A Simple Preparation of 1,4-Anhydroerythritol[1]

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The application of ion exchange resins for cyclizing glycols[2] prompted us to try this method for the dehydration of erythritol to 1,4-anhydroerythritol. Earlier methods of preparing 1,4-anhydroerythritol[3,4,5] which involve the use of mineral acids requires several hours of heating and give low yields. Himel, *et al.*,[6] reported higher yields with sulfonic acid catalysts.

1,4-Anhydroerythritol is a stable glycol which has utility as an intermediate for the preparation of polyesters, polyethers, and as a plasticizer.

We have found that nearly quantitative yields of 1,4-anhydroerythritol can be obtained simply by heating erythritol in a distillation flask containing a strong acid cation exchange resin followed by vacuum distillation. It is important that the product be distilled from the reaction mixture as it is formed to avoid side reactions. No decrease in yield was observed with successive use of the same sample of resin. A number of strong acid resins such as Amberlite[7] IR-120 and 200 and Dowex 50W[7] were found to be satisfactory catalysts.

EXPERIMENTAL

A distillation flask containing 10 g. of erythritol and 1 g. of Amberlite 200 was placed in an oil bath which had been preheated to about 140°. The system was subjected to about 0.5 mm. pressure and within 10 min. 1,4-anhydroerythritol began to distill out of the flask. The temperature was allowed to rise to 180°, at which cyclization was somewhat more rapid. The distillation required only about 25 min. for complete removal of the product. Five additional 10-g. portions of erythritol were dehydrated using the same sample of resin to give a total of 48.15 g. (94.2%) of relatively pure 1,4-anhydroerythritol. Accounting for the product retained in the distillation flask and condenser increased the yield to about 98%.

The product was redistilled to yield 45.75 g. of pure erythritan, b.p. 105–107° (0.2–0.5 mm.) n_D^{26} 1.478. Identification was made through the di-*p*-nitrobenzoate, m.p. 173–174°.

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[1] Erythritan or 3,4-dihydroxytetrahydrofuran.

[2] E. Switak, P. Mastagli, and Z. Zafiriadis, *Compt. rend.*, **237**, 1713 (1953).

[3] A. Henninger, *Ann. Chim. phys.*, [6] **7**, 224 (1886).

[4] P. Carre, *Ann. Chim. phys.*, [8] **5**, 345 (1905).

[5] H. Klosterman and F. Smith, *J. Am. Chem. Soc.*, **74**, 5336 (1952).

[6] C. M. Himel and L. O. Edmonds, U. S. Patent 2,572,566 (1951).

[7] Trade names are given as part of the exact experimental conditions and not as an endorsement by the U. S. Department of Agriculture of the products named over those of other manufacturers.

Alkylfurylcarbinols and Alkylthienylcarbinols with Choleretic Activity

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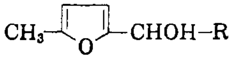
The main choleretic principle of the plant *Curcuma domestica* was identified by Dieterle and Kaiser,[1] and by Grabe,[2] as *p*-tolylmethylcarbinol, and similar secondary alcohols have also been found to display this type of biological activity.[3,4] Replacement of the benzene nucleus by a furan ring reduces somewhat this activity but does not suppress it entirely.[4] Recently, butylphenylcarbinol was found highly active in this respect, and has since been introduced into therapeutics.[5]

This paper reports the synthesis of a wide series of alkyl(5-methyl-2-furyl)carbinols (I), alkyl-2-thienylcarbinols (II), and alkyl(5-methyl-2-thienyl)carbinols (III), prepared for determination of choleretic activity, by the reaction of the appropriate alkylmagnesium bromide on 5-methyl-2-furaldehyde, 2-thenaldehyde, and 5-methyl-2-thenaldehyde. The substances obtained thus are listed in Table I, and in Table II are listed some alkylarylcarbinols bearing methyl substituents in the benzene nucleus, which were prepared in a similar way, and for the same purpose. All the carbinols, obtained in 75–85% yield, were colorless or very pale yellow oils with odors less pronounced and more pleasant than that of methyl-*p*-tolylcarbinol. All displayed choleretic activity in rats, to a greater or lesser degree.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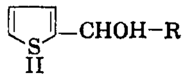
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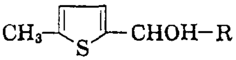
III

