Isotopic analysis by mass spectrometry proved to be difficult, as the sample underwent back exchange while in the ion source. Rapid analysis indicated that the product consisted of 94 ± 2% diethyl malonate-d_2, 6 ± 2% diethyl malonate-d_1, and 0 ± 2% diethyl malonate, though the actual per cent of diethyl malonate-d_2 was probably somewhat higher than these figures imply.

Reduction of Diethyl Malonate-d_2 with Lithium Aluminum Deuteride.—Lithium aluminum deuteride (6.6 g., 0.157 mole) was transferred under anhydrous atmospheric conditions to a 500-ml. three-necked flask containing 250 ml. of ethyl ether freshly distilled from lithium aluminum hydride. The flask was sealed and the deuteride slurry was stirred overnight. In a nitrogen atmosphere a solution of 21.6 g. (0.133 mole) of diethyl malonate-d_2 in 30 ml. of ethyl ether (dried as above) was slowly added during a 1.5-hr. period to the lithium aluminum deuteride slurry. After refluxing for 48 hr. in an inert atmosphere, 50 ml. of deuterium oxide was cautiously added to the cooled reaction mixture. The heterogeneous system was refluxed for an additional 2 hr. and then filtered. The residue from the filtration was continuously extracted for 18 hr. with tetrahydrofuran. The organic extracts were combined and the solvents were removed *in vacuo*. The product, isolated by distillation employing a semimicro spinning band column, b.p. 95–96° (4.5 mm.), was obtained in 54% yield (6.48 g.).

Reaction of 1,3-Propane-d_6-diol with Acetyl Bromide.[12]—Acetyl bromide (Eastman White Label) was slowly distilled through a 4-in. Vigreux column. A fraction, boiling at 77° (17.5 g., 0.12 mole), was collected directly in a receiver containing 10.5 g. (0.13 mole) of 1,3-propane-d_6-diol. The temperature of the reaction mixture was maintained at 0° during the introduction of the bromide. Following the distillation, the receiver was disconnected, stoppered, and left overnight at room temperature. The flask was attached to a reflux condenser and warmed for 1 hr. at 100°. The reaction mixture was roughly divided into two fractions (1, 6.9 g., b.p. 30–60° at 19 mm.; and 2, 20.4 g., b.p. 60–74° at 19 mm.) by distillation *in vacuo*. The initial fraction was discarded. The second portion was warmed with 5 ml. of acetyl chloride for 3 hr. on the steam bath. After removal of the excess reagent by evaporation *in vacuo*, the residue was washed and dried. Distillation through a semimicro spinning-band column afforded 16.3 g. of γ-bromopropyl-d_6 acetate as a colorless liquid, b.p. 89–90° (25 mm.), 67% yield.

Reaction of γ-Bromopropyl-d_6 Acetate with Sodium and Potassium Hydroxide.[7]—γ-Bromopropyl-d_6 acetate (30.5 g., 0.16 mole) was added dropwise but rapidly (20 min.) to a well-stirred (liquid) mixture of sodium hydroxide (25 g.), potassium hydroxide (25 g.) and water (2 g.) which was maintained at a temperature of 160–170°. The volatile products were conducted through a 40-cm. Vigreux column into a Dry Ice cold trap containing sodium hydroxide pellets and finally into a liquid nitrogen cold trap. Both traps were sealed and disconnected from the system 5 min. after the last addition of γ-bromopropyl-d_6 acetate to the reaction mixture. Infrared analysis indicated that the liquid nitrogen trap contained nearly pure ethylene-d_4. The Dry Ice cold trap contained all of the oxetane-d_6 produced, together with some dissolved ethylene-d_4. The olefinic by-product was quantitatively separated from the cyclic ether by repeated low-temperature equilibrations. One trap containing the impure oxetane-d_6 was kept at −125 to −135° in a normal pentane bath; the second trap was kept at liquid nitrogen temperatures. The purified ethylene-d_4 obtained from the residues of the Dry Ice trap was subsequently combined with the material which had been originally obtained from the liquid nitrogen cold trap to give 235 mg. (4.6% yield). Final traces of water were removed from the oxetane-d_6 by treatment with fused sodium hydroxide yielding 4.68 g. (46% yield).

