the HCl gas is expelled by a stream of nitrogen during 90 minutes (40 ml./min.). A minimum volume of about 0.75 ml. should be maintained by the addition of carbon tetrachloride.

Diisopropylphosphorofluoridate.—The fluorination is carried out by the method of Ford-Moore, *et al.*[13] The gas inlet tube is removed and a cooling water jacket is fitted in position; 500 mg. of pulverized ammonium fluoride and 2 ml. of acetone are added. The mixture is refluxed during 2 hours. Next the resulting DFP is purified by steam distillation. The solution is transported into the dropping funnel of a distillation apparatus by means o a syphoning tube fitted with a glass wool filter which is inserted into the reaction vessel. The distillation apparatus consists of a round flask of 750 ml. and a large surface condenser in vertical position. The residual precipitate in the reaction vessel is refluxed during one minute with an additional amount of acetone and also transported. The mixture is dropped carefully into the boiling water (7 ml. distillate/min.) and the distillate (40 ml.) is cooled with ice. The distillate is evacuated (20 min., 15 mm. at 20°) to expel acetone and carbon tetrachloride. To remove acidic impurities the solution is percolated through a column of Amberlite IR4 (10 × 1 cm.) pre-washed with NaOH and water and cooled down to 0° (3 ml./min.). The DFP content of the solution is assessed by essentially the same colorimetric method as has been described by Epstein, *et al.*,[14] for sarin. However in the case of DFP it is necessary to use a phosphate buffer at *p*H 11.1 instead of *p*H 8.8. The absorption of the unknown solution is compared with that of freshly prepared standard solutions containing 0.1 to 0.3 mg. of DFP/10 ml. The purity of the DFP^{32} end product is checked by the comparison of its DFP content according to the colorimetric analysis against that based on the radioactivity of the solution (the radioactivity of 1 mg. of P of the starting material corresponds to that of 9.89 mg. of DFP). The average yield amounts to 80 mg. of a purity of 95 ± 5% and a specific activity of 200 microcuries per mg. The DFP^{32} solution must be stored in Pyrex ampoules at low temperature to minimize hydrolysis.

DFP in Peanut Oil.—A filter apparatus consisting of a centrifuge tube fitted with a Zeiss asbestos filter and containing the required quantity of peanut oil is sterilized. A solution of DFP in water is sterilized by slowly pressing it through the asbestos filter. The centrifuge tube is detached and stoppered. After agitating during one minute and centrifuging during ten minutes the oil layer is recovered with a sterile syringe (the partition coefficient of DFP in oil–water amounts to 6–7). The DFP content of the oil is determined on the basis of its radioactivity. Intramuscular injections of DFP^{32} in oil in quantities up to 1 mg. of DFP have been given to a great number of patients and have never produced undesirable toxic effects.

Radiation Hazard.—The operator is protected by two large removable perspex shields (10 mm.).

Materials.—Red phosphorus (British Drug Houses, BDH). A lot of finely divided phosphorus is collected by decanting a suspension of red phosphorus in water. The collected material is boiled with water and filtered. The procedure is repeated until the supernatant is acid free. Finally the filtered material is washed with dry acetone and dried above P_2O_5 *in vacuo*. Carbon tetrachloride A.R. (BDH). The carbon tetrachloride is boiled with a small quantity of PCl_3, agitated with a Na_2CO_3 solution, washed with water, dried with P_2O_5 and distilled. Ammonium fluoride A.R. (BDH): this material is thoroughly dried by an azeotropic distillation with dry carbon tetrachloride.

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(13) A. H. Ford-Moore, L. C. Lermit and C. Strattford, *J. Chem. Soc.*, 1776 (1953).

(14) J. E. Epstein, THIS JOURNAL, **78**, 341 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, SOUTHWESTERN MEDICAL SCHOOL OF THE UNIVERSITY OF TEXAS]

Ethers of Phloroglucinol

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The syntheses of phloroglucinol mono-, di-, tri- and mixed-ethers are reported. These compounds represent a series of homologs prepared in conjunction with antitubercular studies.

In 1934, Woodward, Kingery and Williams[2] reported a study of the fungicidal activities of various phenols against *Monilia tropicalis*. The 3,5-dialkylphenols showed considerable fungicidal activity but because of their relative insolubility their medical usefulness was limited. In a search for more effective fungicidal agents, a series of 3,5-dialkyloxyphenols (phloroglucinol dialkyl ethers) have been prepared. Monoalkyl ethers were also formed in the preparation of our phloroglucinol diethers.

