of such generally deactivating groups as isopropyl or *t*-butyl for a β-hydrogen atom of ethyl β-bromopropionate, on the reactivity of the halogen of β-bromoesters. It should be noted, however, that while the presence of these alkyl groups does not materially affect the rate at which these esters give up their bromine, such substitution does greatly affect the rate of addition of piperidine to the olefinic ester to form a tertiary amine.

The substitution of a carbethoxy group in the β-position to the halogen of cyclohexyl bromide changes it from an extremely inert halide to one with a quite high reactivity toward piperidine However, the ethyl 2-bromocyclohexanoate is not as reactive as the other β-bromo-esters with an α-hydrogen that have been studied and the resulting olefin, ethyl cyclohexenoate, shows a surprising inability to add piperidine across its double bond.

Summary

The rate and course of the reaction between piperidine and a number of β-bromo-esters with branched chains are reported. It is shown that those β-bromo-esters that have no α-hydrogen atom are extremely inert, while those that have such a hydrogen atom are very reactive regardless of the nature of the branching of the carbon chain. Such branching, however, greatly reduces the ability of the unsaturated ester that is formed from the bromo-ester to add piperidine to form a tertiary amine.

MADISON, WISCONSIN RECEIVED JANUARY 26, 1940

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF NORTH CAROLINA]

Vicinal Substituted Resorcinols. I. Alkyl Resorcinols. The Synthesis of γ-Ethyl, γ-*n*-Propyl and γ-*n*-Butyl Resorcinols

BY ALFRED RUSSELL, JOHN R. FRYE AND WM. L. MAULDIN

The occurrence of γ-isoamylresorcinol as a fission product of natural rotenone, the possible value as antiseptics of γ-alkyl resorcinols and the potential usefulness as initial materials in various types of syntheses of γ-substituted resorcinols make it of considerable interest to exploit possible routes to such compounds.

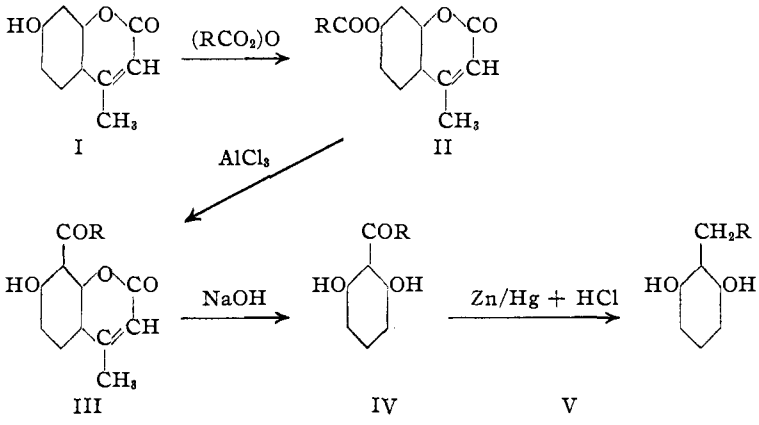
It is comparatively easy to obtain good yields of β-substituted derivatives of resorcinol; thus by treatment of resorcinol by a modification of the Gattermann process[1] it is possible to obtain upward of 90% of the theoretical amount of β-resorcylaldehyde; by carboxylation of resorcinol[2] some 60% of the theoretical amount of β-resorcylic acid may be obtained; again treatment of resorcinol with aliphatic acids and anhydrous zinc chloride gives good yields of alkyl β-resorcyl ketones, a process that involves ester formation followed by a Fries rearrangement; moreover, the ketones so obtained reduce readily by the Clemmensen method to the corresponding β-alkylresorcinols and this process is actually used in the manufacturing of hexylresorcinol.[3] There has also recently been described[4] the synthesis of some *n*-5-(or α)-alkyl resorcinols through the intermediate ketones obtained by the action of appropriate Grignard reagents on 3,5-dimethoxybenzamide.

