3'-bromo isomer* consisted of: converting a sample, consisting of flat plates of m.p. 59–66°, into the dibenzoate, which melted at 95.5–96° after recrystallization from ethanol and which possessed the analysis shown in Table I; hydrolysis of 3 g. of the dibenzoate by refluxing it for one hour with 5 g. of potassium hydroxide in 25 ml. of diethylene glycol and 8 ml. of water; and isolating the liberated dihydroxy compound. The latter was accomplished by cooling and acidifying the alkaline diethylene glycol solution. The solid was separated and dissolved in ether and the acidic materials removed by extraction into sodium bicarbonate solution. Evaporation of the ether left a red oil which, after solution in toluene, yielded crystals of the 3'-bromo isomer of m.p. 59–66°, even after repeated recrystallization.

Bromine determination was carried out by the method of Lemp and Broderson.[14]

EAST LANSING, MICH.

(9) G. M. Bennet and B. Jones, *J. Chem. Soc.*, 1818 (1935).

(10) E. H. Huntress, *Organic Chlorine Compounds*, John Wiley and Sons, Inc., New York, 1948, p. 44.

(11) R. L. Shriner, R. C. Fuson and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th Ed., John Wiley and Sons, Inc., New York, 1956, p. 212.

(12) R. C. Huston and K. R. Robinson, *J. Am. Chem. Soc.*, **73**, 2483 (1951).

(13) C. F. Koelsch, *J. Am. Chem. Soc.*, **53**, 304 (1931).

(14) J. F. Lemp and H. J. Broderson, *J. Am. Chem. Soc.*, **39**, 2069 (1917).

[CONTRIBUTION FROM THE CHEMICAL ABSTRACTS SERVICE]

Stereo Numbers: A Short Designation for Stereoisomers[1]

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Received May 26, 1959

A new method of designation for stereoisomers is proposed. Its advantage is conciseness.

The practice of designating a stereoisomer by individual reference to its asymmetric centers, as in, *e.g.*, *trans-anti-trans*-perhydrophenanthrene,[2] leads to cumbersome names for compounds containing several asymmetric centers. As a consequence, methods of nomenclature have been elaborated which achieve shorter names. These shorter names, however, were attained at the expense of uniformity in nomenclature, by taking advantage of peculiarities inherent in each particular field of stereochemistry. This fragmentation was aided by the requirement of correlating compounds to a steric prototype (which has become unnecessary since the advent of methods for determining absolute configurations).

Thus, carbohydrate chemists have developed a system of prefixes,[3] each one of which denotes the configuration at several asymmetric carbon atoms (Table I).

Carbohydrates containing more than 4 asymmetric centers can be named by combining the

(1) Paper presented before the 135th ACS meeting, Boston, Mass., April 1959.

(2) R. P. Linstead, *Chem. & Ind. (London)*, **15**, 510 (1937).

(3) Rules of Carbohydrate Nomenclature, *Chem. and Eng. News*, **31**, 1776 (1953).