Preparations

Rhamnohexonic Lactone.—To 400 g. of ice were added successively aqueous solutions of 100 g. of rhamnose hydrate (200 cc.), 105 g. of barium acetate monohydrate (150 cc.) and 32 g. of sodium cyanide (100 cc.). After keeping in ice for an hour and then in the refrigerator for seventy hours (negative Fehling's test), 122 g. of barium hydroxide octahydrate was added and the mixture boiled for six hours, adding water to maintain about half the original volume. The barium was balanced with sulfuric acid, 15 g. of carbon added, the mixture boiled for thirty minutes and the barium sulfate filtered off and washed with water. The calculated sulfuric acid (141.6 cc. of 4.61 *N*) was added to balance the sodium ions, and the combined solutions from three runs distilled to dryness under reduced pressure. The residue was mixed with 500 cc. of 95% ethanol, the distillation repeated and the organic products extracted from sodium sulfate by hot 95% ethanol followed by methanol. Concentration of the alcohol solution under reduced pressure gave several crops of colorless crystals and a sirup which yielded more crystals with acetone as solvent; air-dried; yield, about 200 g. consisting of α-rhamnohexonic acid, its lactone and ester. The sirup was doubtless a mixture of α- and β-rhamnohexonic acid and their derivatives. To convert the acid and ester into lactone, a solution of the crystals in 2 liters of water was evaporated to dryness on the steam-bath, the operation repeated with less water and the residue heated at 100° for several hours, washed with cold acetone and dried at 95–100° for three hours; yield of lactone, 175 g. (55%).

Ethyl Rhamnohexonate.—Recrystallization of crude lactone from absolute ethanol followed by fractionation from 95% ethanol yielded some ester (about 5% of the lactone).

Anal. Calcd. for $C_9H_{18}O_7$: C, 45.35; H, 7.62; OC_2H_5, 18.91. Found: (micro) C, 45.46; H, 7.46; OC_2H_5, 18.59.

Rhamnohexonic Amide.—A suspension of 5 g. of pure lactone in 100 cc. of absolute ethanol was saturated with dry ammonia. The lactone soon dissolved and after an hour the amide which crystallized (5.2 g.; m. p. 175°) was filtered off; evaporation of the filtrate made the yield quantitative. It is difficultly soluble in hot absolute ethanol or methanol and insoluble in ether.

Anal. Calcd. for $C_7H_{15}O_6N$: C, 40.17; H, 7.23; N, 6.70. Found: (micro) C, 40.48, 40.13; H, 6.86, 7.05; N (Kjeldahl), 6.69, 6.65.

The reaction of dry ammonia with 2 g. of pure ethyl ester in 250 cc. of hot absolute ethanol solution gave the theoretical yield of amide.

We are indebted to Dr. R. T. K. Cornwell for the analyses.

Summary

It is shown that crystalline *l*-α-rhamnohexonic lactone may be prepared in 55% yield by a convenient modification of the Kiliani synthesis, using *l*-rhamnose, sodium cyanide and barium acetate in aqueous solution. Ethyl rhamnohexonate is described and the equilibrium rotations of the acid, ester and lactone are shown to be $[\alpha]^{20}_{D}$ +74° in water. Rhamnohexonic amide, prepared from both the ester and lactone, shows m. p. 177.5–178° (corr.) and $[\alpha]^{20}_{D}$ −19.9° in water which vary widely from the values found by Mikšic, who prepared the compound from the nitrile. The sign of rotation of the amide and phenylhydrazide agrees with the amide and phenylhydrazide rules.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE CHEMICAL AND BACTERIOLOGICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Preparation and Germicidal Properties of Some Derivatives of 4-*n*-Butylresorcinol

BY MAURICE L. MOORE, A. A. DAY AND C. M. SUTER

Although the bactericidal properties of many derivatives of resorcinol have been studied, there is little information available concerning the compounds containing two or more unlike substituents. The present communication deals chiefly with some halogen and mercury derivatives of 4-*n*-butylresorcinol, a compound readily obtainable by a modification[1] of the synthesis originally employed by Johnson and Lane.[2]

Chlorination of *n*-butylresorcinol with sulfuryl chloride gives a compound identical with that obtained by reduction of the ketone resulting from the condensation of 4-chlororesorcinol with *n*-butyric acid, thus establishing its structure as 6-chloro-4-*n*-butylresorcinol. Chlorination of *n*-butyrylresorcinol with sulfuryl chloride followed by reduction of the chloro ketone also gives this same compound.[3]

The structure of the chlororesorcinol obtained from resorcinol and sulfuryl chloride deserves some comment. It was first prepared by Reinhard,[4]

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(1) Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926).