However, the preparation of vicinal (or γ) substituted resorcinols has been attended with such difficulty that very few such compounds have been made and the yields have been poor. The tedious synthesis of 2,6-dihydroxyacetophenone[5] or vicinal resacetophenone starting with *m*-dinitrobenzene gives a yield amounting at the best to only a few per cent. of the theoretical. The synthesis of γ-resorcylaldehyde which has been described recently gives only a small yield of aldehyde.[6]

The synthesis of 4-methyl-7-hydroxy-8-acetylcoumarin (III, R = CH_3) is on record[7] and from this compound by fission with alkali 2,6-dihydroxyacetophenone[8] is obtained in better than 90% yield. It is obvious that a Clemmensen reduction of 2,6-dihydroxyacetophenone would give γ-ethylresorcinol and such a reduction of 2,6-dihydroxyisovalerophenone recently has been described[9] yielding γ-isoamylresorcinol.

(1) Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).
(2) "Organic Syntheses," Volume X, John Wiley and Sons, Inc., New York, N. Y., 1930, p. 94.
(3) U. S. Patents 1,649,667 and 1,197,168.
(4) Suter and Weston, THIS JOURNAL, **61**, 234 (1939).
(5) Mauthner, *J. prakt. Chem.*, **139**, 290 (1934).
(6) Shah and Laiwalla, *J. Chem. Soc.*, 1828 (1938).
(7) Limaye, *Ber.*, **65**, 375 (1932).
(8) Baker, *J. Chem. Soc.*, 1954 (1934).
(9) Robertson and Subramanian, *ibid.*, 278 (1937).

This general route to γ-alkyl resorcinols appears to be very satisfactory and has now been applied to the preparation of γ-ethyl-, γ-*n*-propyl- and γ-*n*-butylresorcinols. Attempts to prepare the corresponding γ-*n*-hexylresorcinol have not been successful up to the present as the intermediate 4-methyl-7-caproyloxycoumarin did not undergo the Fries rearrangement.



Preliminary tests[10] indicate that saturated aqueous solutions of each of the three alkyl resorcinols described are ineffective against *B. typhosus* and *Staph. aureus*. Further tests are in progress and will be described in a later report.

Experimental Part

4-Methyl-7-hydroxycoumarin.—A mixture of acetoacetic ester (260 g.) and resorcinol (220 g.) was added in portions to 2000 cc. of concentrated sulfuric acid in a round-bottom flask which had been immersed in an ice-bath and mechanically stirred until the temperature of the sulfuric acid was below 5°. Mechanical stirring was continued during the addition of the acetoacetic ester–resorcinol mixture. The temperature was kept below 10° until the end of the addition and it was allowed to stand overnight at room temperature.

The mixture was poured, with stirring, onto ice (6 kg.) in a beaker. The product was filtered, washed twice with water, dissolved in 5% sodium hydroxide (1500 cc.) filtered and reprecipitated by the slow addition of dilute hydrochloric acid with mechanical stirring.

The precipitate was washed thoroughly with water and air-dried overnight. It recrystallizes from 95% ethanol in white needles, m. p. 187°, yield 290 g.

4 - Methyl - 7 - acetoxycoumarin.—4 - Methyl - 7 - hydroxycoumarin (286 g.) was refluxed with twice its weight of acetic anhydride for one and one-half hours. The reaction mixture was poured into cold water with stirring. The 4-methyl-7-acetoxycoumarin was collected, washed thoroughly with cold water to remove all acetic acid and the product air-dried for four days, when it was sufficiently pure for the next step, yield 333 g. Recrystallized from alcohol it formed slender white needles, m. p. 151°.

4-Methyl-7-hydroxy-8-acetylcoumarin.—Dry 4-methyl-7-acetoxycoumarin (200 g.) was thoroughly mixed with powdered anhydrous aluminum chloride (450 g.) in a 5-liter round-bottom flask, this immersed in an oil-bath at 125° and the temperature raised slowly over two and one-half hours to 170°. The reaction mixture was cooled, and 2400 cc. of dilute hydrochloric acid (1 hydrochloric acid to 7 water) added dropwise over a period of about five hours. It was then heated on a steam-bath for one-half hour while being stirred mechanically. The product was filtered, washed, recrystallized from 95% ethanol and dried; yield 197 g. It forms golden yellow leaflets, m. p. 163°.

