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Coumarins. III. A Novel Synthesis of *o*-Hydroxybenzaldehydes[1]

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The catalytic hydrogenation of salicyloyl chloride at a mild temperature gave a high yield of salicylaldehyde. A similar partial reduction of substituted salicyloyl chlorides provided the corresponding salicylaldehydes in appreciable yields. Attempts to prepare other isomeric hydroxybenzoyl chlorides were, however, unsuccessful. The relationship between the structure of salicyloyl chlorides and the ease of their conversion to salicylaldehydes is discussed. Moreover, the formylation of phenol with dichloromethyl methyl ether and the selective ortho-formylation are described.

The potential use of *o*-hydroxybenzaldehydes as key materials not only for coumarin synthesis but

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TABLE 1. ACID-CATALYZED FORMYLATION OF PHENOLS

Starting phenol	Products, benzaldehydes substituents	Yield, % A[a]	Yield, % B[a]	Bp, °C/mmHg or mp, °C
Phenol	2-Hydroxy	15	30	64—65/10
	4-Hydroxy	68	5	114.5—115
o-Cresol	4-Hydroxy-3-methyl	43	38	115—116
p-Cresol	2-Hydroxy-5-methyl	37	30	55.5—56
Guaiacol	4-Hydroxy-3-methoxy	25[b]		82—83
Hydroquinone	2,5-Dihydroxy	30[c]		97—98

a) Procedures (See experimental).
b) Optimum catalyst used was stannic chloride. The phenol : I : $SnCl_4$ ratios were 1 : 1.5 : 2. The analytical sample was purified through bisulfite method.
c) The yield was determined by isolating the product as the semicarbazone, mp 247—249°C, hydrolysis of which with oxalic acid gave the aldehyde.

also for the preparation of their Schiff bases[3] has roused recent interest in new methods of synthesizing compounds in this class, particularly salicylaldehyde itself. A survey of the literature has indicated that the most general way of preparing salicylaldehyde involves the formylation of phenol, the halogenation of *o*-cresyl esters followed by hydrolysis, the hydrogenation of salicylic acid, and the methylolation of phenol followed by oxidation.[4]

In the present study we have examined (1) the acid-catalyzed formylation of phenols with dichloromethyl methyl ether (I), (2) the selective ortho-formylation of phenol with I, and (3) the catalytic hydrogenation of salicyloyl chlorides to salicylaldehydes. Dichloromethyl methyl ether was previously shown[5] to be a desirable reagent for the formylation of aromatic hydrocarbons. However, it there appears to have been no report[6] concerning the formylation of phenols with I. We have found that I reacts with phenols in the same way as with aromatic hydrocarbons.

$$Cl_2CH\text{-}O\text{-}CH_3$$
(I)

When phenol was treated with I in the presence of excess aluminum chloride at a low temperature, salicylaldehyde (15%) and para-hydroxybenzaldehyde (68%) were isolated from the reaction mixture. Under identical conditions, substituted phenols were allowed to react with I to give the corresponding hydroxybenzaldehydes in appreciable yields. The substitution of ethyl orthoformate for I likewise led to the introduction of the formyl group into an aromatic nucleus. The data, summarized in Table 1, indicate the scope of these procedures and show that I may be preferable to ethyl orthoformate as a formylating reagent.

In general, the acid-catalyzed formylation of phenol, as described above, would be of little value for salicylaldehyde synthesis because the formylation may lead to the predominant formation of para-isomer. Therefore, selective ortho-formylation was attempted. Recently Casnati, Crisafulli and Ricca[7] reported that the reaction of phenoxymagnesium halides with an excess of ethyl orthoformate gave the corresponding *o*-hydroxybenzaldehydes without any detectable amount of the para-isomer. On the other hand,

TABLE 2. CATALYTIC HYDROGENATION OF SALICYLOYL CHLORIDE

Exp. No.	Procedures[a]	Reaction Temp., °C[b]	Reaction hr	Yield of IIIa %
1	A	128	2	8
2	A	120	2	44
3	A	80	6	80
4	B	80	6	80
5	B	57	11.5	79
6	C	80	9.5	43[c]
7	D	75	8.5	58[c]

a) See Experimental section.
b) Maximum temperature, reached at the end of the reaction.
c) Based on salicylic acid.