Vapor phase chromatography indicated a sample purity of at least 99.9%. With a column of nitromethylpimelonitrile at 27°, a retention time of 14.22 min. was observed for oxetane-d_6, whereas a value of 13.38 min. was recorded for oxetane. The isotopic content of the product was found to be 98.8 atom % D by mass spectrometry.

Acknowledgment.—The authors gratefully acknowledge the support of this research by the National Science Foundation (NSF-G6230), and wish to express their appreciation to Professor Klaus Biemann for the mass spectrometric analyses.

(12) M. T. Bogert and E. M. Slocum, *J. Am. Chem. Soc.*, **46**, 767 (1924).

Use of Cation-Exchange Resins in Organic Reactions. II. C-Acylation of Phenols

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A number of methods are available for the preparation of hydroxy aromatic ketones such as the Friedel–Crafts, the Houben–Hoesch, and the Fries reactions, or modifications of these. In the case of phenols with two hydroxyl groups *meta* to each other it was found[1,2] that, by heating the appropriate dihydric phenol with an acid anhydride in the presence of 1 drop of concentrated sulfuric acid, good yields of the corresponding hydroxy aromatic ketone were obtained. Since it was shown in part I[3] that cation-exchange resins (sulfonic acid type) were effective in bringing about the von Pechmann reaction, it was decided to use such resins as catalysts in the C-acylation of certain phenols and this paper shows that in this way good yields of ketones can be obtained from 1,3-dihydroxybenzenes.

The cation-exchange resin used was Amberlite IR-120 although Zeokarb 225 was found to be as effective. These resins were found to be stable at the temperatures used, *viz.*, for periods of 1 hr. or more at about 160–170°. The method consists essentially in heating together equimolecular quantities of phenol and acid (or acid anhydride) with an appropriate amount of cation exchange resin at 160° for a certain period of time depending on the nature of the phenol and the acid (or anhydride). The results are summarized in Table I. It should be noted that the phenols giving the best yields of ketone are resorcinol and pyrogallol whereas orcinol and hydroquinone gave the poorest yields. The yields obtained with the carboxylic acids were not much different from those using the corresponding acid anhydrides. Phenol, catechol, 3,5-xylenol, β-naphthol, 4-chlororesorcinol, and *m*-methoxyphenol were unreactive as were formic acid and monochloroacetic acid. The aromatic acids and their anhydrides gave lower yields than the aliphatic ones and did not react at all with phloroglucinol, orcinol, and hydroquinone. Although it has been shown[2] that by using an excess of concentrated sulfuric acid and twice the molecular quantity of acid anhydride diketones were formed in good yield, such compounds were not isolated using even large amounts of cation-exchange resin. For comparison a number of hydroxy ketones were prepared by the sulfuric acid method of Israelstam and Stephen[1] including a number of ketones not previously prepared by them (see Experimental). In addition it was shown that, when equimolecular quantities of resorcinol and acetic acid were heated with half the molecular quantity of concentrated sulfuric acid, a 36% yield of resacetophenone was obtained.

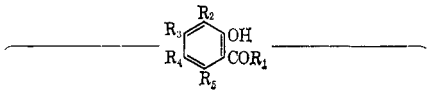
As in the case of the interaction of orcinol and an acid anhydride in the presence of sulfuric acid,[2] the

(1) S. S. Israelstam and H. Stephen, *J. S. African Chem. Inst.*, **26**, 41 (1943).

(2) S. S. Israelstam, *ibid.*, **26**, 49 (1943).

(3) E. V. O. John and S. S. Israelstam, *J. Org. Chem.*, **26**, 240 (1961).

