[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY, EAST LANSING, MICH.]

Alkylation of Phenol with a Homoallylic Halide[1,2]

BY HAROLD HART, JAMES L. CORBIN, CHARLES R. WAGNER, AND CHING-YONG WU

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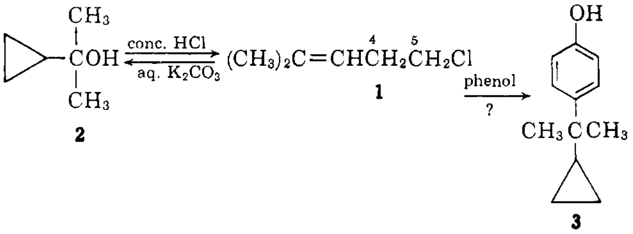
Phenol reacts with 2-methyl-5-chloro-2-pentene (1) to give 5,5-dimethylhomochroman (4), 1,1-dimethyl-5-tetralol (7), and 1,1-dimethyl-7-tetralol (10) in nearly equal amounts, without benefit of a Friedel-Crafts type catalyst. The products may be rationalized in terms of nucleophilic attack by the oxygen or *ortho* or *para* carbon atom of phenol on the primary carbon atom of the homoallylic cation derived from 1. Deuterium labeling experiments showed that carbons 4 and 5 of 1 become equivalent under the reaction conditions.

Tertiary, allyl, or benzyl halides are known to alkylate aromatic compounds which are highly susceptible to electrophilic attack, such as phenol, without benefit of the usual Friedel–Crafts type of catalyst. Thus *t*-butyl chloride,[3] α-phenethyl chloride,[4] or trityl chloride,[5] when heated with phenol, evolve hydrogen chloride and give nuclearly alkylated phenols. Presumably phenol is a sufficiently potent ionizing solvent to furnish kinetically significant quantities of carbonium ions from reactive alkylating agents.

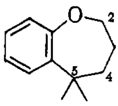
It was the purpose of the present research to extend this reaction to homoallylic halides, which are known to be particularly reactive in solvolysis reactions.[6] 2-Methyl-5-chloro-2-pentene (1) was selected as the halide for study, because although it is a primary chloride, it might be expected to furnish the tertiary dimethylcyclopropylcarbinyl cation in ionizing solvents, and the latter ought spontaneously to alkylate phenol.[3-5] Support for this expectation comes from the reconversion of 1 to dimethylcyclopropylcarbinol (2) on alkali treatment.[7] Accordingly, 1 was heated with an excess of phenol, with the anticipation that 3 would be the predominant reaction product. In fact three products were obtained, none of which was 3; it is the purpose of this paper to describe the results and some mechanistic studies of this reaction.



Results

When 1 was heated with a four-mole excess of phenol at 150°, hydrogen chloride evolved rapidly. Treatment of the reaction mixture led to a neutral and a phenolic fraction.

The Neutral Product.—The neutral product (28% yield) was shown to be the previously unknown 5,5-dimethylhomochroman 4, the structural assignment being based on the following evidence. Infrared bands indicated that the compound was an aromatic ether, a 1,2-disubstituted benzene, and had a *gem*-dimethyl group. The n.m.r. spectrum was consistent with 4 and eliminated 5, a possible rearrangement product,[8] or structures analogous to 4 and 5 with reverse orientation of the *gem*-dimethyl group. The spectrum had a sharp singlet at 8.67 τ (6 methyl protons) and a triplet at 6.14 τ (methylene adjacent to oxygen) as well as complex multiplets at 8.1–8.5 τ (4 aliphatic protons) and 2.8–3.2 τ (4 aromatic protons). Finally, 4 was synthesized independently as shown. Reaction of chloride 1 with phenol under alkaline conditions gave the liquid ether 6, whose structure was proved by hydrogenation to phenyl isohexyl ether. Although 6 was not altered by treatment with hydrogen chloride at 150°, treatment with a drop of sulfuric acid at room temperature gave a nearly quantitative yield of 4. The ultraviolet absorption spectrum[9] and remarkable basicity[10] of 4 have been discussed elsewhere.



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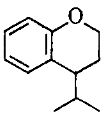
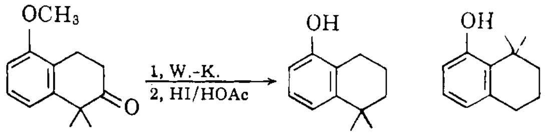


5

$$1 + C_6H_5OH \xrightarrow[K_2CO_3]{\text{acetone}} \underset{6}{C_6H_5OCH_2CH_2CH{=}C(CH_3)_2} \xrightarrow{H^+} 4$$

The Phenolic Products.—The first phenol isolated from the reaction (29% yield) had a melting point of 113–114°, was isomeric with 4, and readily formed a number of phenolic derivatives. Its ultraviolet absorption spectrum lacked a band in the 287–290 mμ region, eliminating structures (such as 3) with an alkyl group *para* to the hydroxyl.[11] The infrared spectrum indicated 1,2,3-substitution of the benzene ring, making unlikely position isomers of 3, and the n.m.r. spectrum showed only three aromatic protons (3.1–3.6 τ). The remainder of the n.m.r. spectrum was consistent with either 7 or 8. The latter seemed unlikely in view of the ease with which the compound formed typical phenolic derivatives. Structure 8 was also inconsistent with the shift in λ_{max} from 274 to 291 mμ when an ethanolic solution of the phenol was made 0.1 *N* in sodium hydroxide.[12] Finally, the structure was confirmed by independent synthesis *via* Wolff–Kishner reduction of 1,1-dimethyl-5-methoxy-2-tetralone (9)[13] followed by acid cleavage of the ether.



