After two more recrystallizations the compound, m.p. 106.5–107.2°, was pure.

Anal. Calcd. for $C_{11}H_9BrN_2O_6$: C, 38.28; H, 2.63; N, 8.12. Found: C, 38.16; H, 2.82; N, 8.00.

1-Bromo-1-hydroxymethylcyclopropane *p*-Toluenesulfonate.—A solution of 9.5 g. (0.05 mole) of *p*-toluenesulfonyl chloride in 25 ml. of dry pyridine was cooled to 0° and added to a cooled solution of 6.60 g. (0.0437 mole) of 1-bromo-1-hydroxymethylcyclopropane in 25 ml. of dry pyridine. The reaction mixture was stirred 2 hr. and poured into ice water. The crystalline product was recrystallized from carbon tetrachloride and there was obtained 6.70 g. (0.0219 mole or 50%) of 1-bromo-1-hydroxymethylcyclopropane *p*-toluenesulfonate, m.p. 57–58°. A small sample recrystallized from hexane had m.p. 57.0–58.0°.

Anal. Calcd. for $C_{11}H_{13}BrSO_3$: C, 43.28; H, 4.30; Br, 26.18. Found: C, 44.89; H, 4.45; Br, 26.91.

1-Bromo-1-diethylaminomethylcyclopropane.—A solution of 6.30 g. (0.0206 mole) of 1-bromo-1-hydroxymethylcyclopropane *p*-toluenesulfonate and 6.1 g. (0.083 mole) of diethylamine in 25 ml. of tetrahydrofuran was heated under reflux for 17 hr. The reaction mixture was cooled and poured into 100 ml. of 10% potassium hydroxide solution. The solution was extracted with three 150-ml. portions of ether and the extracts were combined, dried over magnesium sulfate, filtered, and dried over potassium hydroxide. Distillation through a semimicro column yielded 2.84 g. (0.0139 mole or 67%) of 1-bromo-1-diethylaminomethylcyclopropane, b.p. 61–73° (11 mm.), $n^{25}D$ 1.4709. Redistillation afforded a heart cut, b.p. 60° (7 mm.), $n^{25}D$ 1.4700, which was pure.

Anal. Calcd. for $C_8H_{16}BrN$: C, 46.61; H, 7.83. Found: C, 47.01; H, 7.86.

A sample of 1-bromo-1-diethylaminomethylcyclopropane (0.30 g.) added to picric acid in ether gave 1-bromo-1-diethylaminomethylcyclopropane picrate (0.65 g.), which when recrystallized from methyl cyclohexane–ethyl acetate had m.p. 137–138°.

1-Bromo-1-diethylaminomethylcyclopropane Picrate.—In a 50-ml. round-bottomed flask were placed 20 ml. of tetrahydrofuran and 7.4 g. (0.105 mole) of diethylamine. 1-Bromo-1-bromomethylcyclopropane (5.6 g., 0.026 mole) was added cautiously. After about 5 min., diethylamine hydrobromide began to separate. The reaction mixture was allowed to stand 64 hr., and then was poured into aqueous potassium hydroxide. The solution was extracted with ether, the ether extracts were combined and dried, and the product was distilled in a semimicro column. There was obtained 3.07 g. of impure 1-bromo-1-diethylaminomethylcyclopropane, b.p. 46–52° (10 mm.). NMR analysis of the product indicated the presence of the amine. A sample of this material was treated with a solution of picric acid in ether. Recrystallization of the crude product from methylcyclohexane afforded pure 1-bromo-1-diethylaminomethylcyclopropane picrate, m.p. 136–137°.

Anal. Calcd. for $C_{14}H_{19}N_4O_7Br$: C, 38.63; H, 4.40; N, 12.87. Found: C, 38.86; H, 4.36; N, 13.24.

The picrate was identical with the sample prepared from 1-bromo-1-hydroxymethylcyclopropane *p*-toluenesulfonate as shown by mixed melting point (136.5–137.5°) and comparison of the infrared spectra, which were identical.