(2) Johnson and Lane, *ibid.*, **43**, 348 (1921).

(3) Chloro-*n*-butylresorcinol has also been described very recently by Read, Reddish and Burlingame, THIS JOURNAL, **56**, 1377 (1934).

(4) Reinhard, *J. prakt. Chem.*, [II] **17**, 322 (1878).

who described it as a colorless solid melting at 89°. This preparation has been repeated more recently[5] and the same properties recorded for the reaction product. Recently Clark[6] claims to have proved the structure of this compound by preparing it from 2,4-diaminochlorobenzene by hydrolysis of the corresponding diazonium compound. Clark could hardly have had 4-chlororesorcinol, however, as the compound he obtained was isolated from the reaction mixture by steam distillation and collected as crystals in the condenser. 4-Chlororesorcinol is very soluble in water and practically non-volatile with steam, and hence could not possibly be obtained in this manner. Repetition of Clark's experiments failed to give a compound melting at 89° such as he describes. Furthermore, the chlororesorcinol obtained by the present authors by the sulfuryl chloride method invariably melted sharply at 105° rather than the 89° previously reported by other investigators. This compound was shown to be 4-chlororesorcinol by analysis and by conversion into 4,6-dichlororesorcinol dimethyl ether whose structure has been established previously.[7] At present we are not able to account for the difference in the melting points of our compound and that obtained by Reinhard.

The bromo-*n*-butylresorcinol was obtained by the bromination of *n*-butylresorcinol in ether solution according to the method of Klarmann.[8] Although resorcinol is converted readily into the 4-resorcylic acid by the action of sodium bicarbonate in aqueous solution,[9] treatment of *n*-butylresorcinol in a similar manner gave a very small yield of an acid with a neutral equivalent corresponding to that of 6-*n*-butyl-4-resorcylic acid.

Mercuration of 4-chloro-6-*n*-butylresorcinol with mercuric acetate according to the procedure of Sandin[10] gave the 2-acetoxymercuri compound, while by the method of Whitmore and Hanson[11] an anhydromercuri compound resulted. This was converted into the 2-acetoxymercuri compound by recrystallizing from glacial acetic acid. Mercuration of 4-chloro-6-*n*-butyrylresorcinol gave exactly analogous results. The dimercurated product from *n*-butylresorcinol also apparently contained one anhydromercuri group. Conversion of the acetoxymercuri compounds into the corresponding chloromercuri derivatives presented some difficulty. Treatment with sodium chloride solution in the usual manner gave very small yields. With hydrochloric acid somewhat better results were obtained but the presence of even a slight excess of the acid resulted in the removal of the mercury group from the ring. Chloromercuri-6-*n*-butyryl-4-chlororesorcinol was noticeably more stable to hydrochloric acid than the corresponding *n*-butyl compound.

The phenol coefficients were determined according to the method of the U. S. Food and Drug Administration[12] at a temperature of 20°. Stock solutions of the compounds tested were made up in 20% alcohol as the solvent and the various lower concentrations obtained by dilution of these solutions with water. The only mercury compound which was soluble enough to be tested was the 2-chloromercuri-4-chloro-6-*n*-butylresorcinol. The results are briefly summarized in Table I. Results for 4,6-dichlororesorcinol and di-*n*-butylresorcinol obtained by other workers are included for purposes of comparison. The solubilities are approximate values.

TABLE I

Compound	Phenol coefficient *B. typhosus*	*Staph. aureus*	Soly. 20% alcohol at 25°—g./100 cc.
Resorcinol	0.34	0.34	
4-Chlororesorcinol	1.20	1.34	
4,6-Dichlororesorcinol[5]	3.14	3.9	
4-*n*-Butylresorcinol	21.0	14.0	0.5
Di-*n*-butylresorcinol[13]	16.0		
4-Chloro-6-*n*-butylresorcinol[14]	47.0	35.0	.2
4-Bromo-6-*n*-butylresorcinol	35.0	53.0	.2
2-Chloromercuri-4-chloro-6-*n*-butylresorcinol	140	75	.025
6-*n*-Butyl-4-resorcylic acid	Not effective		.1

The bromo-*n*-butylresorcinol shows the "quasi-specific" activity noted by Klarmann[15] and co-workers in other bromo compounds in that it is more effective toward *Staph. aureus* than toward *B. typhosus*, whereas for the chloro compound the reverse is true. The introduction of the carboxyl group reduced the activity enough to prevent

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(5) Klarmann, *J. Bact.*, **17**, 440 (1929).