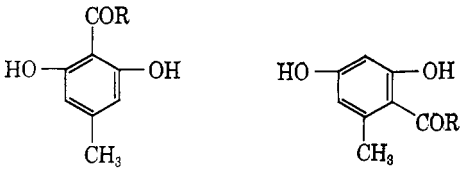
TABLE I



R_1	R_2	R_3	R_4	R_5	Phenol	R_3 [acid, R_3COOH; anhydride, $(R_3CO)_2O$]	% yield: Anhydride	% yield: Acid	% yield: By other methods in lit.	M.p., °C.: Found	M.p., °C.: Lit.
CH_3	H	OH	H	H	Resorcinol	CH_3	83.5	87.0	94[c]	145	146[r]
C_2H_5	H	OH	H	H	Resorcinol	C_2H_5	82.5	76.1	79[c]	102–104	97–99[r]
n-C_3H_7	H	OH	H	H	Resorcinol	n-C_3H_7	82.3	73.4	81[c]	68–70	68[r]
i-C_3H_7	H	OH	H	H	Resorcinol	i-C_3H_7		68.5	79[c]	67–69	67–68.5[d]
C_6H_5	H	OH	H	H	Resorcinol	C_6H_5	30.8	25.7	89[e]	144–146	144[r]
$C_6H_5CH_2$	H	OH	H	H	Resorcinol	$C_6H_5CH_2$		41.0	86[f]	114–116	114–115[r]
CH_3	OH	OH	H	H	Pyrogallol	CH_3	84.0	75.0	90[g]	169–171	169–170[r]
C_2H_5	OH	OH	H	H	Pyrogallol	C_2H_5	78.8	77.7	80[g]	128–130	126–127[r]
n-C_3H_7	OH	OH	H	H	Pyrogallol	n-C_3H_7	80.5	70.8	79[g]	98–99	101–102[h]
C_6H_5	OH	OH	H	H	Pyrogallol	C_6H_5	16.4	13.7	44[g]	141–143	140–141[i]
$C_6H_5CH_2$	OH	OH	H	H	Pyrogallol	$C_6H_5CH_2$		33.8	60[j]	135–136	141–142[k]
CH_3	H	CH_3	H	OH	Orcinol	CH_3	20.4	15.0	49[l]	147–149	145–146[r]
C_2H_5	H	CH_3	H	OH	Orcinol	C_2H_5	19.0	13.8	80[m]	130–132	129[r]
n-C_3H_7	H	CH_3	H	OH	Orcinol	n-C_3H_7	19.2	16.0	40[n]	120–122	120–121[n]
CH_3	H	OH	H	OH	Phloroglucinol	CH_3[a]	39.0	0	93[o]	220–222	213–214[r]
C_2H_5	H	OH	H	OH	Phloroglucinol	C_2H_5[a,b]	41.5	0	73[o]	174–176	170–171[r]
n-C_3H_7	H	OH	H	OH	Phloroglucinol	n-C_3H_7[a,b]	32.2	0	72[o]	185–186	179–180[p]
CH_3	H	H	OH	H	Hydroquinone	CH_3	27.3	21.8	66[c]	202–204	202[q]
C_2H_5	H	H	OH	H	Hydroquinone	C_2H_5	0	0	71[c]		
n-C_3H_7	H	H	OH	H	Hydroquinone	n-C_3H_7	0	0	72[c]		