Characterization of the Products from the Claisen Rearrangement of Allyl 3-Methylphenyl Ether and of Allyl 3-Methyl-4,6-dichlorophenyl Ether[1]

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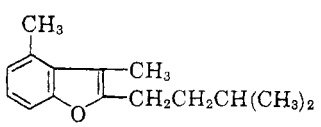
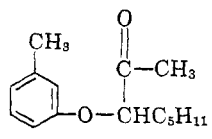
The Claisen rearrangement of allyl 3-methylphenyl ether has been shown by vapor phase chromatography analysis to yield a mixture of about 47% of 3-methyl-6-allylphenol (E) and 53% of 2-allyl-3-methylphenol (D). The structure of the latter has been established by relating it to the product of rearrangement of allyl 3-methyl-4,6-dichlorophenyl ether. The action of hydrazine and palladium on charcoal in Methyl Cellosolve on 2-allyl-3-methyl-4,6-dichlorophenol (G) leads to 2-propyl-3-methylphenol.

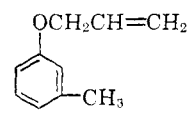
The synthesis of a degradation product from fumagillin,[2] 2-isoamyl-3,4-dimethylbenzofuran (A), required the study of methods for obtaining substitution in the 2-position of 3-methylphenol. This was accomplished satisfactorily by using 3-methyl-4,6-dichlorophenol,[2] with subsequent reductive removal of the halogen atoms. It was observed, however, that cyclization of the unblocked compound B yielded 40% of A, along with 60% of the isomeric 2-isoamyl-3,6-dimethylbenzofuran. In connection with synthetic approaches to compounds in the fumagillin series, it was desirable to examine various procedures for preparing 1,2,3-substituted compounds derived from 3-methylphenol. We have studied the Fries reaction[3] in



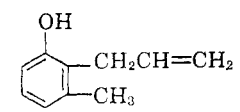
A



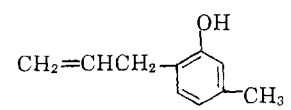
B



C



D



E

(1) Supported in part by Grant E-1138 of the U.S. Public Health Service.

(2) D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3096 (1961).

(3) S. E. Cremer and D. S. Tarbell, *J. Org. Chem.*, **26**, 3653 (1961).

this connection, and in the present paper report on the Claisen rearrangement of allyl 3-methylphenyl ether (C).

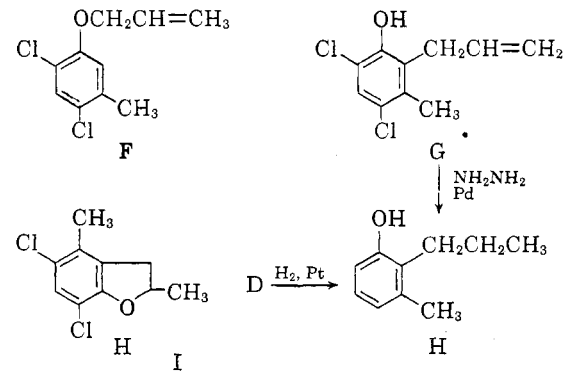
The rearrangement[4] of C was stated,[5] on the basis of an involved analytical procedure, to yield, when the rearrangement was carried out without solvent at 210–230°, 82% of E, 12% of D, and 6% of the 4 - allyl isomer. In another study,[6] the amount of the 6-allyl isomer E was determined by an isotope dilution procedure, and the remainder of the product was assumed to be the 2-allyl isomer D. In runs in carbitol at 160 and 200°, the product consisted of 40% of E and 60% of D.

The 2-allyl isomer D, in which we were interested primarily, does not seem to have been characterized, and we have therefore reinvestigated the rearrangement of C and have analyzed the mixture by vapor phase chromatography. The product, obtained in 57% yield when the rearrangement was carried out in refluxing dimethylaniline, consisted of about 47% of the 6-allyl isomer E and 53% of the 2-allyl compound D; a small amount of material (less than 1%) was observed in some vapor phase chromatography runs, which may have been the 4-allyl isomer. It had a shorter retention time than the other two isomers, and was not starting material. The yield and the proportion of isomers obtained by rearrangement of C without solvent at 210–230° were similar to those obtained in refluxing dimethylaniline.

