and filtered. The precipitate (63 mg.), crystallized from benzene, melted at 192–194°. The analytical sample of Vb melted at 194–196°; $[\alpha]_D^{27}$ +172° (ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.52; H, 7.69. Found: C, 75.14; H, 7.76.

The same compound was obtained from either IIa or IIc on heating with pyridine hydrochloride for 1 hr. at 200°.

An alternative route led via the Schotten-Bauman benzoylation of 2-hydroxyestradiol (IVf) to give the dibenzoate which on oxidation with chromic acid in acetic acid gave 2-hydroxyestrone, 2,3-dibenzoate (Vc) m.p. 172–174° from ethanol.

Anal. Calcd. for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.66; H, 6.10.

Mild alkaline hydrolysis of the above under a nitrogen atmosphere gave 2-hydroxyestrone (Vb).

4-Hydroxyestrone (Ve).[15] Pyridine hydrochloride fusion of 200 mg. 4-hydroxyestrone, 3-methyl ether (Vd) gave 138 mg. of product which crystallized from benzene-methanol with a m.p. 260–265° dec. The analytical sample obtained from the same solvent melted at 266–270° dec. with sublimation; $[\alpha]_D^{27}$ +155° (ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 74.99; H, 7.67.

(15) The diacetate of this compound has been prepared by oxidation with lead tetracetate, A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **80**, 5683 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY, GLASGOW]

Compounds Related to a Possible Precursor of Diploicin[1]

C. R. SMITH, JR.[2]

The synthesis of compounds related to a possible biosynthetic precursor of diploicin (IVb) a chlorine-containing lichen substance, is described. The relative ease of decarboxylation of 3,5-dichloro-*o*-orsellinic acid and two of its derivatives is discussed. 2,4-Dichloroörcinol undergoes diacylation preferentially, despite steric factors which should favor monoacylation.

Recent work on oxidative coupling of phenols, involving one-electron-transfer oxidizing agents, has elucidated the true nature of the crystalline dimer obtained by oxidizing *p*-cresol with alkaline ferricyanide (I).[3] Usnic acid (II), a lichen metabolite, has been synthesized by a similar process.[3] Scott has also utilized this coupling process in carrying out the partial synthesis of (±)-dehydrogriseofulvin and (±)-geodin methyl ether from related benzophenone derivatives.[4] Brockmann and coworkers have demonstrated related oxidations of hypericin precursors.[5] Bruice oxidized 3-methoxymesitol with alkaline ferricyanide and obtained only linear coupling and hydroxylation products,[6] in contrast to I and II, which resulted from free radical coupling followed by ionic cyclization. The concept of oxidative coupling of phenols as a biogenetic mechanism has been discussed in detail by Barton and Cohen.[7]

Diploicin (IVb), a chlorine-containing lichen metabolite,[8] was selected as a prospective further example of a natural product which could be synthesized by oxidative coupling of a phenolic precursor *in vitro*. The structure of diploicin, which is obtained from *Buellia canescens*, was elucidated by Nolan and co-workers.[9,10,11] Our initial objective was preparation of a compound such as IIIb, whose blocking groups could be readily removed. A subsequent conversion IIIa→IVa, effected by oxidative cyclization through electron pairing, was envisioned as follows:

I   II
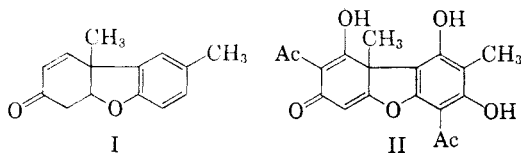
(1) This investigation was supported by Research Grant EF-5415 from the National Institutes of Health.

(2) National Heart Institute Research Fellow, University of Glasgow, 1955–56. Present address, Northern Regional Research Laboratory, Peoria, Illinois.

(3) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 1956, 530.

(4) A. I. Scott, *Proc. Chem. Soc. (London)*, 1958, 195.