[a] In the case of the acid, only an unknown compound, m.p. 273–275°, was obtained. [b] In the case of the anhydride, the ketone was obtained only on one occasion; on repetition only the unknown compound, m.p. 273–275°, was obtained [c] H. Oelschlager, *Arch. Pharm.*, **288**, 102 (1955). [d] A. R. L. Dohme, E. C. Cox, and E. Miller, *J. Am. Chem. Soc.*, **48**, 1688 (1926). [e] E. N. Zilberman and N. A. Rybakova, *Zh. Obshch. Khim.*, **30**, 1992 (1960); *Chem. Abstr.*, **55**, 6429c (1961). [f] S. S. Karmarkar, *J. Sci. Ind. Research* (India), **20B**, 334 (1961). [g] T. W. Campbell and G. M. Coppinger, U. S. Patent 2,686,123 (April, 1954); *Chem. Abstr.*, **49**, 4203*h* (1955). [h] T. B. Johnson and F. A. Lane, *J. Am. Chem. Soc.*, **43**, 348 (1921). [i] R. Padke and R. C. Shah, *J. Indian Chem. Soc.*, **27**, 349 (1950). [j] K. S. Bhumgara, R. D. Desai, and W. S. Waravdekar, *Proc. Indian Acad. Sci.*, **25A**, 322 (1947). [k] E. Noelting and V. Kadiera, *Ber.*, **39**, 2056 (1906). [l] R. D. Desai and M. Ekhlas, *Proc. Indian Acad. Sci.*, **8A**, 194 (1938). [m] R. D. Desai and C. K. Mavani, *ibid.*, **25A**, 341 (1947). [n] R. D. Desai and M. M. Gaitonde, *ibid.*, **25A**, 364 (1947). [o] H. P. Howells and J. O. Little, *J. Am. Chem. Soc.*, **54**, 2451 (1932). [p] W. Riedl, *Ann.*, **585**, 38 (1954). [q] M. Nencki and N. Sieber, *J. prakt. Chem.*, [2]**23**, 147 (1881). [r] See ref. 1.

ketone obtained using the cation-exchange resin was the ketone I and not the isomer II which is obtained in the Houben–Hoesch reaction with the corresponding nitrile.



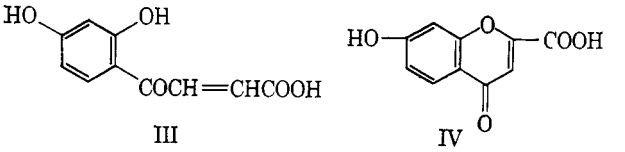
I II

Although phloroacetophenone, phloropropiophenone, and phlorobutyrophenone were obtained from phloroglucinol and the corresponding acid anhydrides in the presence of resin, its reactions with the corresponding carboxylic acids gave the same unknown compound, $C_{17}H_{22}O_{10}$, m.p. 273–275°, whichever acid was used. The same compound was also obtained, however, when phloroglucinol and the resin alone were heated together in diisopropyl ketone as a solvent. It is possible that the phloroglucinol is merely converted to a phloroglucide,[4] the acids only acting as a solvent.

It should be noted that acetyl chloride also readily reacts with resorcinol and other phenols in the presence of cation exchange resin to give fair yields of ketone.

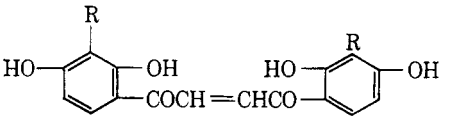
When phenols were heated with either carboxylic acids or acid anhydrides at lower temperatures, *e.g.*, 100°, phenolic esters were isolated. The latter on heating with resin isomerized to the hydroxy ketone by a Fries-type rearrangement. It would seem, therefore, that the initial stage in the C-acylation of phenols is O-acylation followed by rearrangement.

Interesting results were obtained in the reaction between maleic anhydride and certain phenols using cation exchange resin as a condensing agent. Barr, Dean, and Locksley[5] showed that when equimolecular quantities of resorcinol and maleic anhydride were warmed with anhydrous aluminum chloride in ethylene dichloride as solvent at 80° for 1 hr., a mixture was obtained of β-(2,4-dihydroxybenzoyl)acrylic acid (III) and 7-hydroxychromanone-2-carboxylic acid (IV).



III IV

However, using cation-exchange resin with or without solvent, a mixture was obtained of fumaric acid and 1,2-bis(2′,4′-dihydroxybenzoyl)ethylene (Va).



Va, R=H
b, R=OH

(4) C. F. Cross and E. J. Bevan, *J. Chem. Soc.*, **99**, 1456 (1911); E. Schwenk, *J. prakt. Chem.*, [2]**103**, 105 (1921).

(5) K. P. Barr, F. M. Dean, and H. D. Locksley, *J. Chem. Soc.*, 2425 (1959).

With pyrogallol and maleic anhydride 1,2-bis(2′,3′,4′-trihydroxybenzoyl)ethylene (Vb) was obtained. Phenol, hydroquinone, orcinol, and phloroglucinol did not react.