In a survey of the fungicidal activity of phloroglucinol monohexyl ether against a number of pathogenic fungi, Dr. Morris Moore[3] found that this compound had particularly high activity against various species of *Actinomyces*. Therefore, this series of phloroglucinol mono- and di-ethers was tested against *Mycobacterium tuberculosis* because of the generally held phylogenetic relationship between it and the *Actinomyces*. Against a 607-like strain it was found that phloroglucinol monohexyl ether was especially potent[4]; however, none of the phloroglucinol ethers were found to be highly active against a virulent strain of *Mycobacterium tuberculosis* (H37Rv).

Several investigators[5,6] have reported the preparation of ethyl and methyl ethers of phloroglucinol. Kaufler[7] and his co-workers reported the synthesis of the benzyl ethers of phloroglucinol. Herzig[8] reported the preparation of ethyl and methyl ethers of phloroglucinol by treating an absolute alcohol solution of the phenol with hydrogen chloride. Since these early reports, little work has been done on this type of derivative although as late as 1920, Freudenberg[9] prepared phloroglucinol dimethyl ether in 70–80% yields.

Attempted preparation of phloroglucinol ethers using the Williamson type synthesis gave negative

(1) Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma.

(2) G. J. Woodward, L. B. Kingery and R. J. Williams, *J. Lab. Clin. Med.*, **19**, 1216 (1934).

(3) Personal communication to M. N. H.

(4) This testing was performed by Dr. Andres Goth, who will report his results elsewhere.

(5) W. Will, *Ber.*, **17**, 2106 (1883).

(6) H. Weidel and J. Pollak, *Monatsh.*, **21**, 22 (1901).

(7) F. Kaufler, *ibid.*, **21**, 998 (1901).

(8) J. Herzig, *ibid.*, **15**, 701 (1895).

(9) K. Freudenberg, *Ber.*, **53**, 1425 (1920).

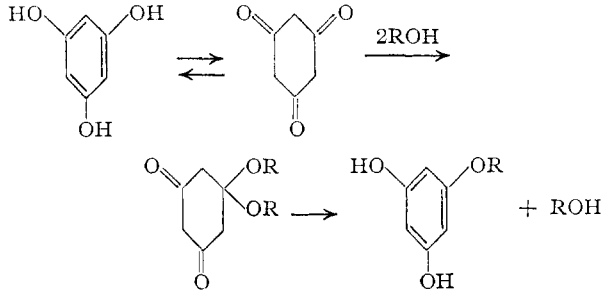
TABLE I

MONO-ETHERS

Compound	Reaction time, days	Crude yield, %	M.p., °C.[a] Pure	Formula	Analyses,[b] % Calculated Carbon	Calculated Hydrogen	Found Carbon	Found Hydrogen
Butyl[c]	7	30	92	$C_{10}H_{14}O_3$	65.89	7.75	65.81, 65.93	7.68, 7.72
Amyl[d]	7	30	86.5–87	$C_{11}H_{16}O_3 \cdot H_2O$	61.66	8.47	61.74, 61.60	8.32, 8.42
Hexyl	8	45	75–76	$C_{12}H_{18}O_3 \cdot H_2O$	63.13	8.83	63.44, 63.37	8.72, 8.67
Heptyl	7	19	80–81	$C_{13}H_{20}O_3 \cdot H_2O$	64.43	9.15	64.49, 64.56	9.02, 9.08
Octyl	3	..	72–73	$C_{14}H_{22}O_3 \cdot H_2O$	65.60	9.44	65.54, 65.69	9.44, 9.51
Undecyl	8	28	78–79	$C_{17}H_{28}O_3 \cdot H_2O$	68.42	10.14	68.54, 68.46	10.06, 10.13
Cetyl	7	30	82–83	$C_{22}H_{38}O_3$	75.38	10.93	75.24, 75.14	10.74, 10.69
Octadecyl[e]	17	..	87–89	$C_{24}H_{42}O_3$	76.14	11.18	75.94, 76.03	11.13, 11.22
Isoamyl	10	24	66–67	$C_{11}H_{16}O_3$	67.32	8.22	67.17, 67.27	8.08, 8.16
sec-Hexyl	14	16	81–82	$C_{12}H_{18}O_3 \cdot H_2O$	63.13	8.83	63.29, 63.15	8.76, 8.81
β-Phenylethyl	7	15	89–89.5	$C_{14}H_{14}O_3$	73.04	6.13	73.27, 73.20	6.28, 6.21
γ-Phenylpropyl	10	20	78–79.5	$C_{15}H_{16}O_3$	73.75	6.60	73.79, 73.88	6.46, 6.54
Phenoxyethyl	10	..	88–89.5	$C_{14}H_{14}O_4 \cdot H_2O$	63.63	6.10	63.80, 63.72	6.05, 6.08
γ-Chloropropyl	4	..	62–63	$C_9H_{11}O_3Cl \cdot H_2O$	Cl, 16.07		Cl, 16.06, 16.17	