The crude rearrangement product from C deposits a compound[7] of m.p. 51–52°, which was proved[5] to be the 6-allyl compound E. The structure of the 2-allyl isomer D was established in the present work by relating it to the product of rearrangement of allyl 3-methyl-4,6-dichlorophenyl ether F, as indicated below. The dechlorination of G using hydrazine–palladium in Methyl Cellosolve proved more difficult than in earlier cases,[2,3,8] and was accompanied by reduction of the double bond, to yield 2-propyl-3-methylphenol (H), which was obtained crystalline.[9] Compound H was also obtained by catalytic reduction of D, which had been separated by vapor phase chromatography from the rearrangement product from C.

In one run in which F was rearranged by refluxing without solvent, a crystalline product was formed to which was assigned the dihydrobenzofuran structure I, on the basis of its analysis, and infrared and n.m.r. spectra.

The formation of a considerable proportion of



the vicinal product D in the rearrangement of C is to be contrasted with the complete absence of the corresponding product in the Fries rearrangement of 3-methylphenyl acetate.[10] The Claisen rearrangement is known to proceed through a cyclic transition state,[11] and these observations point up the fact that cyclization reactions, such as the formation of A from B, and reactions which proceed through a cyclic transition state, are not subject to the same steric hindrance effects which dominate intermolecular reactions.[12]

Experimental[13]

Allyl 3-methylphenyl ether (C) was prepared in the usual way[14] from 3-methylphenol, allyl bromide, and potassium carbonate in dry acetone.

Rearrangement of C.—The ether C (4.74 g.) was refluxed in 20 ml. of dimethylaniline for 8.5 hr. The cooled solution was dissolved in 100 ml. of petroleum ether (b.p. 30–60°), and extracted thrice with 20% aqueous sodium hydroxide (25-ml. portions). The basic solutions were combined and washed twice with petroleum ether (50-ml. portions). They then were carefully acidified with concentrated aqueous hydrochloric acid (7:3 acid to water) (100 ml.). The acid solution was diluted with water to dissolve the sodium chloride formed and extracted twice with ether (50 ml. each). The ether solutions were washed with water (100 ml.) and then dried over magnesium sulfate. After evaporating the ether, the liquid was distilled; this gave 2.62 g. of product (57%), b.p. 80° (1.2 mm.).

Another portion of C was rearranged by refluxing for 3 hr. at atmospheric pressure; the b.p. rose from 211 to 239°. The product was worked up as above. The ether C was unaffected by refluxing in dimethylformamide for 20 min.

Materials obtained by both methods of rearrangement were combined; cooling to 0° and warming yielded a crystalline product, m.p. 51–52°, which was 6-allyl-3-methylphenol[5] (E). The **α-naphthylurethan** of this compound was prepared by heating it with α-naphthyl isocyanate

(4) The preliminary study of this reaction by L. Claisen and O. Eisleb, *Ann.*, **401**, 57 (1913), did not determine the proportion of isomers.

(5) L. Dubravkova, I. Jezo, P. Sefcavic, and Z. Vaticky, *Chem. Zvesti*, **12**, 24 (1958).

(6) W. N. White and C. D. Slater, *J. Org. Chem.*, **26**, 3631 (1961). We are indebted to Professor White for sending us a copy of this paper prior to publication.

(7) This compound was observed, but not identified, by Claisen.[4]

(8) W. L. Mosby, *Chem. Ind.* (London), 1348 (1959).

(9) I. L. Kotlyarevskii, *et al.*, *Izv. Sibirsk. Otd. Akad. Nauk. SSSR*, No. 6, p. 54 (1958) [*Chem. Abstr.*, **54**, 6607 (1960)], report H as an oil.

(10) A. H. Blatt, "Org. Reactions," Vol. I, John Wiley & Sons, New York, 1942, p. 358; and survey of subsequent literature.

(11) (a) D. S. Tarbell, *ibid.*, II, John Wiley & Sons, New York, 1944, p. 16; (b) J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952); H. Schmid and K. Schmid, *Helv. Chim. Acta*, **35**, 1879 (1952).