EXPERIMENTAL

Preparation of intermediates. 5-Methyl-2-furaldehyde was prepared by formylation of 2-methylfuran with dimethylformamide in the presence of phosphorus oxychloride; 2-thenaldehyde and 5-methyl-2-thenaldehyde were obtained in the same way from thiophene and 2-methylthiophene. *p*-

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[1] H. Dieterle and P. Kaiser, *Arch. der Pharm.*, **270**, 413 (1932); **271**, 339 (1933).

[2] F. Grabe, *Arch. exp. Pathol. Pharmakol.*, **176**, 673 (1934).

[3] H. Langecker, A. Harwart, and K. Junkmann, *Arch. exp. Pathol. Pharmakol.*, **225**, 303 (1955); R. Engelhorn, *Arzneimittel-Forsch.* **10**, 255 (1960).

[4] N. P. Buu-Hoï and N. D. Xuong, *Compt. rend.*, **249**, 970 (1959).

[5] In Germany, under the trademark "Cholipin."

TABLE I

ALKYLFURYL- AND ALKYLTHIENYLCARBINOLS

Carbinol	B.P.°, mm.	n_D	Empirical Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
Methyl(5-methyl-2-furyl)	88/18	—	$C_7H_{10}O_2$	66.6	66.5	8.0	8.1
Ethyl(5-methyl-2-furyl)	98/21	—	$C_8H_{12}O_2$	68.5	68.6	8.6	8.9
Butyl(5-methyl-2-furyl)	137/15	1.4842/27°	$C_{10}H_{16}O_2$	71.4	71.3	9.6	9.5
Isobutyl(5-methyl-2-furyl)	129/15	1.4814/27°	$C_{10}H_{16}O_2$	71.4	71.2	9.6	9.7
Amyl(5-methyl-2-furyl)	139/15	1.4701/27°	$C_{11}H_{18}O_2$	72.5	72.5	10.0	10.1
Isoamyl(5-methyl-2-furyl)	133/15	1.4739/27°	$C_{11}H_{18}O_2$	72.5	72.3	10.0	10.3
Hexyl(5-methyl-2-furyl)	151/15	1.4707/27°	$C_{12}H_{20}O_2$	73.4	73.3	10.3	10.3
β-Ethylbutyl(5-methyl-2-furyl)	145/15	—	$C_{12}H_{20}O_2$	73.4	73.2	10.3	10.5
Heptyl(5-methyl-2-furyl)	154/15	1.4808/21°	$C_{13}H_{22}O_2$	74.2	74.0	10.5	10.6
Octyl(5-methyl-2-furyl)	157/15	1.4779/26°	$C_{14}H_{24}O_2$	75.0	74.7	10.8	10.7
Butyl-2-thienyl	141/15	1.5522/27°	$C_9H_{14}OS$	63.5	63.2	8.3	8.2
Isobutyl-2-thienyl	134/15	1.5209/27°	$C_9H_{14}OS$	63.5	63.4	8.3	8.4
Amyl-2-thienyl	144/15	1.5232/27°	$C_{10}H_{16}OS$	65.2	65.0	8.8	9.0
Isoamyl-2-thienyl	138/15	1.5437/27°	$C_{10}H_{16}OS$	65.2	65.2	8.8	9.0
Hexyl-2-thienyl	160/15	1.5239/27°	$C_{11}H_{18}OS$	66.6	66.5	9.2	9.5
β-Ethylbutyl-2-thienyl	149/15	—	$C_{11}H_{18}OS$	66.6	66.5	9.2	9.3
Heptyl-2-thienyl	166/15	1.5207/21°	$C_{12}H_{20}OS$	67.9	67.8	9.5	9.5
Octyl-2-thienyl	169/15	1.5103/26°	$C_{13}H_{22}OS$	69.0	68.8	9.8	9.7
Butyl(5-methyl-2-thienyl)	145/15	1.5232/27°	$C_{10}H_{16}OS$	65.2	65.0	8.8	8.9
Isobutyl(5-methyl-2-thienyl)	137/15	1.5474/27°	$C_{10}H_{16}OS$	65.2	65.1	8.8	8.8
Amyl(5-methyl-2-thienyl)	147/15	1.5340/27°	$C_{11}H_{18}OS$	66.6	66.4	9.2	9.5
Isoamyl(5-methyl-2-thienyl)	144/15	1.5342/27°	$C_{11}H_{18}OS$	66.6	66.5	9.2	9.3
Hexyl(5-methyl-2-thienyl)	164/15	1.5310/27°	$C_{12}H_{20}OS$	67.9	67.6	9.5	9.8
β-Ethylbutyl(5-methyl-2-thienyl)	153/15	1.5362/21°	$C_{12}H_{20}OS$	67.9	67.8	9.5	9.5
Heptyl(5-methyl-2-thienyl)	171/15	1.5015/20°	$C_{13}H_{22}OS$	69.0	68.8	9.8	9.8
Octyl(5-methyl-2-thienyl)	175/15	1.5129/26°	$C_{14}H_{24}OS$	70.0	69.7	10.1	10.3