3) a) E. B. Cyphers and G. M. McNulty, U. S. Pat. 2580005 (1951); b) J. P. G. Hatcher, E. Atherton, and W. L. Cox, German Pat. 1082597 (1957); c) C. S. Marvel and N. Tarköy, *J. Am. Chem. Soc.*, **79**, 600 (1957); d) C. S. Marvel and N. Tarköy, *ibid.*, **80**, 832 (1958); e) A. P. Terentev, V. V. Rode and E. G. Rukhadge, *Vysokomol. Soed.*, **2**, 1557 (1960); f) H. E. Smith and T. C. Willis, *J. Org. Chem.*, **30**, 2654 (1965).
4) J. B. Grenet and P. Marchand, French Pat. 1337243 (1963).
5) A. Riech, H. Gross and E. Höft, *Chem. Ber.*, **93**, 88 (1960).
6) Independently, A. Riech, H. Gross and G. Matthey [*Chem. Ber.*, **96**, 308 (1963)] have shown the acid-catalyzed formylation of more reactive phenols, such as resorcinol, with I or with ethyl orthoformate. However, the phenols have not included typical simple phenols, such as phenol.
7) G. Casnati, M. Crisafulli and A. Ricca, *Tetrahedron Letters*, **1965** 243.

TABLE 3. PREPARATION OF SUBSTITUTED SALICYLOYL CHLORIDES

Compound[a] No.	R	Reaction condition Solvent[b]	Temp., °C	hr	Yield[c] %	Mp, °C bp, °C/mmHg	IR, cm^{-1} O-H	C=O
IIb	3-CH_3	P	25—55	6 1/2	77	77—79/1	3300	1690
IIc	5-Cl	L	45—70	4	69	56.5—57[d]	3150	1677
IId	4-OCH_3	P	20—40	4 1/2	60	154.5—156[e]	3050	1657 1632
IIe	5-OCH_3	P	20—40	2 2/3	100		3350	1700

a) Found: C, 44.39; H, 2.32%. Calcd for IIc: C, 44.01; H, 2.12%.
b) P: petroleum ether, L: ligroin.
c) The yield of crude products is nearly quantitative.
d) The solvent for recrystallization is benzene.
e) The solvent for recrystallization is petroleum ether.

TABLE 4. SYNTHESIS OF SUBSTITUTED SALICYLALDEHYDES

Compound No.	R	Specified reaction condition Solvent[a]	Temp., °C[b]	hr	Yield %	Bp, °C/mmHg mp, °C	IR, cm^{-1} O-H	C=O
IIIb	3-CH_3	T	87	2	55[c]	55—57/1	3120	1655 1645
IIIc	5-Cl	T	80	3 1/2	82[d]	100.5[e]	3250	1688 1670
IIId	4-OCH_3	X	90	4	38[c]	41—41.5[f]	3450	1668 1645
IIIe	5-OCH_3	X	94	9 3/4	38[c]	80/0.5	3160	1665 1630

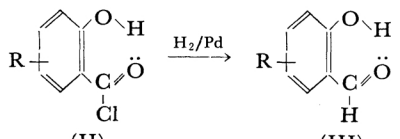
a) T: toluene, X: xylene.
b) Maximum temperature, reached at the end of the reaction.
c) The yield based on the acid was obtained by procedure B.
d) Obtained by procedure B.
e) Recrystallized from carbon tetrachloride.
f) Recrystallized from petroleum ether - benzene.

Yaroslavsky[8] showed that the reaction of aryldiazonium salts with dimethylformamide provided *o*-hydroxybenzaldehydes in a low yield. In the former procedure it seemed that dichloromethyl methyl ether could better be substituted for the orthoformate in preparing salicylaldehyde. We explored this possibility under a variety of conditions, using phenoxy magnesium bromide, magnesium phenolate, and aluminum phenolate.