9 7 8

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[1] For a preliminary report of this work, see J. L. Corbin, H. Hart, and C. R. Wagner, *J. Am. Chem. Soc.*, **84**, 1740 (1962).

[2] We are indebted to the Petroleum Research Fund of the American Chemical Society (Grant 488-C) and to the National Science Foundation (G 14289) for financial support.

[3] H. Hart and J. H. Simons, *J. Am. Chem. Soc.*, **71**, 345 (1949).

[4] H. Hart, W. L. Spliethoff, and H. S. Eleuterio, *ibid.*, **76**, 4547 (1954).

[5] H. Hart and F. A. Cassis, *ibid.*, **76**, 1634 (1954).

[6] For a leading reference, see S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

[7] T. A. Favorskaya and Sh. A. Fridman, *Zh. Obshchei Khim.*, **15**, 421 (1945).

[8] *Cf.* H. A. Bruson and J. W. Kroeger, *J. Am. Chem. Soc.*, **62**, 36 (1940).

[9] H. Hart and C. R. Wagner, *Proc. Chem. Soc.*, 284 (1958).

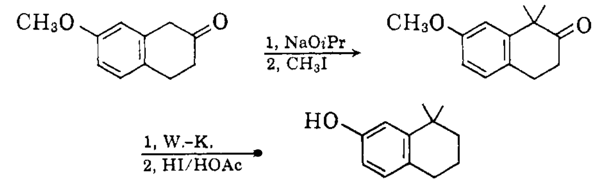
[10] E. M. Arnett and C-Y. Wu, *J. Am. Chem. Soc.*, **82**, 5660 (1960).

[11] H. Hart, *Anal. Chem.*, **24**, 1500 (1952); H. Hart and E. A. Haglund, *J. Org. Chem.*, **15**, 396 (1950).

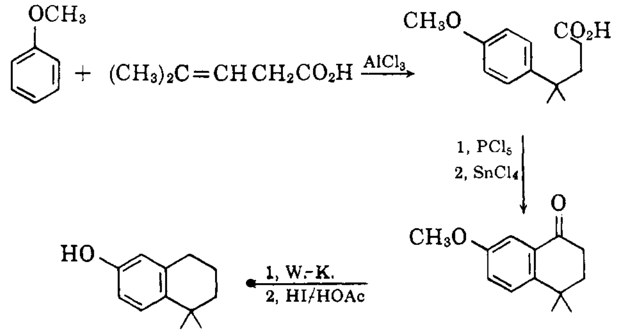
[12] Unhindered phenols show a bathochromic shift of about 16–20 mμ in 0.1 *N* base, whereas hindered or partially hindered phenols may require 0.5 *N* base or more to show a similar shift: N. D. Coggeshall and A. S. Glessner, *J. Am. Chem. Soc.*, **71**, 3150 (1949).

[13] J. W. Cornforth, R. H. Cornforth, and R. Robinson, *J. Chem. Soc.*, 689 (1942).

During the structural work on ether **4**, an attempt to cleave it with hydrogen bromide in acetic acid led to a small amount of a phenol, m.p. 83.3–83.9°, isomeric with **7**. Larger amounts were obtained by one of us,[14] by passing hydrogen chloride into a heated mixture of phenol and 2,2-dimethyltetrahydrofuran. This material appeared to be a *p*-alkylated phenol (λ_{max} at 287 mμ) except that the intensity of this long wave length band (ϵ 1033) was only a little over half that of the band at 279 mμ (ϵ 1714), whereas these bands usually have comparable intensities.[15] This led to the suspicion that, despite the sharp melting point, the material was a mixture. The methyl ether (a liquid) was prepared, but it showed only one symmetrical peak on gas chromatography. However, a methylene chloride solution of the phenol itself was ultimately resolved into two peaks with equal areas; one of these was due to the already identified tetralol **7**. The other led to isolation of an isomeric phenol, m.p. 105–106°, which proved to be identical with an independently synthesized sample of 1,1-dimethyl-7-tetralol (**10**). The alternative structure **11**, which could not be discounted either on the basis of ultraviolet or n.m.r. spectrum, was synthesized for comparison. It melted at 93–94°, had a slightly different retention time from **10**, and its infrared spectrum was clearly distinguishable from that of **10**; these data eliminated **11** as the structure of the alkylation product. Finally, an equimolar mixture of **7** and **10**, when recrystallized from pentane, gave sharp melting crystals, m.p. 83–84°, which showed no depression with, and had the identical infrared spectrum as, the phenol mixture first isolated.



10



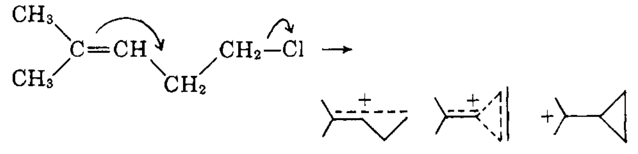
11

Since **10** was obtained only by an indirect route, the original alkylation of phenol with **1** was repeated, and the crude reaction mixture subjected directly to gas chromatography. Peaks corresponding to the three major products **4**, **7**, and **10** showed that they were formed in nearly equal amounts and accounted for about 90% of the product; two minor products, with extremely long retention times and probably corresponding to the reaction of two moles of **1** with one of phenol, were not identified.