(6) Clark, THIS JOURNAL, **55**, 319 (1933).

(7) Jacobs, Heidelberger and Rolf, *ibid.*, **41**, 458 (1919).

(8) Klarmann, *ibid.*, **51**, 605 (1929).

(9) Nierenstein and Clibbens, "Organic Syntheses," John Wiley and Sons, New York, 1930, Vol. X, p. 94.

(10) Sandin, THIS JOURNAL, **51**, 479 (1929).

(11) Whitmore and Hanson, "Organic Syntheses," John Wiley and Sons, New York, 1925, Vol. IV, p. 13.

(12) U. S. Department of Agriculture, Circular No. 198, 1931.

(13) Klarmann, THIS JOURNAL, **48**, 2358 (1926).

(14) Read, Reddish and Burlingame, *ibid.*, **56**, 1378 (1934), have reported very recently the phenol coefficient for this compound as 45 for both *B. typhosus* and *Staph. aureus*.

(15) Klarmann, Gates, Shternov and Cox, *ibid.*, **55**, 4657 (1933).

measuring the phenol coefficient of the acid when 20% alcohol was the solvent.

Although the 2-chloromercuri-4-chloro-6-*n*-butylresorcinol is unstable to strong acids, neither its alcoholic nor acetic acid solution gave a precipitate with hydrogen sulfide. In pyridine solution,[16] however, precipitation of mercuric sulfide occurred immediately.

Experimental

4-Chlororesorcinol.—This was obtained by the method of Reinhard[4] in 95% yields. The product distilled at 147° (18 mm.) and melted at 105°. Because of the melting point being different than previously reported, it was analyzed.

Anal. Calcd. for $C_6H_5O_2Cl$: Cl, 24.57. Found: Cl, 24.45.

An attempt to prepare this compound by Clark's method[6] was unsuccessful. The distillate from the steam distillation of a solution of 25 g. of 4-chlororesorcinol in 100 cc. of water gave a very faint coloration with ferric chloride, indicating practical non-volatility of the chlororesorcinol with steam.

4,6-Dichlororesorcinol.—Chlorination of the 4-chloro compound with sulfuryl chloride gave a 96% yield of sublimed material, m. p. 112–113°. Reinhard reports 77° for the product obtained from water solution and Mettler[17] gives 101° as the melting point for material which distilled at 254°. Methylation with methyl sulfate in sodium hydroxide solution gave 4,6-dichlororesorcinol dimethyl ether, m. p. 116–117°, which agrees with the properties of this compound reported by others.[18] This compound was also obtained by chlorination of 4-chlororesorcinol dimethyl ether with sulfuryl chloride in ether solution.

4-Chloro-6-*n*-butyrylresorcinol.—To 9 g. (0.05 mole) of *n*-butyrylresorcinol (m. p. 69–71°) dissolved in 100 cc. of dry ether was added dropwise with stirring 7 g. (0.05 mole) of sulfuryl chloride. The ether was removed on the steam-bath and the residue crystallized from a mixture of 1 part benzene and 3 parts carbon tetrachloride. There was obtained 8 g. of material melting at 79–82°, which after three recrystallizations melted at 84–85°.

Anal. Calcd. for $C_{10}H_{11}O_3Cl$: Cl, 16.55. Found: Cl, 16.75.

The same compound was also obtained by adding 125 g. of chlororesorcinol to a solution of 125 g. of zinc chloride in 225 g. of *n*-butyric acid kept at 125–135°, and heating for two hours. The reaction mixture was poured into cold water and the dark colored solid distilled under reduced pressure. From the fraction boiling at 180–195° (22 mm.) was obtained 114 g. or 62% of the theoretical amount of material melting at 80–82°. Recrystallizing gave a product melting at 83–85° which mixed with the compound obtained from chlorination of *n*-butyrylresorcinol melted at the same temperature.