[a] All melting points are uncorrected. [b] All analyses performed by E. W. D. Huffman, Denver. [c] Active hydrogen (Soltys) Calcd. for $C_{10}H_{14}O_3$: H, 1.107. Found: H, 1.10, 1.06. [d] Dibenzoate: m.p. 73°. *Anal.* Calcd. for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.16, 74.28; H, 5.89, 5.95. [e] Purified by chromatography on alumina.

results. This may be explained, in part, by the lability of phloroglucinol in hot alkaline solution. Also, considerable evidence exists to show that phloroglucinol reacts in many cases as the keto tautomer. The trioxime[10] of this compound has long been known. The fact that the mono- and di-ethers are readily formed by the reaction of alcohols with phloroglucinol in the presence of anhydrous hydrogen chloride indicates the keto form as the reacting species in this particular case. It is therefore proposed that the reaction proceeds through the intermediate ketal according to the scheme



Our method of preparation of the mono-ethers consisted in dissolving anhydrous phloroglucinol and two moles of the alcohol in anhydrous dioxane; the solution was then cooled in an ice-bath, saturated with hydrogen chloride, and kept in the dark at room temperature for a period of one to two weeks.

Our dialkyl ethers were prepared in a similar fashion except that the anhydrous phloroglucinol was dissolved in an excess of the alcohol. The reaction mixture after standing was taken up in ether or benzene and the organic phase washed well with water. The solvent was evaporated on a steam-bath and the unreacted alcohol removed *in vacuo;* the resulting oil was distilled or recrystallized depending on the particular compound. Purification often was facilitated by distillation prior to crystallization.

(10) A. Bayer, *ibid.*, **19**, 159 (1886).

In the preparation of phloroglucinol dialkyl ether, using anhydrous phloroglucinol, excess pure alcohol and anhydrous hydrogen chloride, often monoalkyl ether may be obtained from the reaction mixture. Thus, in the preparations of phloroglucinol di-*n*-octyl ether and phloroglucinol di-(γ-chloropropyl) ether the respective mono-ethers also were isolated. The mono-ether may be separated from the di-ether by fractional crystallization from benzene–hexane, the mono-ether being much the more insoluble. This separation is facilitated by distillation of the crude mixture before fractional crystallization. The mono-ether may also be separated from the di-ether by distribution between aqueous 5% potassium carbonate and petroleum ether, the mono-ether passing preferentially to the alkaline phase; however, nearly all of the mono-ethers were prepared without recourse to this distribution, due to their rapid oxidation in aqueous alkaline solution.

The difficulty in purification of the cetyl and octyl mono-ethers was simplified by separation of unreacted alcohol and reaction products on alumina. The alcohol was removed from the column by benzene while the more polar phenol ether was eluted with a benzene–methanol mixture. In this manner, pure material was prepared without distillation. It should be noted that on heating the mono-ethers polymerize and the residue from a distillation always consisted of resinous material. This property tended to lower the yields when distillation was used in the purification process.

The tributyl ether was synthesized from the dibutyl ether by a Williamson type synthesis using *n*-butyl bromide. The dimethyl mono-*n*-amyl ether was prepared from the readily available dimethyl ether using *n*-amyl iodide.

In the distillation of phloroglucinol mono-ethers a pot-type molecular still (BPS-III-500 of Distillation Products, Inc.) was employed. In the distillation of the di- and tri-ethers a similar still but with a higher column (BPS-I-500) was used.

Only a general preparation, with exceptions as

TABLE II

DI- AND TRI-ETHERS

Name	Reacn. time, days	Crude yield, %	M.p. or b.t., °C.[a]	Formula	Analyses, %[b] Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen
Dipropyl	4	57	47.5–48 92–95 (10 μ)	$C_{12}H_{18}O_3$	68.54	8.63	68.64, 68.57	8.55, 8.59
Dibutyl	2	50	39–40 160–165 (100 μ)	$C_{14}H_{22}O_3$	70.54	9.31	70.56, 70.40	9.31, 9.37
Diamyl	7	20	100 (5–6 μ)	$C_{16}H_{26}O_3$	72.14	9.84	72.06, 71.98	9.45, 9.53
Dihexyl	7	26	115 (6–7 μ)	$C_{18}H_{30}O_3$	73.43	10.27	73.48, 73.43	10.25, 10.34
Diheptyl	7	16	49–50 125–129 (7–8 μ)	$C_{20}H_{34}O_3$	74.48	10.63	74.50, 74.63	10.56, 10.63
Dioctyl	3	...	47–47.5 140 (7–8 μ)	$C_{22}H_{38}O_3$	75.36	10.95	75.34, 75.45,	11.00, 10.93
Di-(γ-chloropropyl)	7	34.5	86–87	$C_{12}H_{16}O_3Cl_2$	Cl, 25.40		Cl, 25.31, 25.41	
Tributyl	..	Quant.	105–110 (150 μ)	$C_{18}H_{30}O_3$	73.42	10.27	73.35, 73.45	10.17, 10.25
Monoamyl dimethyl[c]	..	53	125 (1 mm.)	$C_{13}H_{20}O_3$	69.61	8.99	69.42, 69.51	9.01, 9.07
Monocetyl dimethyl[d]	..	69	48 185 (15 μ)	$C_{24}H_{42}O_3$	76.14	11.18	76.17, 76.21	11.30, 11.23