Phenoxymagnesium bromide, propared from ethylmagnesium bromide and phenol, was reacted with I to give an unidentified crystal mass in a good yield, along with a minute amount of salicylaldehyde. The substitution of magnesium phenolate for phenoxymagnesium bromide led to a similar result, while the similar reaction of aluminum phenolate resulted in the recovery of the starting phenol.

Although the preparation of salicylaldehyde from salicylic acid by electroreduction and chemical hydrogenation has been extensively investigated, we could find no report concerning its synthesis through the catalytic reduction of salicyloyl chloride. Recently Wilson[9] reported the quantitative formation of salicyloyl chloride directly through the reaction of salicylic acid with thoniyl chloride in the presence of a very small amount of a tertiary amine, such as pyridine, at a mild temperature.

While the catalytic hydrogenation of salicyloyl chloride (IIa, R=H) in a refluxing xylene solution in the presence of palladium on barium sulfate and a small amount of quinoline-sulfur gave a low yield of salicylaldehyde (IIIa, R=H) (Exp. 1 in Table 2), the acid chloride IIa was, under mild conditions, readily converted into the corresponding aldehyde IIIa in a high yield (Exp. 3 in Table 2). The same good yield of the aldehyde



(II) (III)

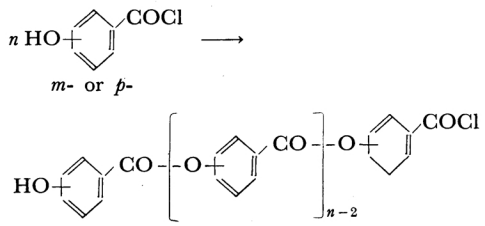
IIIa was secured in the absence of a regulator (Exp. 4 in Table 2). On the other hand, Compound

8) S. Yaroslavsky, *Tetrahedron Letters*, **1965**, 1503.

9) E. H. Wilson, U. S. Pat. 2899458 (1959).

IIIa could be obtaid in 43—58% yields when salicylic acid was treated with thionyl chloride directly, followed by a similar hydrogenation. The data, summarized in Table 2, indicate the effects of the reaction conditions on the yield of the product IIIa.

Attempts to isolate *m*- and *p*-hydroxybenzoyl chlorides by a similar procedure[10] were not successful, presumably because of their simultaneous polyesterification, which is shown below.



Very recently, Nyquist[11] has reported that Compound IIa, like IIIa, possesses a chelate structure. Accordingly, the results described above suggest that the sole availability of the acid chloride IIa among the isomeric hydroxybenzoyl chlorides and its easy convertibility to the aldehyde IIIa might be related to a certain degree to the chelated nature of their structure. The treatment of some substituted salicylic acids with thionyl chloride under similar conditions yields the corresponding acid chlorides IIb-e, which are rarely reported, in good yields. The results, summarized in Table 3, may additionally illustrate the unique behavior of the chelate compounds II.

The palladium-catalyzed reduction of substituted salicyloyl chloride IIb-e with hydrogen under atmospheric pressure in appropriate aromatic hydrocarbons gave the corresponding aldehydes IIIb-e in appreciable yields. Table 4 summarizes the results. The most significant feature in the infrared spectra of III is the shift of the O-H and C-O stretching vibrations to lower frequencies and the splitting of the latter bands into doublets. This hydrogenation reaction gives III almost exclusively whether or not a regulator is present (provided the temperature of reaction does not exceed 100°C).

We conclude, therefore, that the scope and limitation of the easy conversion of II to III may be attributed to their stereochemical natures.