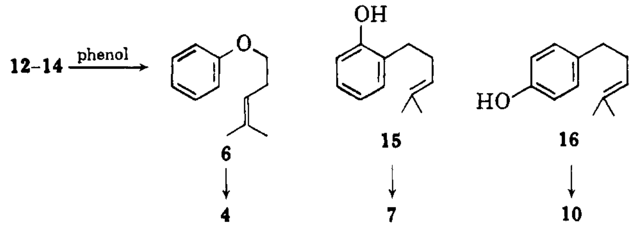
Discussion

The three products **4**, **7**, and **10** obtained from the alkylation of phenol with 2-methyl-5-chloro-2-pentene (**1**) are remarkable in several respects. One is the facile formation of the seven-membered ring in **4**. This ether is not easily cleaved, and is not an intermediate in the formation of phenols **7** and **10**, for it was recovered (over 80%) when subjected to the alkylation conditions.

The *meta* orientation of the carbon bearing the *gem*-dimethyl group in the phenolic products made it clear that, although the double bond was necessary for the reaction (the saturated analog did not react), the latter was not initiated by addition of a proton to the double bond of **1**, followed by electrophilic attack on phenol. All three products could be accommodated by assuming ionization of **1** to a homoallylic cation which might be either unsymmetrical (**12**) or become symmetrical *via* **13** or **14**.[16] Nucleophilic attack at the primary carbon of **12–14** by the oxygen, the *ortho*, or the *para* carbon of phenol would lead to three olefins, **6**, **15**, and **16**, which, in the acidic medium, could cyclize to the observed products. No isomers other than those predicted by this mechanism were observed.



12 **13** **14**



In order to test whether the intermediate was unsymmetrical (**12**) or symmetrical (**13** or **14**), the alkylation was run with 2-methyl-5-chloro-2-pentene-5-d_2 (**17**), synthesized as shown in the scheme. The synthesis was unexceptional in all stages but the last where in fact isomerization of the double bond and of the deuterium label were possibilities. The tertiary alcohol was dehydrated by distillation from freshly fused potassium bisulfate. The major product (gas chromatography) was the desired chloroolefin, but it was contaminated with some 1-olefin (**18**) and 2,2-dimethyltetrahydrofuran. The latter, and most of the former, were removed by preparative gas chromatography. Integration of the n.m.r. spectrum of the purified product showed that it consisted of 79% of the desired **17** (appropriately split vinyl hydrogen at 4.48 τ and allylic methylene at 7.58 τ) contaminated with 13% of the 1-olefin **18** (terminal methylene at 5.28 τ) and 8% of material unlabeled at C-5 (6.48 τ). Since the

$$\begin{tikzcd}
BrCH_2CH_2CO_2C_2H_5 \arrow[r, "\text{1, LiAlD}_4\text{–AlCl}_3", "\text{2, SOCl}_2\text{; 3, KCN}"'] & CNCH_2CH_2CD_2Cl \arrow[d, "\text{1, }C_2H_5OH/HCl"', "\text{2, }CH_3MgI"] \\
\underset{\textbf{17}}{(CH_3)_2C{=}CHCH_2CD_2Cl} & (CH_3)_2C(OH)CH_2CH_2CD_2Cl \arrow[l, "KHSO_4"']
\end{tikzcd}$$

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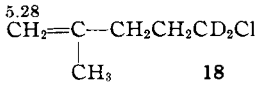
[14] H. Hart, unpublished results.

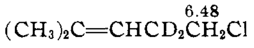
[15] *Cf.* R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, plates 34, 42, 50, 52.

[16] The precise structure of this ion, other than whether or not carbon atoms 4 and 5 of the chloroolefin **1** become equivalent, was not of concern here. For discussion of this problem, see ref. 6, as well as M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 3671 (1961); S. Borčić, M. Nikoletić, and D. E. Sunko, *ibid.*, **84**, 1615 (1962); R. A. Sneen, K. M. Lewandowski, I. A. I. Taha, and B. R. Smith, *ibid.*, **83**, 4843 (1961); G. Witham, *Proc. Chem. Soc.*, 422 (1961); 330 (1962).



$\overset{5.28}{\mathrm{CH_2}}{=}\underset{\mathrm{CH_3}}{\mathrm{C}}\mathrm{-CH_2CH_2CD_2Cl}$

18

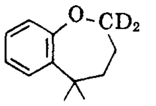


$\mathrm{(CH_3)_2C{=}CHCD_2\overset{6.48}{CH_2}Cl}$

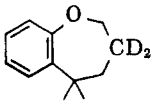
19

n.m.r. spectra of previous intermediates in the synthesis all showed complete label at this carbon, the small amount of unlabeled chloride is presumably due to **19** formed by partial interconversion of C-4 and C-5 during the dehydration step.[17]

The crude chloride (79% **17**, 13% **18**, 8% **19**) was used to alkylate phenol. The 5,5-dimethylhomochroman, isolated by gas chromatography, had an n.m.r. spectrum which showed it to be a 50:50 mixture of **4a** and **4b**. Pertinent bands were a singlet at 6.15 τ



4a

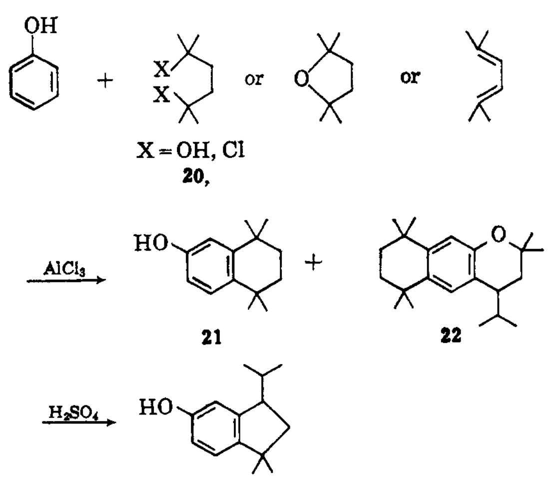


4b

and a complex multiplet at 8.1–8.5 τ with relative areas 1:3. These data are consistent with an average of one proton α to the oxygen, always adjacent to a labeled carbon (as in **4b**); in unlabeled **4**, the α-methylene appears as a triplet. Similar results were obtained for the phenolic products **7** and **10** and are described in the Experimental part.