(5) H. Brockmann, *Proc. Chem. Soc. (London)*, 1957, 304.
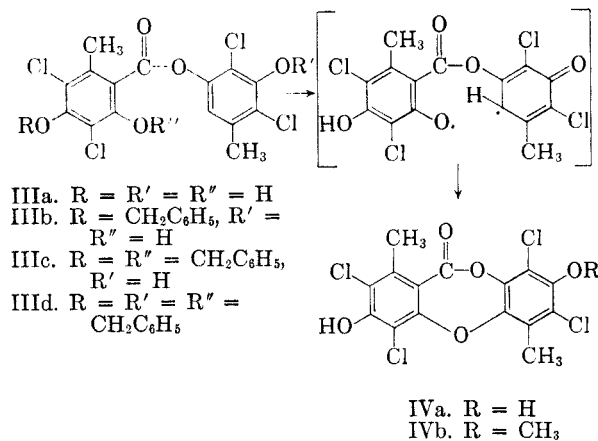
(6) T. C. Bruice, *J. Org. Chem.*, **23**, 246 (1958).

(7) D. H. R. Barton and T. H. Cohen in *Festschrift Arthur Stoll*, Birkhäuser AG, Basel, 1957, p. 117.

(8) For reviews on lichen substances, *cf.* Y. Asahina and S. Shibata, *The Chemistry of Lichen Substances*, Japan Society for Promotion of Science, Tokyo, 1954; S. Shibata in *Encyclopedia of Plant Physiology*, Vol. X, ed. by W. Ruhland, Springer-Verlag, Berlin, 1958, p. 560.

(9) P. A. Spillane, J. Keane and T. J. Nolan, *Sci. Proc. Roy. Dublin Soc.*, **21**, 333 (1936).

(10) T. J. Nolan and D. Murphy, *Sci. Proc. Roy. Dublin Soc.*, **22**, 315 (1940).

(11) T. J. Nolan, J. Algar, E. P. McCann, W. A. Manahan and N. Nolan, *Sci. Proc. Roy. Dublin Soc.*, **24**, 319 (1948).

IIIa. R = R' = R" = H
IIIb. R = CH₂C₆H₅, R' = R" = H
IIIc. R = R" = CH₂C₆H₅, R' = H
IIId. R = R' = R" = CH₂C₆H₅

IVa. R = H
IVb. R = CH₃

Other modes of cyclization are conceivable, such as formation of a spiro ring as in dehydrogriseofulvin. Expression IIIa is analogous to the class of lichen substances known as *depsides*, while diploicin itself (IVb) is a *depsidone* of the orcinol group.[8] None of these lichen-produced lactones have thus far been synthesized.

The synthesis of the dichloroörsellinic acid moiety of III began with the condensation of acetoacetic ester and ethyl crotonate to form V. The method of von Schilling and Vorländer[12] was used with some modifications found necessary. V was aromatized to yield ethyl o-orsellinate (VI) by the method of Pfau.[13] Pfau's procedure employs 20% ferric chloride in acetic acid and gave low yields of impure product in our hands, despite various modifications tried. VI was converted to the dichloro ester VIIa by direct chlorination.[10] VIIa was hydrolyzed to the hitherto unknown acid VIIb by prolonged treatment with either 25% sodium hydroxide at 20° or concentrated sulfuric acid at 0°. Nolan and Murphy had shown previously that conventional hydrolysis with boiling dilute alkali produced concurrent decarboxylation (VIIa → X).[10]

VIIa, when treated with benzyl chloride in ethanolic potassium hydroxide, yielded both monobenzyl and dibenyl ethers (VIIIa and IXa) in a stepwise reaction. It might be anticipated that hydrogen bonding and steric hindrance at the hydroxyl ortho to the carbethoxy group would cause the para-hydroxyl to be attacked preferentially. Consequently, the monobenzyl ether was considered to be the 4-benzyl derivative (VIIIa). Regeneration of VIIa by hydrogenolysis of VIIIa with palladium–calcium carbonate was demonstrated.

It was hoped that the corresponding monobenzyl acid (VIIIb) would be used to prepared IIIb. However, alkaline hydrolysis of the ester grouping even at room temperature resulted in concurrent decarboxylation and formation of decarboxy deriv-

ative XI. Although VIIIb, like VIIb, is a tautomer of a β-keto acid and subject to further activation of its carboxyl by substituent chlorines, it was hardly anticipated that it would be even more susceptible to decarboxylation.

Dibenzyl ether IXa, in marked contrast to VIIa and VIIIa, proved rather resistant to alkaline hydrolysis. It was converted with some difficulty to acid IXb by refluxing with 5% potassium hydroxide in aqueous dioxane. The stability of IXb emphasized the role of the ortho-hydroxyl in facilitating the decarboxylation of VIIb and VIIIb, and substantiated the structure assigned to the latter. On treatment with oxalyl chloride, IXb yielded the corresponding acid chloride.