Experimental

All melting points are uncorrected and were determined in an electrically heated copper block.

Preparation of Hydroxy Aromatic Ketones Using Cation-Exchange Resin.—Equimolecular quantities of the phenol and acid anhydride or carboxylic acid were heated together with that weight of resin (preparation given in part I[3], except that drying lasted for 6 hr.) which is about 45% by weight of the phenol in an oil bath at 160° with constant stirring for 2–3 hr. The solution was then allowed to cool and ethanol was added to extract the reaction product. The filtrate was refluxed with a few drops of concentrated hydrochloric acid reduced to a low volume *in vacuo* and was washed with water to remove any unreacted phenol. When aromatic acids or their anhydrides were used the residue obtained, after removal of the alcohol, was treated with sodium bicarbonate. When resorcinol and isobutyric acid were allowed to react as above an oil separated, and this, on vacuum distillation, gave solid resoisobutyrophenone.

Preparation of Hydroxy Aromatic Ketones Using 1 Drop of Concentrated Sulfuric Acid.—Since the method was published in a journal[2] not readily accessible, a brief description is given here. Equimolecular quantities of the phenol and the acid anhydride were refluxed with 1 drop of concentrated sulfuric acid or polyphosphoric acid for about 10–15 min. (in the case of orcinol and butyric anhydride, 30 min.). The reaction product was poured into water, a small quantity of ethanol and a few drops of concentrated hydrochloric acid were added, and the solution was refluxed for 20–30 min. After removal of the water and alcohol by distillation the solid hydroxy ketone separated out.

The following hydroxy ketones were obtained (melting point, yield): gallobutyrophenone (98–100°, 64.5%); α-orcibutyrophenone (120–122°, 16%); phlorobutyrophenone (184–186°, 32%); 5-chlororestacetophenone (176–177°,[6] 12%); and gallobenzophenone (140–142°, 14%).

Resorcinol Diacetate and Its Conversion to Resacetophenone.—Four grams of resorcinol and either 4 g. of acetic anhydride or 6 g. of acetic acid were heated at about 100° for 15 min. with 2 g. of resin when the solution became orange in color. The product was extracted with ethanol and filtered off from the resin. The ethanol and unreacted anhydride or acid were distilled off and a liquid was obtained, b.p. 164° (5 mm.), which proved to be resorcinol diacetate. Five grams of the latter were heated with 3 g. of resin at 160° for 1 hr. when a dark red product was obtained. After extraction with ethanol it was filtered off from the resin and on suitable treatment yielded 2.5 g. (64%) resacetophenone.

Preparation of Resacetophenone Using Acetyl Chloride.—Resorcinol (5.6 g.), 4.5 g. of acetyl chloride, and 2 g. of cation-exchange resin were refluxed for 2 hr. The reaction product after suitable treatment yielded 4.0 g. (52%) of resacetophenone.

Preparation of 1,2-Bis(hydroxybenzoyl)ethylenes.—Four grams of resorcinol and 4 g. of maleic anhydride were dissolved in 50 g. of ethylene dichloride, 5 g. of cation exchange resin was added, and the mixture was refluxed for 2 hr. when a solid separated. The ethylene dichloride was filtered off, ethanol was added to dissolve the solid, and the resin was removed by filtration. After the removal of the ethanol, the residue was shown to consist of a mixture of 0.5 g. of fumaric acid and 2.1 g. (19%) of 1,2-bis(2′,4′-dihydroxybenzoyl)ethylene, m.p. 254–256° (dec.), identical with that obtained by Rao, *et al.*[7] In a similar way, 4 g. of pyrogallol gave 2.0 g. of 1,2-bis(2′,3′,4′- trihydroxybenzoyl)-ethylene, m.p. 236–238°, identical with that obtained by Bogert and Ritter.[8]

Acknowledgment.—S. S. I. wishes to thank the S. A. Council for Scientific and Industrial Research for a research grant and a research assistantship to P. P.

(6) D. Chakravarti and N. Chakravarty, *J. Indian Chem. Soc.*, **16**, 144 (1939).