Experimental[12]

Materials. Dichloromethyl methyl ether (I) was prepared from methyl formate and phosphorus pentachloride according to the procedure of Riech and his co-workers.[5] 2-Hydroxy-*p*-anisic acid (52%) was obtained from 4-hydroxysalicylic acid by the method of Mauthner,[13] after one recrystallization from aqueous ethanol, mp 164°C (lit.[13] 158—159°C). 6-Hydroxy-*m*-anisic acid was also prepared from the corresponding acid in a 79% yield, in a manner analogous to that described above, after one recrystallization from aqueous ethanol, mp 148°C (lit.[14] 145—146°C). Salicyloyl chloride was synthesized by the action of thionyl chloride on salicylic acid, according to the method of Wilson.[9] The infrared spectra of IIa, determined in either a CCl_4 solution or a neat film, showed no shift of absorption frequencies for the functional groups: $\nu_{max}^{CCl_4}$ 3330 (lit.[11] 3331 cm^{-1}, O-H) and 1720, 1690 (C=O) cm^{-1}: ν_{max}^{Liquid} 3330, 1720, 1691, and 660 (lit.[11] 660 cm^{-1}, O-H out-of-plane deformation) cm^{-1}. The regulator (quinoline-sulfur) prepared from 6 g of quinoline and 1 g of sulfur according to the usual procedure[15] was diluted with 70 m*l* of xylene. Palladium-barium sulfate was prepared by the method of Mozingo.[16] The other materials were obtained from commercial sources.

Acid-catalyzed Formylation of Phenols. *General Procedure A.* A solution of I (0.2 mol) in 20 m*l* of dichloromethane was vigorously stirred, drop by drop, into a suspension of a phenol (0.2 mol) and anhydrous aluminum chloride (0.4 mol) in 100 m*l* of dichloromethane at such a rate as to maintain the temperature of the reaction mixture below 0°C; meanwhile, hydrogen chloride was evolved vigorously. Then the mixture was stirred at room temperature until no more hydrogen chloride was eliminated; thereafter, the deep-colored solution was poured over crushed ice, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was thoroughly washed with water and dried over magnesium sulfate. The removal of the solvent, followed by fractional distillation or recrystallization, gave the analytical samples. The results with individual compounds are shown in Table 1.

B. To a stirred solution of a phenol (0.1 mol) and ethyl orthoformate (0.6 mol) in 100 m*l* of benzene, anhydrous aluminum chloride (0.15 mol) was added, portion by portion. After it had been stirred at 60°C for 15 min, the mixture was treated, drop by drop, with 300 m*l* of cold hydrochloric acid (5%), the temperature being kept below 0°C by external cooling. The organic layer was combined with ether extracts of the aqueous layer, and washed with an aqueous sodium carbonate solution and water. The organic materials were worked up as has been described above for A to afford the results summarized in Table 1.

Attempted Selective Ortho-formylation of Phenol. *A.* To a stirred solution of phenoxymagnesium bromide (0.1 mol), prepared by adding phenol

10) Whereas Wilson[9] may obtain 3-hydroxybenzoyl chloride by his procedure, M. Ronson and R. Huls [*Bull. soc. chim. Belges,* **61**, 599 (1952)] reported that attempts to prepare the acid chloride were unsuccessful.

11) R. A. Nyquist, *Spectrochim. Acta,* **19**, 1655 (1963).

12) All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-S2 and a Hitachi Model ETI-2 spectrophotometers. Gas chromatographic analyses were carried out on a Shimadzu Model GC-1b chromatograph.

13) N. Mauthner, *J. prakt. Chem.,* **159**, 36 (1941).

14) M. Bergmann and P. Dangschat, *Ber.,* **52**, 385 (1919).

15) E. B. Hershberg and J. Cason, "Org. Syntheses," **21**, 84 (1941).

16) P. Mozingo, *ibid.,* **26**, 77 (1946).

(0.1 mol) to a solution of ethylmagnesium bromide (0.1 mol) in 75 m*l* of ether,[7] 17.1 g (0.15 mol) of I was added, drop by drop, the temperature being maintained between 8°C and 12°C. The resulting slurry was stirred at 10±2°C for an hour, 30 m*l* of water was gradually added by external cooling, and then 70 m*l* of 10% hydrochloric acid. The organic layer was separated from the aqueous layer, which then was shaken with ether. After the ether had been removed from the combined organic layers, the resulting residue was steam-distilled. The extraction of the distillate with ether, followed by the drying and evaporation of the solvent, yielded a pale yellow oil (2.5 g). Gas chromatography showed a product consisting 99% of the starting phenol, plus a trace of salicylaldehyde. The residue obtained in the steam distillation was extracted with three 50-m*l* portions of ether and dried over magnesium sulfate. The ether was then removed by distillation, yielding 9.2 g of a crude material, mp 40—49°C. Recrystallization from aqueous ethanol afforded an unidentified product, mp 52—53°C: ν_{max}^{KBr} 1600, 1500 (C=C), 1303, 1195, 1020, 970, 780, 760, and 695 cm^{-1}.