4-Chloro-6-*n*-butylresorcinol.—This was obtained both by chlorination of *n*-butylresorcinol with sulfuryl chloride and by reduction of the corresponding ketone. The latter method gave the better results. From the reduction of 45 g. of 4-chloro-6-*n*-butyrylresorcinol with 125 g. of zinc amalgam and 400 cc. of 1:1 hydrochloric acid was obtained 33 g. or 79% of the theoretical amount of material melting at 67–70°. Recrystallization from dilute alcohol gave a melting point of 70–71°.

Anal. Calcd. for $C_{10}H_{13}O_2Cl$: Cl, 17.71. Found: Cl, 18.02.

2,4-Dichloro-6-*n*-butyrylresorcinol.—A solution of 11 g. (0.05 mole) of 4-chloro-6-*n*-butyrylresorcinol in 75 cc. of anhydrous ether was treated with a slow stream of chlorine gas for an hour. The ether was removed, the residue washed several times with water and recrystallized several times from 50% alcohol. There resulted 4.5 g. or a 36% yield of product melting at 121–124°. Further crystallization from a mixture of petroleum ether and benzene gave a product melting at 124–125°.

Anal. Calcd. for $C_{10}H_{10}O_3Cl_2$: Cl, 28.51. Found: Cl, 28.57.

4-Bromo-6-*n*-butylresorcinol.—To a solution of 10 g. (0.06 mole) of *n*-butylresorcinol in 100 cc. of dry ether was added slowly with stirring 9.6 g. (0.06 mole) of bromine. The ether solution was washed with water several times and dried over anhydrous sodium sulfate. The ether was evaporated and the residue upon recrystallization from a mixture of benzene and carbon tetrachloride (1:3) gave colorless crystals of m. p. 67–68°.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: Br, 32.73. Found: Br, 32.98.

6-*n*-Butyl-4-resorcylic Acid.—Vigorous stirring of 15 g. of 4-*n*-butylresorcinol for ten hours with 250 cc. of a hot solution of sodium bicarbonate through which carbon dioxide was passing gave upon acidifying the aqueous layer 0.8 g. of a colorless crystalline solid. This was recrystallized from dilute alcohol and melted at 172–173° with decomposition and evolution of gas.

Anal. Calcd. for $C_{11}H_{14}O_4$: neutral equiv., 210. Found: neutral equiv., 209.5.

Mercuration of 4-Chloro-6-*n*-butylresorcinol.—Mercuration of 4-chloro-6-*n*-butylresorcinol according to the method of Whitmore and Hanson[11] gave a product insoluble in alcohol which was apparently mostly the anhydro compound. It melted[19] above 225°.

Anal. Calcd. for $C_{10}H_{11}O_2ClHg$: Hg, 50.26. Found: Hg, 49.0.

Recrystallization from acetic acid converted it into the acetoxy compound, m. p. 153–154°. This was also obtained by mercuration of 4-chloro-6-*n*-butylresorcinol in alcohol solution.

Anal. Calcd. for $C_{12}H_{15}O_4ClHg$: Hg, 43.71. Found: Hg, 43.0.

Warming with dilute hydrochloric acid converted the mercury compound into 4-chloro-6-*n*-butylresorcinol. m. p. 69–71°. When dissolved in either 0.01 *N* sodium hydroxide or pyridine and treated with hydrogen sulfide, a precipitate of mercuric sulfide formed immediately.

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(16) Kharasch, THIS JOURNAL, **46**, 1212 (1924).

(17) Mettler, *Ber.*, **45**, 802 (1912).

(18) Honig, *ibid.*, **11**, 1039 (1878); Auwers and Pohl, *Ann.*, **405**, 279 (1914); Jacobs, Heidelberger and Rolf, THIS JOURNAL, **41**, 463 (1919).

(19) The melting points or decomposition points of the mercury compounds are uncorrected. All other temperatures are corrected.

To obtain the chloromercuri compound, 2 g. of 2-acetoxymercuri-4-chloro-6-*n*-butylresorcinol was suspended in 10 cc. of water and 1 cc. of alcohol. The mixture was treated with 0.5 cc. of concd. hydrochloric acid and stirred for thirty minutes. A substance was produced which when crystallized from warm dilute alcohol gave 0.8 g. of a white solid melting at 144–145°. Mixed with the original acetoxymercuri compound it melted at 113–118°.

Anal. Calcd. for $C_{10}H_{12}O_2Cl_2Hg$: Hg, 46.05. Found: Hg, 46.68.