TABLE II

ALKYLARYLCARBINOLS

Carbinol	B.P., mm.	n_D	Empirical Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
Amyl-*p*-tolyl	150/15	1.5065/27°	$C_{13}H_{20}O$	81.2	81.0	10.5	10.6
Isoamyl-*p*-tolyl	147/15	1.5063/27°	$C_{13}H_{20}O$	81.2	81.3	10.5	10.8
Hexyl-*p*-tolyl	169/15	1.5092/27°	$C_{14}H_{22}O$	81.5	81.2	10.8	10.9
β-Ethylbutyl-*p*-tolyl	158/15	1.5128/21°	$C_{14}H_{22}O$	81.5	81.6	10.8	10.7
Heptyl-*p*-tolyl	177/15	1.5008/20°	$C_{15}H_{24}O$	81.8	81.6	11.0	11.3
Octyl-*p*-tolyl	182/15	1.4965/27°	$C_{16}H_{26}O$	82.0	81.9	11.2	11.3
Methyl-3,4-xylyl	150/18	—	$C_{10}H_{14}O$	80.0	79.8	9.4	9.7
Ethyl-3,4-xylyl	140/18	—	$C_{11}H_{16}O$	80.4	80.3	9.8	9.9
Methyl-2,5-xylyl	127/16	—	$C_{10}H_{14}O$	80.0	79.8	9.4	9.5
Ethyl-2,5-xylyl	134/18	—	$C_{11}H_{16}O$	80.4	80.3	9.8	9.9

Tolualdehyde and 3,4- and 2,5-dimethylbenzaldehyde were prepared from *p*-methyl-, 3,4-dimethyl- and 2,5-dimethylbenzyl chloride with hexamethylenetetramine by means of the Sommelet reaction (60–65% yields).

Grignard reactions. To an ice-cooled ethereal solution of the appropriate alkylmagnesium bromide (1.15 moles), the aldehyde (1 mole, dissolved in its volume of anhydrous ether) was added in small portions with stirring. The reaction was completed by a brief heating on the water bath; after cooling, the reaction product was treated with an ice-cooled aqueous solution of ammonium chloride, the ethereal layer washed with water and dried over sodium sulfate, the solvent distilled, and the residue vacuum-fractionated.

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Potential Anticancer Agents. XLIX.[1] Analogs of Chlorambucil. VII.[2] Nitrogen Mustards Derived from Cinnamic Acid

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The previous paper of this series[2] described the synthesis of some ring isomers of Chlorambucil (XV) and Norchlorambucil. In the synthesis of *o*-Norchlorambucil, *o*-[bis(2-chloroethyl)amino]hy-