V

VI

VIIa. R = C₂H₅
VIIb. R = H

IXa. R = C₂H₅
IXb. R = H

VIIIa. R = C₂H₅
VIIIb. R = H

XI

X

XII

XIV
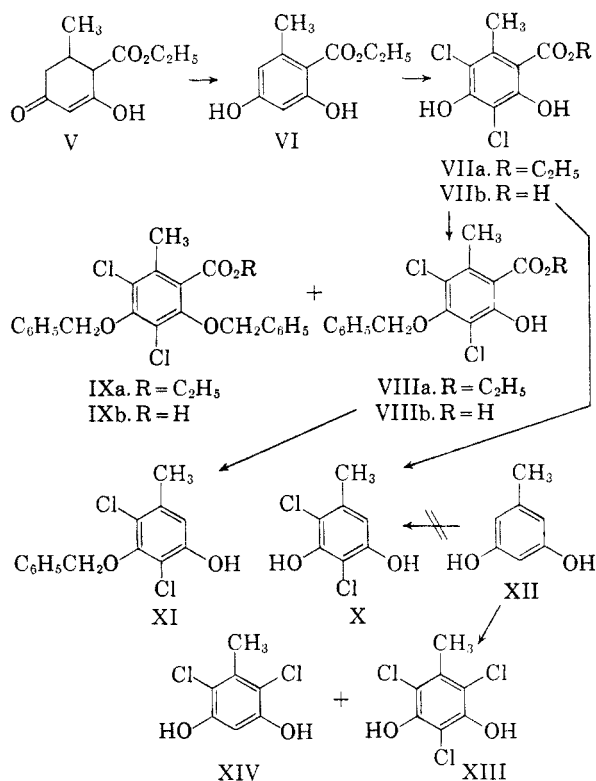
XIII

Synthesis of the 2,4-dichloroörcinol moiety (X) required to produce III was attempted by chlorination of orcinol (XII). The only products obtained, however, were 2,4,6-trichloroörcinol (XIII), and the previously unreported 2,6-dichloroörcinol (XIV). Consequently, X had to be prepared by hydrolysis and decarboxylation of difficultly accessible VIIa.

The stage was then set for the attempted preparation of IIIc. It was expected that the 5-hydroxyl of X, being much less hindered sterically than the 3-hydroxyl, could be acylated preferentially, especially with a bulky acyl group like IXb. However, when X was acylated with the acid chloride of IXb, the only product which could be characterized appeared to be a *diacyl* derivative. Though not obtained pure, elementary analyses together with its infrared spectrum and its negative response to

(12) R. von Schilling and D. Vorländer, *Ann.*, **308**, 184 (1899).

(13) A. St. Pfau, *Helv. Chim. Acta*, **16**, 283 (1933).

a ferric chloride test supported the diacyl formulation XV rather than IIIc. This wholly unexpected result was rationalized by assuming that because

XV
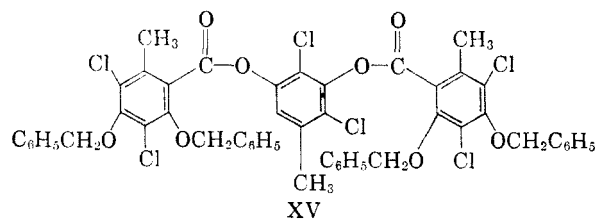
of its electron-withdrawing character, an acyl substituent, once attached to the 5-hydroxyl, increased the acidity of the 3-hydroxyl sufficiently that the latter could compete successfully for unreacted acyl chloride molecules, resulting in formation of XV.

Efforts were then directed towards preparation of IIId from intermediates having all interfering hydroxyl groups blocked. Earlier experiments had fortuitously provided an elegant method for preparing XI, which accordingly was acylated with the acid chloride of IXb. The low overall yield at this point, however, so reduced the quantity available for this experiment that the small amount of solid product could not be adequately characterized. Its infrared spectrum was similar to that of XV, as would be expected.