From these results it is clear that carbons 4 and 5 of **1** become equivalent during its reaction with phenol. The question remained whether this equilibration might not in fact occur prior to the alkylation step, *via* ionization (to **13** or **14**) followed by return to a mixture of **17** and **19** by recombination with chloride ion. This was indeed the case. Labeled chloride recovered (90%) after heating with excess phenol at 125° for 10 min., conditions which gave no detectable alkylation, was a 50:50 mixture of **17** and **19**, as indicated by its n.m.r. spectrum. The alkylation, then, seems to involve rapid and reversible ionization of **1**, with rate-determining nucleophilic attack of phenol on a primary carbon of the carbonium ion.[18]

Finally, mention should be made of the relation between our work and earlier experiments on "cyclialkylation." The term was coined by Bruson and Kroeger[8] to describe the formation of cyclic products from the reaction of a bifunctional alkylating agent with an aromatic compound. For example, they reported that 2,5-dimethylhexyl-2,5-dichloride **20** (or the corresponding diol, diene, or tetrahydrofuran) reacted with phenol and a Friedel–Crafts catalyst to give products with additional rings, formulated as **21–23**. Although these structures were not rigorously proved, the evidence for formation of additional carbocyclic rings is good. Chloride **20** is structurally related to **1**, except that both reaction sites are tertiary, whereas in our chloride, one is tertiary, the other primary. Cyclialkylation *via* **20** and also *via* hydride transfer[19] or dienes[20] may involve ordinary carbonium ions; whether these, or cyclopropylcarbinyl cations, are involved probably depends on whether the involved carbon atoms are primary, secondary, or tertiary.



X = OH, Cl

20,

21

22

23

Experimental[21]

Alkylation of Phenol with 2-Methyl-5-chloro-2-pentene (1).—A solution of 15.7 g. (0.133 mole) of 2-methyl-5-chloro-2-pentene in 64 g. (0.68 mole) of phenol was heated at 150° for 12 hr., during which time hydrogen chloride evolved. After cooling, residual hydrogen chloride was removed by aspiration for several minutes. The crude reaction mixture on gas chromatography (10% silicone, 181°) showed three main products (90%) in approximately equal amounts (retention times 15, 50, and 56 min.), in addition to unreacted phenol and two minor products (10%) with retention times 98 and 137 min. The latter were not investigated.

The reaction mixture was dissolved in 200 ml. of methylene chloride and extracted once with 250 ml. of 20% aqueous potassium hydroxide, followed by extraction with Claisen solution.[22] After drying (sodium sulfate) and removal of the solvent from the neutral fraction, there was isolated 6.5 g. (28%) of 5,5-dimethylhomochroman (**4**), b.p. 85–95° at 1.9 mm., m.p. 47–48° after recrystallization from petroleum ether (30–60°). It showed infrared bands at 1382 and 1368 cm.$^{-1}$ (*gem*-dimethyl), 1286 and 1226 cm.$^{-1}$ (aromatic ether), 1980, 1945, 1910, 751 cm.$^{-1}$, and no band at 700 cm.$^{-1}$ (1,2-disubstitution on the benzene ring). The ultraviolet absorption maxima in cyclohexane appeared at 271.5 mμ (ϵ 725) and 266 mμ (ϵ 700). The n.m.r. spectrum in carbon tetrachloride showed a sharp singlet at 8.67 τ (*gem*-dimethyl; seven-membered ring "flipping" rapidly so that these are equivalent at room temperature), complex multiplet at 8.2–8.5 τ (4 methylene protons), triplet at 6.14 τ (methylene α to the oxygen), and complex pattern at 2.8–3.2 τ (4 aromatic protons).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.99; H, 9.10.

The alkaline extracts were acidified with hydrochloric acid and the organic product was taken up in methylene chloride and dried over sodium sulfate. Removal of the solvent and unreacted phenol using a Vigreux column and reduced pressure left a residue which gave 6.7 g. (29%) of 1,1-dimethyl-5-tetralol (**7**), b.p. 85–95° at 0.08 mm., m.p. 112.5–113.5° from hexane. Its infrared spectrum showed bands at 3600, 1264 cm.$^{-1}$ (phenolic hydroxyl) and 1389, 1368 cm.$^{-1}$ (*gem*-dimethyl group), and a 5–6 μ pattern characteristic of 1,3- or 1,2,3-substitution on benzene.[23] The ultraviolet spectrum in cyclohexane showed maxima at 278.5 mμ (ϵ 1340) and 271.5 mμ (ϵ 1290). The broad λ_{max} at 274 mμ in ethanol was shifted to 291 mμ in 0.1 *N* ethanolic sodium hydroxide. The n.m.r. spectrum in carbon tetrachloride had a sharp singlet at 8.80 τ (*gem*-dimethyl), a broad multiplet 8.2–8.4 τ (4 aliphatic methylene protons), a triplet at 7.43 τ (2 benzylic protons), a singlet at 5.01 τ (hydroxyl), and a multiplet at 3.1–3.7 τ (3 aromatic protons).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.73; H, 9.32.