Found: C, 66.10: H, 5.06%.

This material was treated with a 20% sodium hydroxide solution to yield the starting phenol; it gave a negative Beilstein test.

The substitution of ether for tetrahydrofuran as a reaction solvent gave the same results.

B. A solution of 23.4 g (0.25 mol) of phenol in 200 m*l* of xylene was added to a solution prepared by stirring a mixture of 3 g (0.125 g-atom) of magnesium and 40 m*l* of absolute ethanol. After the ethanol had been thoroughly removed by atmospheric distillation, the mixture was diluted with 150 m*l* of xylene. To this mixture a solution of 28.4 g (0.25 mol) of I in 30 m*l* of xylene was then slowly added at 15—17°C. With vigorous stirring the resulting mixture was warmed on a steam bath at 40—45°C for 2 hr and then worked up as has been described above for A. The starting phenol (7.2 g) was recovered from the steam distillate, and 10.9 g of the product (mp 52—53°C) described above was obtained from the steam-distillation residue. The substitution of magnesium as a catalyst for aluminum resulted in the recovery of the starting phenol.

Preparation of Substituted Salicyloyl Chlorides IIb-e. The procedure of Wilson[9] could be substantially applied to the preparation of IIb-e from the corresponding salicylic acids. Thionyl chloride (0.21 mol) was added, drop by drop, to a suspension of 0.2 mol of a substituted salicylic acid and 0.1 g of pyridine in 150 m*l* of ligroin or petroleum ether. After the gas evolution slowed down, the mixture was warmed on a steam bath under the conditions shown in Table 3. The removal of the excess thionyl chloride and solvent by a water pump, followed by fractional distillation or recrystallization, gave the corresponding acid chloride. The results with individual compounds are shown in Table 3.

The Catalytic Hydrogenation of Salicyloyl Chlorides II to Salicylaldehydes III. *Procedure A.* Xylene or toluene (102 m*l*), 0.34 m*l* of a quinoline-sulfur solution, and 6.8 g of 5% palladium-barium sulfate were put into a dry 200-m*l*, four-neck, round-bottom flask equipped with a sealed stirrer, a thermometer, a reflux condenser with a drying tube attached, a dropping funnel, and a hydrogen-inlet tube. A slow stream of dry hydrogen was then passed through the stirred mixture for 10 min. After the addition of pure II (0.2 mol) to the reaction mixture, the resulting mixture was gradually heated on a Mantol heater at such a controlled temperature as to keep almost constant the elimination rate of hydrogen chloride gas, which was titrated from time to time. When no more hydrogen chloride was formed at the maximum temperature shown in Tables 2 and 4, the reaction mixture was chilled and filtered. The concentration at the water-pump pressure, followed by fractional distillation or recrystallization, gave the product III.

Salicylaldehyde (IIIa), bp 50—53°C/3.5 mmHg, was identified by comparing its infrared spectrum with that of an authentic sample and by gas chromatographic analysis. The identification of the other products, IIIb-e is described in Table 4.

B. This reaction was carried out in the absence of the regulator as above.

C. Into a mixture prepared by the action of thionyl chloride on a salicylic acid in xylene containing a very small amount of pyridine, dry hydrogen was passed in order to remove the resulting hydrogen chloride. A hydrogenation procedure similar to that described above for B was then followed.

D. In a solution of salicyloyl chloride in petroleum ether prepared by the usual procedure, the hydrogenation reaction was carried out as above except that xylene was gradually added, drop by drop, to the mixture at such a rate as to keep its volume constant.

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