EXPERIMENTAL[14]

Preparation of ethyl 1,2-dihydro-o-orsellinate (V).[12] Twenty-three grams of sodium (1 mole) was added to 300 ml. of absolute ethanol, warming slightly to dissolve the last few grams. Then were added successively 126 g. (1 mole) of ethyl acetoacetate and 102 g. (1 mole) of ethyl crotonate. The mixture was refluxed with continuous stirring for 2 hr. A slurry of sodium enolate appeared 20 to 25 min. after addition of the reagents was complete, and the mixture gradually thickened to a paste. At the end of 2 hr., the mixture was chilled and acidified with 5% sulfuric acid. Considerable sodium sulfate separated out, which was removed by filtration. The filtrate was diluted with 200 ml. of water, then extracted with chloroform. The solvent was removed, yielding 174 g. of oily product, which was chilled until crystallization began, then diluted with 60 ml. of 40–60° petroleum ether and let stand overnight. A yield of 80 g. of product was obtained upon filtration. This material was satisfactory for dehydrogenation after thorough drying, but could be recrystallized from petroleum ether–benzene; m.p. 87–89° (lit.,[12] m.p. 89–90°).

Dehydrogenation of ethyl 1,2-dihydro-o-orsellinate (V). The following was typical: 40 g. of V was refluxed 1 hr. with 8.0 g. of anhydrous ferric chloride (or the equivalent amount of ferric chloride hexahydrate) and 400 ml. of 20% aqueous acetic acid. The mixture was then diluted with 200 ml. of water and extracted with ether. The ether extract was, in turn, extracted repeatedly with 50 ml. portions of saturated sodium carbonate, then evaporated, yielding 17.5 g. of VI as a dark amorphous solid. This was recrystallized from benzene—first crop, 7.0 g., m.p. 122–129°; second crop, 2.3 g., m.p. 120–125°. A second recrystallization produced mate-

rial melting at 131–132° (lit.,[13] m.p. 131–132°). Changes in Pfau's published procedure, such as varying reaction time and concentration of ferric chloride, produced even poorer yields.

Chlorination of ethyl o-orsellinate (VI). This preparation was carried out by a procedure similar to that applied to methyl o-orsellinate by Nolan and Murphy.[10] A 55 g. portion (0.281 mole) of VI was dissolved in 3 l. of chloroform chilled in an ice bath. There was added slowly and with mechanical stirring 310 ml. of chlorine (2.2 × 0.281 mole) in carbon tetrachloride. After 45 min., 45 ml. of pyridine was added; the mixture was subsequently freed of pyridine by extraction with water. After drying, the solution was evaporated to a small volume; half this volume of carbon tetrachloride was added. A yield of 69 g. of ethyl 3,5-dichloroörsellinate (VIIa) was collected, m.p. 160–163° (lit.,[10] m.p. 159–161°).

Hydrolysis of ethyl 3,5-dichloro-o-orsellinate (VIIa). *A. Sulfuric acid method.* A 3.00 g. portion of VIIa was dissolved in ice cold conc. sulfuric acid and let stand 6 days at 0°. The mixture was then poured into ice water and extracted with ether. The ether, upon evaporation, yielded 2.69 g. of acid VIIb, m.p. 195–200°; 0.91 g. of this acid was purified by dissolving it in ether, extracting it with 0.1N sodium bicarbonate, liberating it with hydrochloric acid, and extracting with ether. From the ether was obtained 0.53 g., 202–207° dec. After three recrystallizations from benzene-ether, the acid melted at 210–211° dec.

Anal. Calcd. for $C_8H_6Cl_2O_4$: C, 40.53; H, 2.55; Cl, 29.92. Found: C, 40.75; H, 2.79; Cl, 29.64.

B. 25% Sodium hydroxide method. One gram of VIIa was dissolved in 30 ml. of 25% sodium hydroxide and let stand 7 days at room temperature. The solution was then diluted with water, acidified and extracted with ether. Upon evaporation, 0.91 g. of VIIb was obtained, m.p. 185–195° dec.

Ethyl 3,5-dichloro-o-orsellinate 4,6-dibenzoate. VIIa (12.0 g.) was dissolved in 68 ml. of methyl ethyl ketone. Potassium carbonate (6 g.) was added and the mixture was heated to reflux; 13.2 g. of benzoyl chloride dissolved in 12 ml. of methyl ethyl ketone was added dropwise and refluxing continued 3.5 hr. The mixture was then filtered and evaporated, yielding a foamy solid which was extracted with chloroform. The chloroform solution was extracted with 0.1N sodium hydroxide, dried, and evaporated to yield 5.9 g. of dibenzoate, which crystallized on trituration with ethanol. This was recrystallized four times from ethanol; 0.39 g., m.p. 109–110°, was obtained.