Compound **7** formed an aryloxyacetic acid derivative, m.p. 141–142° from water; neut. equiv. calcd. 234.1, found 236.2, 236.7. It also gave a β-naphthylurethan, m.p. 164–165° from ethanol, and a benzoate, m.p. 84–85° from aqueous ethanol.

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[17] An attempted synthesis of **17** by reaction of 2,2-dimethyltetrahydrofuran-5-d_2 with Lucas reagent gave complete equilibration of **17** and **19**.

[18] The reaction cannot simply involve S$_N$2 attack at C_5 followed by ring closure, with the ionization equilibrium as an unrelated side reaction, because the saturated analog of **1** did not alkylate phenol.

[19] L. R. C. Barclay, J. W. Hilchie, A. H. Gray, and N. D. Hall, *Can. J. Chem.*, **38**, 94 (1960), and references cited therein.

[20] T. F. Wood and J. Angiolini, *Tetrahedron Letters*, 1 (1963).

[21] Melting points are uncorrected. Analyses are by Spang Microanalytical Laboratory, P. O. Box 1111, Ann Arbor, Mich. The n.m.r. spectra were obtained on either a Varian Model A-60 or HR-60 instrument, using tetramethylsilane as an internal reference. Infrared spectra were determined on a Perkin–Elmer Model 21 instrument, using sodium chloride cells; ultraviolet spectra were obtained on a Beckman DK-2, but extinction coefficients were measured more accurately on a Beckman DU instrument. Gas chromatographic separations were made on a Perkin–Elmer Model 154 or Beckman Megachrom, usually on columns packed with 10% silicone on Chromosorb W.

[22] G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945).

[23] C. W. Young, R. B. Der Vall, and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

Anal. Calcd. for $C_{23}H_{23}NO_2$ (urethan): C, 79.95; H, 6.71. Found: C, 79.48; H, 6.99. Calcd. for $C_{19}H_{20}O_2$ (benzoate): C, 81.40; H, 7.19. Found: C, 81.13; H, 7.27.

In addition to **7**, a higher boiling phenolic fraction (95–115° at 0.08 mm.) amounting to 4.0 g. was collected; it partially solidified and was mainly 1,1-dimethyl-7-tetralol (**10**) as described in another part of the Experimental section.

2-Methyl-5-phenoxy-2-pentene (**6**).—A mixture of 96.7 g. (0.7 mole) of anhydrous potassium carbonate, 47 g. (0.5 mole) of phenol, 59.2 g. (0.5 mole) of 2-methyl-5-chloro-2-pentene, and 140 ml. of acetone was stirred at reflux for 4 days. The cooled reaction mixture was added to 200 ml. of water and extracted with several portions of ether. The combined ether layers were washed with 20% aqueous sodium hydroxide, dried over sodium sulfate, and distilled. There was recovered 28.6 g. (48%) of unreacted chloride and 33.5 g. (79% based on unrecovered chloride) of **6**, b.p. 85–90° at 1 mm., $n^{20}D$ 1.5112.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.76; H, 9.09.

Hydrogenation (ethanol, platinum oxide, low pressure) gave phenyl isohexyl ether, b.p. 77–80° at 1 mm., $n^{25}D$ 1.4883, which curiously does not seem to have been reported previously.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.17. Found: C, 80.48; H, 10.25.

Its structure in turn was proved by cleavage with 48% hydrobromic acid to phenol (60%) and isohexyl bromide (68%), which, *via* its Grignard reagent, was converted by conventional methods to 5-methylhexanoamide, m.p. 101–102° from aqueous ethanol (lit.[24] 102–103°).

5,5-Dimethylhomochroman (**4**) **from 2-Methyl-5-phenoxy-2-pentene** (**6**).—To 0.5 g. of **6** there was added, at room temperature, 2 drops of concentrated sulfuric acid. After several minutes, water was added and the crystalline product, separated and recrystallized, gave 0.45 g. of **4**, m.p., m.m.p. 47–48°, infrared identical with the product obtained from the alkylation reaction.

Compound **6** was recovered (97%) after bubbling hydrogen chloride through a sample (no solvent) heated at 150° for 5 hr.

1,1-Dimethyl-5-tetralol (**7**) **from 1,1-Dimethyl-5-methoxy-2-tetralone** (**9**).—A mixture of 1.4 g. (6.9 mmoles) of 1,1-dimethyl-5-methoxy-2-tetralone,[13] 2.0 ml. of 85% hydrazine, 2.4 g. of potassium hydroxide, and 18 ml. of ethylene glycol was refluxed for 3 hr. After distillation until the pot temperature reached 190° and further reflux for 2.5 hr., the cooled reaction mixture was extracted with ether, and the combined ether extracts were washed with water and dried over sodium sulfate. Removal of the solvent left a residue of 1.0 g. (77%) of crude 1,1-dimethyl-5-methoxytetralin (infrared showed no carbonyl) which was cleaved directly by refluxing for 2 hr. with 4 ml. of hydriodic acid in 4 ml. of glacial acetic acid. Dilution with water and recrystallization from hexane gave 0.5 g. of **7**, colorless needles, identical with product from the alkylation (m.p., m.m.p., infrared spectrum). In the n.m.r. spectrum in carbon tetrachloride, which was consistent with the structure, the methyl protons appeared at 8.79 τ and the benzylic methylenes at 7.43 τ.