(12) *Cf.* R. C. Fuson and Q. F. Soper, *J. Org. Chem.*, **9**, 193 (1944). R. C. Fuson, W. D. Emmons, and R. Tull, *ibid.*, **16**, 648 (1951); R. C. Fuson and W. C. Hammann, *J. Am. Chem. Soc.*, **74**, 1626 (1952);

(13) All melting points are uncorrected. Microanalyses are by Mr. V. Landeryou and Micro-Tech Laboratories. All infrared spectra were taken on the pure liquid unless otherwise specified. We are indebted to Dr. L. D. Colebrook for n.m.r. determinations.

(14) Ref. 11a, p. 26.

and two drops of dry pyridine[15]; the product was recrystallized from petroleum ether (b.p. 100–115°) to obtain the analytical sample, m.p. 128.5–129°.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.33; H, 6.12; N, 4.70.

Allyl 3-Methyl-4,6-dichlorophenyl Ether (F).—This was prepared from 3-methyl-4,6-dichlorophenol (35.4 g., Aldrich Chemical Co. product), 24.2 g. of allyl bromide, 28 g. of powdered potassium carbonate, and 60 ml. of dry acetone, as above, and was obtained in 90% yield (38.2 g.), b.p. 90–91° (0.6 mm.), $n^{25}D$ 1.5490.

Anal. Calcd. for $C_{10}H_{10}Cl_2O$: C, 55.32; H, 4.64; Cl, 32.67. Found: C, 55.12; H, 4.54; Cl, 32.96.

Rearrangement of F to 2-Allyl-3-methyl-4,6-dichlorophenol (G). I.—The ether F (13.92 g.) was heated at 244–288° for 4.75 hr. at atmospheric pressure. After cooling, the viscous liquid was dissolved in petroleum ether (100 ml., b.p. 30–60°) and was extracted twice with 50-ml. portions of Claisen's alkali. The resulting basic solution was washed twice with petroleum ether (50-ml. portions) and then carefully acidified with concentrated hydrochloric acid. The resulting product was stirred with water and extracted twice with ether; the combined ether extracts were dried, the solvent was removed and the residue was distilled. The product [3.37 g., 23%, b.p. 82–88° (0.4 mm.)] was a slightly yellowish liquid, and gave a dark blue color with ferric chloride.

Anal. Calcd. for $C_{10}H_{10}Cl_2O$: C, 55.32; H, 4.64; Cl, 32.67. Found: C, 55.45; H, 4.76; Cl, 32.89.

The neutral fraction yielded, after standing for some time, a crystalline product, which was recrystallized from alcohol–water and melted at 36–38°.

Anal. Calcd. for $C_{10}H_{10}Cl_2O$: C, 55.3; H, 4.64; Cl, 32.67. Found: C, 55.33; H, 4.50; Cl, 32.62.

The infrared spectrum showed no hydroxyl group, and the n.m.r. spectrum showed a singlet with an intensity corresponding to one proton at 2.89 τ (assigned to the proton on the aromatic nucleus), a one proton multiplet at 4.90 τ (assigned to the C-2 proton), a two proton multiplet at 6.96 τ (assigned to the C-3 methylene group), a three proton singlet at 7.81 τ (assigned to the aromatic methyl group), and a three proton doublet [J = 6.6 c.p.s.] at 8.49 τ (assigned to the C-2 methyl group). The spectrum was determined in carbon tetrachloride solution using a Varian V-4300 B spectrometer operating at 60 Mc./sec. Tetramethylsilane was used as an internal standard. This indicated that this compound was the dihydrobenzofuran I.

II.—The ether F (7.46 g.) was refluxed in dimethylaniline (20 ml.) for 8 hr. The cooled solution was dissolved in petroleum ether (100 ml.) and this solution was extracted tiwce with Claisen's alkali (50-ml. portions). The basic solutions were combined and washed twice with petroleum ether (50 ml. each). After carefull acidification with aqueous hydrochloric acid, the acidic solution was diluted with water and extracted four times with ether. The combined ether solutions were washed with water and then dried. The solvent was removed, and distillation of the residue yielded 5.75 g. (77%) of 2-allyl-3-methyl-4,6-dichlorophenol (G), b.p. 131° (5 mm.), $n^{27}D$ 1.5631.