Anal. Calcd. for $C_{24}H_{18}Cl_2O_6$: C, 60.90; H, 3.83. Found: C, 61.28; H, 4.00.

4,6-Dibenzyl and 4-benzyl ethers of ethyl 3,5-dichloro-o-orsellinate. VIIa (7.13 g.) was dissolved in 700 ml. of absolute ethanol containing 10.5 g. of potassium hydroxide; 112 ml. of benzyl chloride was added to the mixture. After 24 hr., 4 g. additional potassium hydroxide was added. At the end of 3 days, the reaction mixture was partitioned between water and ether. Upon concentrating the ether layer, additional aqueous liquor separated out and was combined with the original aqueous layer.

The strongly alkaline aqueous layer was acidified and extracted with ether. From the ether was obtained 5.05 g. of dark oily material. This was triturated with and crystallized from ether; 1.45 g. of solid monobenzyl ether (VIIIa) was obtained. This was recrystallized from benzene, yielding 0.83 g., m.p. 179–180°. A 36.6 mg. sample of VIIIa was subjected to hydrogenolysis in ethyl acetate solution with 10% palladium on calcium carbonate; 2.61 cc. were consumed, 5% in excess of theory for one mole. The product (35 mg.) melted at 160–161° and showed no depression of melting point when mixed with VIIa.

Anal. Calcd. for $C_{17}H_{16}Cl_2O_4$: C, 57.48; H, 4.54; Cl, 19.96. Found: C, 57.42; H, 5.08; Cl, 20.22.

The ether layer from the above partitioning was dried over sodium sulfate and concentrated. The bulk of the excess benzyl chloride was removed by vacuum distillation leaving

(14) Melting points were determined in capillary tubes in a hot block apparatus, except as noted, and are corrected. Infrared spectra were determined with a Unicam Infrared Spectrophotometer as Nujol mulls.

a dark, partially crystalline residue, 6.47 g. This was chromatographed on 200 g. of activity V alumina; 4.13 g. of dibenzyl ether (IXa) was obtained by elution with 300 ml. of benzene. A 0.85 g. portion of this was recrystallized twice from 60-80° petroleum ether, yielding 0.22 g., m.p. 77-78°.

Anal. Calcd. for $C_{24}H_{22}Cl_2O_4$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.44; H, 4.48; Cl, 15.75.

Hydrolysis of ethyl 3,5-dichloro-o-orsellinate 4,6-dibenzyl ether (IXa). A 5% potassium hydroxide solution was prepared from 12.5 g. of potassium hydroxide, 112.5 g. of dioxane and 125 ml. of water. A 4.13 g. portion of IXa was refluxed overnight in 200 ml. of this potassium hydroxide solution; the solution tended to separate into two phases, but vigorous reflux maintained satisfactory mixing. After cooling, the mixture was partitioned between water and chloroform. The basic layer was acidified and extracted with chloroform; 1.48 g. of solid acid was obtained on evaporating the extract. This was recrystallized from benzene-petroleum ether; first crop, 0.77 g., m.p. 180-182°; second crop, 0.10 g.

A 13.8-mg. portion of this acid was subjected to hydrogenolysis in ethyl acetate in the presence of 10% palladium-on-calcium carbonate. There was an uptake of 1.79 cc. of hydrogen compared to the theoretical amount of 1.58 cc.

Anal. Calcd. for $C_{22}H_{18}Cl_2O_4$: C, 63.32; H, 4.35; Cl, 17.00. Found: C, 63.52; H, 4.35; Cl, 16.90.

Hydrolysis and decarboxylation of ethyl 3,5-dichloro-o-orsellinate 4-benzyl ether (VIIIa). A 0.120-g. position of VIIIa was dissolved in 40 ml. of 12% aqueous sodium hydroxide (the most concentrated in which it was soluble), and let stand 3 days at room temperature. The solution was then diluted with water, acidified, and extracted with chloroform. A residue of 0.082 g. was obtained from the chloroform after drying; this was chromatographed on activity V alumina. By benzene elution, 0.050 g. of crystalline material was obtained, m.p. 94-95° (Kofler) after drying *in vacuo* at 45°. This substance was shown by elemental analyses and infrared spectrum (OH peak at 3406 cm.$^{-1}$, no carbonyl peak) to be *2,4-dichloroörcinol 3-benzyl ether* (XI) rather than the desired acid (VIIIb).