The same compound was obtained in 16% yield by pouring a solution of the acetoxy compound in hot 95% alcohol into a saturated sodium chloride solution.

An acetic acid or alcoholic solution of the chloromercuri compound did not give a precipitate of mercuric sulfide when treated with hydrogen sulfide. An alcoholic solution after standing for four months still gave no precipitate. A slight cloudiness was evident when the hydrogen sulfide was passed into a 0.01 *N* sodium hydroxide solution of the compound while a pyridine solution gave a heavy precipitate.

Mercuration of 4-Chloro-6-*n*-butyrylresorcinol.—Mercuration of 4-chloro-6-*n*-butyrylresorcinol carried out as with the *n*-butyl derivative and also according to the method of Sandin[10] gave a compound which was of the anhydro type. It melted at 227–230° when recrystallized from a mixture of acetic acid and alcohol. It was insoluble in alcohol alone.

Anal. Calcd. for $C_{10}H_9O_3ClHg$: Hg, 48.57. Found: Hg, 47.87.

Warming the above anhydro compound with dilute hydrochloric acid or pouring its solution in glacial acetic acid into a saturated sodium chloride solution gave a small amount of 2-chloromercuri-4-chloro-6-*n*-butyrylresorcinol, which when recrystallized from alcohol melted at 218–220°.

Anal. Calcd. for $C_{10}H_{10}O_3Cl_2Hg$: Hg, 44.62. Found: Hg, 44.3.

Mercuration of *n*-Butylresorcinol.—Mercuration in glacial acetic acid solution[11] gave 4-acetoxymercuri-6-*n*-butylresorcinol, m. p. 164–165°.

Anal. Calcd. for $C_{12}H_{16}O_4Hg_2$: Hg, 47.22. Found: Hg, 46.9.

By treatment with dilute hydrochloric acid the chloromercuri compound resulted. This melted at 105–107°. Only a trace of material was obtained.

Mercuration of *n*-butylresorcinol with an excess of mercuric acetate in alcohol gave a bright yellow compound melting above 230°.

Anal. Calcd. for $C_{12}H_{14}O_4Hg$: Hg, 64.38. Found: Hg, 63.6.

The analysis indicates this to be the anhydromercuri-acetoxymercuri compound.

Mercury Analyses.—The mercury analyses were effected by decomposing the compounds with hydrochloric acid and precipitating the mercury as the sulfide.[20]

Summary

1. Previous evidence for the structure of 4-chlororesorcinol has been questioned and another proof of its structure given.

2. A number of halogen and mercury derivatives of 4-*n*-butylresorcinol has been prepared.

3. The bactericidal properties of these compounds have been investigated.

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[20] Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., New York, 1921, p. 362.

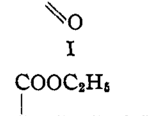
EVANSTON, ILLINOIS RECEIVED JULY 27, 1934

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

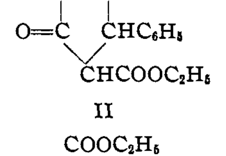
The Acetoacetic Ester Condensation. IX. The Condensation of Ethyl α-Carbethoxy-β-phenyl-γ-isobutyrylbutyrate[1]

BY RICHARD F. B. COX AND S. M. MCELVAIN

In a recent paper[2] it was suggested that the condensation of ethyl α-isobutyryl-α'-carbethoxy-β-phenylglutarate (I) to the cyclohexanedione (II) together with the reported condensation of 1,1-dimethyl-2,3-dicarbethoxy-3-diethylmalonatecyclopropane (III) to the cyclobutane derivative[3] (IV) led to the conclusion that an acetoacetic ester condensation would take place between a carbethoxy group and a carbon carrying a single hydrogen atom only when the condensing carbethoxy group is a part of a monosubstituted malonic ester structure. However, the mechanism for the condensation which was



I



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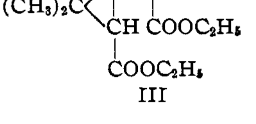

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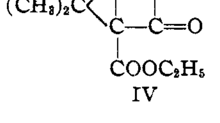

IV

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[1] This work was supported in part by a grant from the Wisconsin Alumni Research Foundation.

[2] Cox, Kroeker and McElvain, THIS JOURNAL, **56**, 1173 (1934).

[3] Perkin and Thorpe, *J. Chem. Soc.*, **79**, 736 (1901); *cf.* also ngold and Thorpe, *ibid.*, **115**, 330 (1919).