[a] All melting points are uncorrected. B.t. temperatures refer to bath temperatures; figure in parentheses denotes pressure. [b] Analyses performed by E. W. D. Huffman, Denver. [c] Prepared from the dimethyl ether and amyl iodide following the directions used for the tributyl. [d] Prepared from dimethyl ether and cetyl bromide as in *c*.

noted, will be given. Table I gives the results obtained for the mono-ethers along with the properties and analytical data. The equivalent information for the di-, tri- and mixed-ethers is given in Table II.

Experimental

Phloroglucinol Monoamyl Ether.—A solution of 75.6 g. (0.6 mole) of anhydrous phloroglucinol and 105.6 g. (1.2 moles) of *n*-amyl alcohol in 200 ml. of dioxane (freshly distilled from sodium) was cooled in an ice-bath and saturated with anhydrous hydrogen chloride. After standing in the ice-bath for 2–3 hours, then at room temperature in the dark for 10 days, the reaction mixture was dissolved in ether and washed four times with water. The ether phase was then evaporated to dryness, the unreacted alcohol being removed *in vacuo*. The residue was distilled in high vacuum at a pressure of 3–4 μ. The distillate after crystallizing once from benzene–*n*-hexane mixture was pure enough for use in further experiments. Recrystallization thrice from benzene and hexane gives 36.2 g. (31%) colorless crystals, m.p. 86–87°. The analytical data will be found in Table I.

Phloroglucinol Monocetyl Ether.—Anhydrous hydrogen chloride was bubbled through a solution of 3.2 g. (0.013 mole) of cetyl alcohol and 0.75 g. (0.006 mole) of anhydrous phloroglucinol in 40 ml. of dioxane. Only occasional cooling was employed since the alcohol tended to come out of solution at ice-bath temperature. The reaction mixture was allowed to stand at room temperature for seven days, then taken up in benzene and washed well with water. The residue obtained after evaporation of the benzene was chromatographed on alumina. The unreacted alcohol was removed from the column by washing with benzene, after which the reaction product is obtained by elution with methanolic benzene. The product also can be separated by partition between 80% methanol and hexane, but the yield by this method is inferior to that obtained by chromatography. In the chromatographic procedure 2.1 g. (30% yield) was obtained, m.p. 82–83°.

Phloroglucinol Mono-γ-chloropropyl Ether.—This compound was prepared by the general method as outlined for the mono-ether, trimethylene chlorohydrin being used as the alcohol.

Phloroglucinol Diamyl Ether.—Ten grams (0.08 mole) of anhydrous phloroglucinol was dissolved in 100 ml. of *n*-amyl alcohol and saturated with anhydrous hydrogen chloride while being cooled in ice-water. After standing for seven days at room temperature the mixture was taken up in benzene and washed well with water. After evaporation of the benzene and removal of the unreacted alcohol *in vacuo* the di-ether was obtained by extraction of the residue with hot hexane. The organic extracts were combined, washed well with 3% potassium carbonate, and the di-ether extracted with *N* sodium hydroxide. On acidification of the sodium hydroxide extract an oil separated which was extracted with ether. The ether extract was washed well with water and evaporated to dryness. The residue was distilled twice at a bath temperature of 100° and a pressure of 5–6 μ to give 4.3 g. (20% yield) of a viscous oil which defied attempts at crystallization.

Phloroglucinol Tributyl Ether.—Phloroglucinol dibutyl ether, 1.2 g. (0.005 mole), was dissolved in 5 ml. of *n*-butyl chloride. To this mixture was added 7.0 ml. of a solution of potassium hydroxide in butanol (5.0 g. potassium hydroxide in 55 ml. of butanol) and the solution refluxed for 30 minutes. The reaction mixture was taken up in benzene, washed with water and the benzene solution evaporated to dryness, the butanol being removed *in vacuo*. The residue was dissolved in hexane, washed well with *N* sodium hydroxide and then with water. The solvent was evaporated and the residue distilled at a bath temperature of 105–110° at 150 μ.

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