The **α-naphthylurethan** was prepared as above, and melted at 129.3–129.6°.

Anal. Calcd. for $C_{21}H_{17}Cl_2NO_2$: C, 65.29; H, 4.44; N, 3.63. Found: C, 65.32; H, 4.72; N, 3.82.

Separation of 6-Allyl-3-methylphenol (E) and 2-Allyl-3-methylphenol (D) by Vapor Phase Chromatography.—The determination of isomer ratios and the separations were made on an A-110C Aerograph instrument equipped with a disc integrator and a Brown recorder. A 6-ft.-25% Reoplex 400 on chromosorb column was used for determining the isomer ratios, while a 12 ft. × ⅜ in. Reoplex 400 preparative column was used to effect the separations. When determining the isomer ratio, optimum results were obtained with 0.1 to 3- μl. samples, a flow rate of 57 cc./min., and a temperature within the range of 142–158°. The retention times at 142° were 49.1 and 54.9 min.

The rearrangement of C without solvent showed, on 18 vapor phase chromatography analyses, 44.1 ± 3.6% (average deviation) of the 6-allyl isomer E and 55.9 ± 3.6% of the 2-allyl compound D. This same rearrangement, when carried out in dimethylaniline, showed 47 ± 1.3 % of E and 53 ± 1.3% of D. The maximum value for E was 49.2%, while the minimum was 42.9%.

The material from the first vapor phase chromatography peak (E) was identical (melting point, infrared spectrum, α-naphthylurethan) with that obtained by cooling the crude reaction mixture. Its properties are described above. The 2-allyl compound (D), obtained from the second peak, was a liquid, $n^{28}D$ 1.5315. The **α-naphthylurethan** was prepared as above and melted at 144–144.5°.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.64; H, 6.22; N, 4.70.

Preparation of 2-Propyl-3-methylphenol (H).—I. By Catalytic Reduction of 2-Allyl-3-methylphenol (D).—The sample from the second peak from the vapor phase chromatography separation (44 mg.), 2-allyl-3-methylphenol, was reduced catalytically with platinum and hydrogen in 20 ml. of ethyl ether as solvent. The product, m.p. 29–32°, had an infrared spectrum in carbon tetrachloride solution identical to that of the product obtained from dechlorination of G, below.

II. By Action of Hydrazine and Palladium on 2-Allyl-3-methyl-4,6-dichlorophenol (G).—The phenol G (2.81 g.) was refluxed for 136 hr. in 60 ml. of Methyl Cellosolve with 1 g. of palladium on charcoal (5%) and 12 ml. of hydrazine (99%). Hydrazine was added after 22 hr. (10 ml.), 45 hr. (8 ml.), 70 hr. (10 ml.), and finally after 120 hr. (5 ml.). The reaction mixture was then filtered and the solvent removed under vacuum. Water (20 ml.) was added to the resulting solid, and the solution was extracted with ether (100 ml.). The ether was dried and, after filtering, the ether was evaporated. The product, 2-propyl-3-methylphenol, was distilled and collected on a cold finger to yield 1.45 g. (75%) of a white solid, m.p. 34–35°.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.48; H, 9.37.

A vapor phase chromatography analysis of this solid showed greater than 99.3% purity and 100% reduction. (The retention times of the impurities were much less than the retention time of the reduced compound. From previous experiments, these impurities do not appear to be partial reduction products or unreacted starting material.) The conditions for the vapor phase chromatography separation were the same as those reported above.

The α-naphthylurethan of 2-propyl-3-methylphenol melted at 128.5–129°.

Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.87; H, 6.84; N, 4.58.

This α-naphthylurethan showed a marked mixed m.p depression with the α-naphthylurethan of 2-allyl-3-methyl-4,6-dichlorophenol and showed no depression with the α-naphthylurethan prepared from the compound obtained by catalytic reduction of 2-allyl-3-methylphenol.

(15) *Cf.* D. S. Tarbell, R. C. Mallatt, and J. W. Wilson, *J. Am. Chem. Soc.*, **64**, 2229 (1942).