2,6 - Dihydroxyacetophenone.—4 - Methyl - 7 - hydroxy - 8 - acetylcoumarin (197 g.) was placed in a 5-liter three-neck flask fitted with a dropping funnel, reflux condenser, and tube leading to the bottom of the flask. The solid was covered with water and nitrogen was passed in until the air was displaced. One and one-half times the theoretical quantity of sodium hydroxide solution of such concentration (165 g. of sodium hydroxide in 1350 cc. of water) that the final solution was about 12% sodium hydroxide, was added. The reaction mixture was heated on a steam-bath for five hours and then cooled. The alkaline mixture was neutralized with dilute sulfuric acid, and the precipitated 2,6-dihydroxyacetophenone collected, washed, and dried, yield 127 g. On recrystallization from water it forms stout yellow needles, m. p. 154–56°.

Vicinal Ethylresorcinol.—2,6 - Dihydroxyacetophenone (18 g.) was mixed with amalgamated zinc (45 g.) and hydrochloric acid (90 cc., 12% HCl) added. The whole was refluxed vigorously for five hours, with the addition of concentrated hydrochloric acid (15 cc.) at the end of each hour, cooled and extracted with ether. The ethereal extract was dried, the ether removed and the residue vacuum distilled. The solid distillate recrystallized from gasoline in long, slender, glittering needles, m. p. 94.5°; yield 8.5 g. *Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.5; H, 7.25. Found: C, 69.4; H, 7.22.

4-Methyl-7-propionoxycoumarin and 4-Methyl-7-butyroxycoumarin.—From 220 g. of 4-methyl-7-hydroxycoumarin and 450 cc. of propionic anhydride, by refluxing for two hours, 262 g. of the propionoxy derivative was obtained as white needles from ethanol, m. p. 148.5°. Using the same amount of butyric anhydride and heating at 180° for three hours, 240 g. of the butyroxy derivative resulted as white needles from methanol, m. p. 91°. *Anal.* (propionoxy) Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.18. Found: C, 66.9; H, 5.22. (butyroxy) Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.3; H, 5.63.

4 - Methyl - 7 - hydroxy - 8 - propionylcoumarin and 4 - Methyl - 7 - hydroxy - 8 - butyrylcoumarin.—From 120 g. of the propionoxy compound and 300 g. of aluminum chloride heated to 120° and then over three hours to 170°

(10) Arranged through the courtesy of the Röhm and Haas Company, Inc.

there was obtained 90 g. of the rearrangement product as yellowish leaflets from ethanol, m. p. 187°. In a like manner 13 g. of the butyroxy compound gave 9.6 g. of rearrangement product as yellowish leaflets from ethanol, m. p. 141°. *Anal.* (propionyl) Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.18. Found: C, 67.2; H, 5.34. (butyryl) Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.1; H, 5.8.

2,6-Dihydroxypropiophenone and 2,6-Dihydroxybutyrophenone.—155 grams of the propionyl derivative treated with one liter of 12% aqueous sodium hydroxide for six hours on the steam-bath and in a nitrogen atmosphere gave, after cooling and acidification, 66 g. of 2,6-dihydroxypropiophenone, yellow needles from 25% aqueous methanol, m. p. 133.5°. By analogous treatment 16 g. of the butyryl derivative gave 9.4 g. of 2,6-dihydroxybutyrophenone as yellow needles from 25% aqueous methanol, m. p. 106°. *Anal.* (propiophenone) Calcd. for $C_9H_{10}O_3$: C, 65.1; H, 6.0. Found: C, 64.8; H, 6.0. (butyrophenone) Calcd. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7. Found: C, 66.9; H, 6.8.