Cleavage of 5,5-Dimethylhomochroman.—A solution of 4 g. of 5,5-dimethylhomochroman, 33 ml. of glacial acetic acid, and 18 ml. of 48% hydrobromic acid was refluxed for 30 hr. From the phenolic product worked up in the usual manner, there was isolated 1.2 g. of material, m.p. 83.3–83.9° from petroleum ether (30–60°) which, although it appeared to be a single compound, was shown to be a 1:1 mixture (see below) of 1,1-dimethyl-5-tetralol and 1,1-dimethyl-7-tetralol.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.43; H, 9.40.

The ultraviolet spectrum had maxima at 287 mμ (ϵ 1033), 279 mμ (ϵ 1714), and 273 mμ (ϵ 1336). A methylene chloride solution gas chromatographed on 10% silicone at 181° showed two peaks nearly equal in area, with retention times of 50 and 56 min. The compounds were separated in this way, and the former shown to be (retention time, infrared) identical with 1,1-dimethyl-5-tetralol (**7**) previously obtained. The latter was identical (infrared) with synthetic 1,1-dimethyl-7-tetralol (**10**) and was different in retention time (56 *vs.* 57 min.) and infrared spectrum from synthetic 1,1-dimethyl-6-tetralol (**11**) (see below).

5,5-Dimethylhomochroman was recovered (83%) when its solution (6.6 g., 0.037 mole) in 7.0 g. (0.075 mole) of phenol was heated at 150° and treated with gaseous hydrogen chloride for 5 hr. Neither tetralol (**7** or **10**) was formed under these conditions.

1,1-Dimethyl-7-tetralol (**10**).—A solution of 18.4 g. (0.104 mole) of 7-methoxy-2-tetralone[25] in 30 ml. of isopropyl alcohol was added with stirring to a cooled sodium isopropoxide solution prepared by dissolving 5.1 g. (0.22 mole) of sodium in 100 ml. of absolute isopropyl alcohol. Methyl iodide (45 g., 0.32 mole) was added dropwise to the orange solution, which became colorless as sodium iodide precipitated. The mixture was refluxed 2 hr., cooled, and 5 ml. of sulfuric acid in 300 ml. of water was added. The organic layer and ether extracts were combined, washed with water, and dried over sodium sulfate. After removal of the solvent *in vacuo*, the residue was distilled through a vacuum-jacketed tantalum spiral column, yielding 16 g. (76%) of colorless liquid, b.p. 99–101.5° at 0.4 mm., which crystallized on standing. Recrystallization from dilute methanol, then petroleum ether (30–60°), gave colorless needles of 1,1-dimethyl-7-methoxy-2-tetralone, m.p. 53.5–54.3°. Its infrared spectrum had bands at 1385 and 1364 cm.$^{-1}$ (*gem*-dimethyl group).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; OCH_3, 15.18. Found: C, 76.32; H, 7.73; OCH_3, 15.04.

It gave an oxime in the usual way; m.p. 148–149° from petroleum ether (60–90°).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.34; H, 7.80; N, 6.45.

A mixture of 4.4 g. (0.0216 mole) of the ketone, 5.5 ml. of 85% hydrazine, 7.5 g. of potassium hydroxide, and 55 ml. of ethylene glycol was refluxed for 30 min. Water and hydrazine were distilled until the pot temperature reached 186°, after which reflux was continued for 2 hr. After cooling, 60 ml. of water was added and the solution extracted with ether, the extracts were dried (sodium sulfate) and distilled, yielding 3.0 g. (73%) of crude 1,1-dimethyl-7-methoxytetralin (no C=O in the infrared). The crude ether (2.0 g., 0.0105 mole) was refluxed with 10 ml. of 47% hydriodic acid and 25 ml. of glacial acetic acid for 8 hr. Ice was added, and the crystals which separated were recrystallized from petroleum ether (60–90°) yielding 1.5 g. (81%) of colorless needles of 1,1-dimethyl-7-tetralol (**10**), m.p. 105–106°. The infrared spectrum in carbon disulfide showed a hydroxyl band (2.8 μ). The spectrum was superimposable on that of the product isolated from gas chromatography of the alkylation product. The ultraviolet maxima in cyclohexane were at 287.5 mμ (ϵ 2140), 279.5 mμ (ϵ 2270), and 272.5 mμ (ϵ 1590). In the n.m.r. spectrum in carbon tetrachloride, which was consistent with the structure, the *gem*-dimethyl appeared at 8.88 τ and the benzylic methylenes at 7.38 τ.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.63; H, 9.11.

The phenol gave an aryloxyacetic acid derivative in the usual way; m.p. 180–182° from aqueous ethanol. This was identical (m.p.) with the same derivative prepared from **10** isolated from the alkylation reaction.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.76.

A mixture of 50 mg. of **10** and 50 mg. of **7**, recrystallized from 2 ml. of hexane, gave 90 mg. of product, m.p. 83–84°, which was identical (m.m.p., infrared spectrum) with the mixture isolated from the cleavage of **4** with HBr–acetic acid (*vide supra*).