Anal. Calcd. for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; Cl, 25.04. Found: C, 59.96; H, 4.39; Cl, 25.32.

Experiments were carried out directed towards deliberate hydrolysis and decarboxylation of VIIIa by refluxing with 1% aqueous sodium hydroxide. Some XI could be isolated by chromatographing products obtained on activity V alumina, but a satisfactory reproducible method was not established.

Acylation of 2,4-dichloroörcinol (X). The acid chloride of IXb was prepared by refluxing 0.380 g. (0.91 mmole) of the acid with excess oxalyl chloride 2 hr. in a micro reflux assembly with careful exclusion of moisture. Excess oxalyl chloride was removed by vacuum. A 0.178-g. portion (0.92 mmole) of 2,4-dichloroörcinol, prepared according to the procedure of Nolan and Murphy,[10] was dissolved in dry pyridine and added to the acid chloride. The mixture was let stand overnight, then most of the pyridine was removed by vacuum. The residue was partitioned between ether and 0.1N sodium bicarbonate. The ether was dried and evaporated, yielding 0.56 g. of XV. This was recrystallized twice from ethanol-ether; 0.105 g. was obtained, m.p. 104-106°. The infrared spectrum had a peak at 1750 cm.$^{-1}$ (carbonyl)

but none in the OH region. The ferric chloride test was negative.

Anal. Calcd. for $C_{51}H_{38}Cl_6O_8$: C, 61.77; H, 3.86; Cl, 21.46. Found: C, 62.54; H, 3.95; Cl, 21.22.

Calcd. for $C_{29}H_{22}Cl_4O_5$ (monoacyl derivative): C, 58.80; H, 3.75; Cl, 23.95.

This experiment was repeated twice with variations. In the first instance, mechanical stirring was used and the acid chloride was added to X. In the second instance, the latter procedure was used, but with a twofold excess of X. In both cases, the products appeared to be the same diacyl derivative (XV).

Acylation of 2,4-dichloroörcinol 3-benzyl ether (XI). This was carried out in a manner similar to that described in the preceding section, except that X was replaced by its 3-benzyl ether (XI). A solid product was isolated by chromatography whose infrared spectrum indicated acylation had taken place (no OH peak) and which was similar to that of XV. The quantity in hand was too small for further characterization.

Chlorination of orcinol (XII). Orcinol (10.6 g.) was dissolved in 1.5 l. of chloroform chilled in an ice bath. Two moles of chlorine in carbon tetrachloride, plus 10% excess, was added slowly with mechanical stirring. After addition was completed, the mixture was extracted twice with 250-ml. portions of 0.1N sodium bicarbonate. The solution was then dried and concentrated to a small volume. Half this volume of petroleum ether was added and 5.8 g. of solid was collected, m.p. 101-105°. This was recrystallized from chloroform-petroleum ether, then three times from benzene, yielding a substance melting at 165.5-167° after sublimation. The melting point and elementary analyses indicated that this must be *2,6-dichloroörcinol* (XIV) rather than the desired 2,4-dichloroörcinol (lit.,[10] m.p. 121°).

Anal. Calcd. for $C_7H_6Cl_2O_2$: C, 43.55; H, 3.14; Cl, 36.74. Found: C, 43.72; H, 3.37; Cl, 37.05.

A second compound was obtained by concentrating the mother liquor from the first crystallization of XIV and recrystallizing the resulting residue from benzene. This proved to be *2,4,6-trichloroörcinol* (XIII), m.p. 123-124° (lit., m.p. 123°[15]; 127°[16]).

Anal. Calcd. for $C_7H_5Cl_3O_2$: C, 36.96; H, 2.22; Cl, 46.77. Found: C, 36.79; H, 2.40; Cl, 46.58.

Separation of XIII and XIV was also effected by chromatographing combined residues from recrystallizations on silica gel. Both compounds were eluted by collecting successive fractions with 9:1 benzene-ether. The trichloro compound was eluted first. No 2,4-dichloroörcinol (X) was obtained from the reaction mixture.

(15) J. Stenhouse, *Ann.*, **163**, 174 (1872).
(16) Th. Zincke, *Ber.*, **26**, 311 (1893).