(7) N. V. C. Rao, T. R. Seshadri, and V. Venkateswarlu, *Proc. Indian Acad. Sci.*, **26A**, 299 (1947).

(8) M. T. Bogert and J. J. Ritter, *J. Am. Chem. Soc.*, **47**, 526 (1925).

Phenolic Metabolite of "Low-Iron Fermentation" of *Streptomyces griseus*. Characterization of 2,3-Dihydroxybenzoic Acid

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In studies[1,2] dealing with the relationship of streptomycin biogenesis to some oxidation–reduction systems operative in *Streptomyces griseus*, strain Z-38, it was observed that, with a substantial elimination of cytochromes due to reduced iron content in the fermentation medium, a distinct inhibition of streptomycin formation resulted and a phenolic metabolite of unknown structure accumulated. The compound was isolated as an amorphous solid and was considered to be a derivative of an intermediate in the biosynthesis of streptomycin since it suppressed, after its addition to an iron(II)-containing medium, the production of streptomycin. This effect could be reversed by the addition of streptidine.

The crude yellow amorphous sodium salt[3] of the phenol was converted to the free phenol, which was purified by treatment with carbon and was crystallized from hot water. The colorless compound was also purified by sublimation, m.p. 204–205° (cor.). Analytical data indicated the empirical formula $C_7H_6O_4$ for the phenol and the similarity of the melting point with that reported for 2,3-dihydroxybenzoic acid (205°) suggested the identity of the phenol. This suggestion was confirmed by the fact that the unknown phenol and 2,3-dihydroxybenzoic acid[4] had superimposable n.m.r.[5,6] and infrared spectra.

The metabolite, 2,3-dihydroxybenzoic acid, has been isolated as its glycine conjugate from low-iron fermen-

(1) V. Musilek and R. Nomi, Abstracts, *Intern. Congr. Microbiol.* (Montreal), 66 (1962).

(2) V. Musilek, *Science*, **137**, 674 (1962).

(3) We thank Dr. V. Musilek, Institute of Microbiology, Czechoslovak Academy of Sciences, Prague, for the sample of this compound.

(4) We thank Dr. J. B. Neilands of the University of California for this sample.

(5) We are grateful to Mr. W. S. Fleming for determining the n.m.r. spectra.

(6) The identity of the unknown phenol was suggested before analytical data were obtained by analysis of its n.m.r. spectrum. First-order[7] analysis of the spectrum of the unknown phenol (2,3-dihydroxybenzoic acid) gave the following absorption positions and coupling constants for the protons present: H-4, τ 3.00; H-5, τ 3.20; H-6, τ 2.74; $J_{4,5}$ = 8.0 c.p.s.[8]; $J_{4,6}$ = 2.6 c.p.s.; $J_{5,6}$ = 7.0 c.p.s. As an aid in the interpretation of the n.m.r spectrum of the unkown phenol, the spectra of several model compounds were analyzed. First-order analysis of the spectrum of 2,4-dihydroxybenzoic acid gave H-3, τ 3.75; H-5, τ 3.66; H-6, τ 2.37; $J_{3,5}$ = 2.3 c.p.s.; $J_{3,6}$ = 0.6 c.p.s.; $J_{5,6}$ = 8.2 c.p.s. First-order analysis of the spectrum of 2,5-dihydroxybenzoic acid gave H-3, τ 3.31; H-4, τ 3.10; H-6, τ 2.77; $J_{3,4}$ = 8.9 c.p.s.; $J_{3,6}$ = 0.8 c.p.s.; $J_{4,6}$ = 2.7 c.p.s. Analysis of these spectra was greatly simplified by the fact that H-6 in all three compounds is strongly deshielded by the carboxylate anion. Hence the absorptions due to these protons occur at lower field than, and are well separated from, the other absorptions present.

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 131.

(8) L. M. Jackman ["Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85] quotes J_{ortho} = 7–10 c.p.s., J_{meta} = 2–3 c.p.s., and J_{para} = 0–1 c.p.s. for the coupling constants of protons of benzene compounds.