1,1-Dimethyl-6-tetralol (**11**).—To a mixture of 5.0 g. (0.038 mole) of aluminum chloride and 95 ml. of anisole, cooled to 0°, was added dropwise 10 g. (0.088 mole) of 4-methyl-3-pentenoic acid.[26] Another 5 g. of aluminum chloride was added and the dark solution stirred for 4 hr. at 0°, then 5.5 hr. at room temperature. Hydrochloric acid (1:1) was added until the precipitated salts dissolved. The organic layer was washed with dilute acid, then water, and extracted with 10% sodium hydroxide. Acidification of the alkaline extract, and extraction with ether, led to 15.4 g. of crude semisolid acid which, on recrystallization from petroleum ether (30–60°), gave 12.0 g. (72%) of 4-methyl-4-(*p*-methoxyphenyl)-pentanoic acid, m.p. 65–66° (lit.[27] value 66.5–67°); neut. equiv. calcd. 222, found 220.

A solution of 5.0 g. (0.0225 mole) of this acid in 20 ml. of benzene was treated at 0° in small portions with 5.5 g. (0.025 mole) of phosphorus pentachloride. The mixture was stirred for 45 min. at room temperature, refluxed for 5 min., then cooled to 0°, and a solution of 6 ml. of stannic chloride in 8 ml. of benzene was added rapidly. The maroon reaction mixture was stirred for 1 hr. at 0° and 15 g. of ice was added, followed by 25 ml. of concentrated hydrochloric acid. The organic layer was washed successively with 20% hydrochloric acid, water, saturated sodium bicarbonate, and water, dried over Drierite, and the solvent removed (rotary evaporator). Distillation of the residue gave 3.7 g. (83%) of pale yellow 4,4-dimethyl-7-methoxy-1-tetralone, b.p. 107–108° at 0.1 mm., $n^{15}D$ 1.5565, with a carbonyl band at 5.92 μ. Its oxime melted at 97–98°, recrystallized from hexane.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 70.96; H, 7.80; N, 6.33.

The ketone was reduced and cleaved with hydriodic acid in a procedure analogous to that described above for the preparation of **10**. From 2.0 g. of 4,4-dimethyl-7-methoxy-1-tetralone there was obtained 0.6 g. of colorless needles of 1,1-dimethyl-6-tetralol (**11**), m.p. 93–94° from hexane. The infrared spectrum had

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bands at 2.80 μ (hydroxyl), 7.22, and 7.32 μ (*gem*-dimethyl group), and 11.45 and 12.52 μ (1,2,4-trisubstitution). It differed markedly in the fingerprint region from the spectrum of the 7-isomer. The ultraviolet maxima (cyclohexane solvent) were at 286 mμ (ϵ 2140), 279.5 mμ (ϵ 2010), 278 mμ (ϵ 2020), and 272 mμ (ϵ 1490).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.22.

The phenylurethan melted at 136–137° (hexane).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74. Found: C, 76.93; H, 7.16; N, 4.98.

3-Bromopropanol-1-d_2.—The procedure of Nystrom[28] for the unlabeled compound was followed. From 23 g. (0.127 mole) of ethyl 3-bromopropionate, 9.8 g. (0.074 mole) of aluminum chloride, and 3.3 g. (0.078 mole) of lithium aluminum deuteride there was isolated 14.8 g. (78.4%) of the bromo alcohol, b.p. 71.5–74° at 10 mm., $n^{22}D$ 1.4840, with C–D bands at 4.52 and 4.74 μ in the infrared. The n.m.r. spectrum in carbon tetrachloride showed a broadened triplet at 7.96 τ (central methylene), a sharp triplet at 6.49 τ ($-CH_2Br$), and a sharp singlet at 6.27 τ (OH) with the correct relative areas.

1-Bromo-3-chloropropane-3-d_2.—Thionyl chloride (14.4 ml., 0.20 mole) was added at 0° dropwise over 45 min. to 14.6 g. (0.0969 mole) of 3-bromopropanol-1-d_2 containing 5 drops of pyridine. The mixture was stirred at room temperature for 8 hr., then refluxed for 2 hr. Hydrolysis on 30 g. of ice followed by extraction with pentane and drying over sodium sulfate gave 13.6 g. (83.5%) of product, b.p. 51–55° at 32 mm. This was, by gas chromatography (20% silicone, 130°), 85% the desired product, and 15% a lower boiling component (dichloride). The n.m.r. spectrum in carbon tetrachloride showed a broad triplet at 7.74 τ (central CH_2) and a sharp triplet at 6.46 τ ($-CH_2Br$) with equal areas (very different from unlabeled chlorobromide, which is an $A_2B_2X_2$ system).

4-Chlorobutyronitrile-4-d_2.—The procedure was essentially that described for the unlabeled compound.[29] From 12.8 g. (0.076 mole) of 1-bromo-3-chloropropane-3-d_2 there was obtained 4.4 g. (56%) of the nitrile, b.p. 72–75° at 12 mm., $n^{23}D$ 1.4433. The n.m.r. spectrum in carbon tetrachloride showed an A_2B_2 pattern in the 7.4–8.1 τ region.

Ethyl 4-Chlorobutyrate-4-d_2.—The procedure was that of Fehnel[30] for unlabeled material. From 4.3 g. (0.041 mole) of 4-chlorobutyronitrile-4-d_2 there was obtained 5.2 g. (83.5%) of colorless ester, b.p. 69–70° at 9 mm., $n^{22}D$ 1.4320. The two methylenes of interest again gave an A_2B_2 pattern from 7.4–8.1 τ in the n.m.r. spectrum (carbon tetrachloride); in addition, there was a triplet at 8.74 τ and quartet at 5.90 τ for the ethyl group.