Vicinal Propylresorcinol and Vicinal Butylresorcinol.—Clemmensen reduction of 36 g. of 2,6-dihydroxypropiophenone for six hours using 90 g. of amalgamated zinc, hydrochloric acid (180 cc. 12%) and with the addition of 15 cc. of concd. hydrochloric acid each hour gave, after separation, vacuum distillation and recrystallization from gasoline, 23 g. of vicinal propylresorcinol as white lustrous needles, m. p. 92.5°.

Using proportionate quantities, and continuing the reduction for seven hours, 60 g. of 2,6-dihydroxybutyrophenone yielded 44 g. of vicinal butylresorcinol as slender white needles from gasoline, m. p. 83°. *Anal.* (propyl) Calcd. for $C_9H_{12}O_2$: C, 71.1; H, 7.9. Found: C, 70.8; H, 8.0. (butyl) Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.44. Found: C, 72.1; H, 8.5.

4-Methyl-7-caproyloxycoumarin.—4-Methyl-7-hydroxycoumarin (17 g.) was dissolved in dry pyridine (25 cc.) and the solution treated with caproyl chloride (35 g.). The whole was heated at the temperature of the steam-bath for ten minutes, cooled and poured into cold water (500 cc.) with good stirring. The solid was collected, washed, dried and recrystallized from methanol. It forms white prisms, m. p. 72°, yield 15.3 g. *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.0; H, 6.6. Found: C, 70.0; H, 6.9.

Summary

6- or β-substituted resorcinols are obtained easily in good yield whatever the nature of the substituting group. Moreover, methods are available for obtaining good yields of resorcinols substituted in the 5- or α-position. However, although some vicinal substituted resorcinols are known, up until the present no easy method has been exploited whereby substituents could be introduced into the resorcinol nucleus in the inaccessible 2-, γ- or vicinal position. Such a process is now described for obtaining vicinal alkyl resorcyl ketones and the corresponding vicinal alkyl resorcinols.

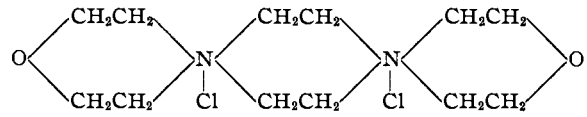
CHAPEL HILL, NORTH CAROLINA
RECEIVED FEBRUARY 14, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BOSTON UNIVERSITY]

Preparation and Polymerization of β-4-Morpholinoethyl Chloride

BY J. PHILIP MASON AND HARRY W. BLOCK[1]

The only morpholinoethyl halide derivative which we have found described in the literature is β-4-morpholinoethyl bromide hydrobromide obtained by Prelog and Blozek[2] by heating triethanolamine hydrobromide with 64% hydrobromic acid in a sealed tube at 160°. Their yield was 25%. We have prepared β-4-morpholinoethyl chloride hydrochloride by treating β-4-morpholineëthanol hydrochloride with thionyl chloride, obtaining a yield of 63.5%, and also by treating β-4-morpholineëthanol with thionyl chloride, obtaining yields varying from 73 to 88%. Treatment of this hydrochloride with alkali yielded a colorless liquid, β-4-morpholinoethyl chloride. After standing for a few days, a solid appeared in the liquid, and the amount of solid increased slowly on standing. It was found that the formation of the solid could be accelerated by refluxing an alcohol solution of β-4-morpholinoethyl chloride. This solid was found to be a dimeric quaternary ammonium salt having the formula



and which can be named N,N′-dispiromorpholinopiperazonium dichloride or N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride. Knorr[3] previously had prepared β-chloroethyldimethylamine and had found that it polymerized on standing or on refluxing in alcohol solution to N,N′-tetra-

(1) Taken from the thesis to be submitted by Harry W. Block to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Prelog and Blozek, *C. A.*, **29**, 4011 (1935).

(3) Knorr, *Ber.*, **38**, 3136 (1905); **39**, 1420 (1906).