2-Methyl-5-chloro-2-pentene-5-d_2 (**17**).—A solution of 5.0 g. (0.033 mole) of ethyl 4-chlorobutyrate-4-d_2 in 30 ml. of ether was added dropwise (30 min.) at 0° to the Grignard reagent from 2.1 g. of magnesium and 13 g. of methyl iodide in 50 ml. of ether. The mixture was stirred for 30 min. at 0° and 2 hr. at room temperature, then hydrolyzed with 55 ml. of saturated ammonium chloride. Extraction with ether, drying (magnesium sulfate), and removal of the solvent afforded 5.4 g. of crude 2-methyl-5-chloro-2-pentanol-5-d_2 (OH, no C=O in the infrared).

The crude alcohol (4.0 g.) was distilled (50–140°) from 0.5 g. of freshly fused potassium bisulfate to give 2.7 g. of a pale yellow liquid which contained (gas chromatography) 2,2-dimethyltetrahydrofuran, 2-methyl-5-chloro-1-pentene-5-d_2, and mainly the desired 2-methyl-5-chloro-2-pentene-5-d_2. The latter was isolated (0.8 g.) by preparative gas chromatography (20% silicone, 115°, retention time 25 min.). Analysis of its infrared and n.m.r. spectra, as explained in the Discussion, showed that the sample consisted of 79% the desired material, 13% of the 1-olefin, and 8% of 2-methyl-5-chloro-2-pentene-4-d_2.

Alkylation of Phenol with 2-Methyl-5-chloro-2-pentene-5-d_2 (**17**).—A mixture of 4.0 g. of phenol and 0.50 g. of chloride (79% the desired isomer, as described immediately above) was heated for 8.5 hr. at 150°, then taken up in 15 ml. of methylene chloride and extracted successively with 10 ml. of 20% potassium hydroxide, two 4-ml. portions of Claisen solution, and water, then dried over sodium sulfate. The residue after removal of the solvent was purified by gas chromatography (175°, 20% silicone) to give 110 mg. (15%) of 5,5-dimethylhomochroman as colorless plates, m.p. 47–48°. The n.m.r. spectrum showed a sharp singlet at 8.66 τ (6 methyl protons), a multiplet at 8.1–8.5 τ (3 methylene protons), a singlet at 6.15 τ (1 proton on carbon adjacent to oxygen), and a complex aromatic spectrum, 2.7–3.2 τ (4 protons).

The alkaline extracts were acidified (hydrochloric acid), extracted with methylene chloride, dried, and distilled to remove most of the unreacted phenol. The residue was purified by gas chromatography (20% silicone, 181°) to give 50 mg. of a mixture of deuterated 1,1-dimethyl-5- and 7-tetralols, the former predominating. This, and the low yield, was a reflection not of the product ratio, but of insufficient heat on the exit line, which resulted in some loss of the 7-isomer. The n.m.r. spectrum in carbon tetrachloride showed a complex multiplet at 3.3–3.7 τ (3 aromatic protons), a sharp singlet at 5.28 τ (OH), a structured peak at 7.35–7.45 τ (1 benzylic proton), a complex multiplet at 8.2–8.6 τ (3 methylene protons), and two unequal peaks, singlets, at 8.77 and 8.84 τ (total 6 methyl protons), consistent with equilibration of carbon 3 and 4 of the tetralols.

In an interrupted alkylation, 2 ml. of unlabeled chloride (**1**) and 6 g. of phenol, heated in a sealed tube at 125° for 1 hr., gave, on gas chromatography, 0.7 g. of recovered chloride and 0.15 g. of crystalline 5,5-dimethylhomochroman. Under identical conditions and reactant ratios, using 0.7 g. of labeled chloride **17**, the recovered chloride was completely equilibrated at C-4 and C-5, as was clear from analysis of its n.m.r. spectrum. Finally, a sample of 0.7 g. of **17** was heated with 2 g. of phenol at 125° for 10 min. Under these conditions the amount of alkylation was negligible (gas chromatography). Yet the recovered (90%) chloride was completely equilibrated between **17** and **19** (n.m.r. analysis).

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[Contribution from the Chemistry Department, Duke University, Durham, N. C.]

Alkylations at the γ-Position of Acetoacetaldehyde and α-Benzylacetoacetaldehyde through their Dicarbanions[1]

By Thomas M. Harris, Sandra Boatman, and Charles R. Hauser

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The dicarbanion of acetoacetaldehyde, prepared from sodioacetoacetaldehyde and a molecular equivalent of potassium amide in liquid ammonia, was alkylated at the γ-position with benzyl, methyl, *n*-butyl, and *n*-octyl halides. The resulting monocarbanions were isolated as their copper chelates. Several were also isolated by cyclization with cyanoacetamide to form the cyanopyridones and by self-condensation to form the triacylbenzenes. Similarly, the dicarbanion of α-benzylacetoacetaldehyde underwent benzylation and butylation at the γ-position. This novel mode of alkylation through dicarbanions furnishes a useful method for the synthesis of a number of β-ketoaldehydes and their derivatives.

β-Diketones such as acetyl- and benzoylacetones have previously been alkylated at their terminal methyl group instead of at their more acidic methylene group by employing, as intermediates, their dicarbanions instead of their monocarbanions.[2] The dicarbanions were prepared by means of two molecular equivalents of an alkali amide in liquid ammonia (eq. 1).

$$RCOCH_2COCH_3 \xrightarrow[\text{liq. NH}_3]{2KNH_2} RCO\bar{C}HCO\bar{C}H_2 \xrightarrow[\text{2, NH}_4\text{Cl}]{\text{1, R}'\text{X}} RCOCH_2COCH_2R' \qquad (1)$$

In the present investigation the dicarbanions of certain β-ketoaldehydes were prepared and alkylated

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