A diglycerol column at 90° was used to separate the products of the 2-methylcyclohexanone reduction, and a Carbowax 20M column at 125° was used to separate the products in the cases of 3,3,5-trimethylcyclohexanone, norcamphor, and camphor.

Association.—The determination of the association of air- and moisture-sensitive compounds by ebullioscopic techniques is described elsewhere.[13,14] The association studies were carried out in tetrahydrofuran at a pressure of 740.0 mm.

Registry No.—I, 17476-04-9; II, 15649-65-7; $LiAl(OMe)_3H$, 12076-93-6; 2-methylcyclohexanone, 583-60-8.

Acknowledgment.—We wish to acknowledge the support of this work by the Petroleum Research Fund (Grant No. 3211-A3, 4) and the Quality Improvement Funds of the Georgia Institute of Technology.

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Structure and Synthesis of Kahweofuran, a Constituent of Coffee Aroma

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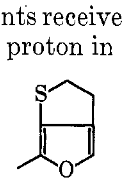
Received August 7, 1970

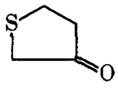
In the course of detailed analyses of coffee concentrates, a substance with the empirical formula C_7H_8OS, but of unknown constitution, was isolated.[1] In the present paper we outline work on the structure and synthesis of this aroma constituent which we have named kahweofuran (Arab. qahweh, coffee).

The infrared spectrum shows no absorptions which could be ascribed to hydroxyl, mercapto, or carbonyl functions, and it was concluded that both oxygen and sulfur atoms are part of heterocyclic rings. The much more revealing nuclear magnetic resonance spectrum exhibits a one-proton signal at δ 6.91 ascribable to a proton attached to either α or β position of a thiophene ring or to the α position of a furan ring.[2] No other aromatic protons are discernible and the unknown consequently is a trisubstituted furan or thiophene. One of these substituents is a methyl group and the chemical shift of the three-proton singlet (δ 2.17) agrees best with the presence of a 2-methylfuran or a 3-methylthiophene.[3] The remaining two substituents are part of a five-membered ring containing two carbon and one heteroatom. Resonances caused by protons attached to these two carbon atoms appear as a A_2B_2 pattern and comparison of the low-field signals centered at δ 3.57 with those present in the spectra of tetrahydrofuran and tetrahydrothiophene strongly suggest the presence of the latter part structure.[4] Structure **1** tentatively generated by these arguments receives further support from the fact that the furan proton in **1** couples to the high-field methylene protons with $J = 1.5$ Hz in full agreement with the situation encountered previously in 3-methylfuran where benzylic coupling to H_2 is 1.2 Hz, while coupling to H_4 is only 0.5 Hz.[5]



1

More definitive evidence in favor of structure **1** for kahweofuran was provided by synthesis. Condensation of 3-ketotetrahydrothiophene (**2**)[6] with ethyl acetate in the presence of sodium hydride gave a mixture of β diketones, containing 85% 2-acetyl-3-keto-tetrahydrothiophene (**3** and **4**) and 15% isomer **5**. The ultraviolet absorption maximum (286 mμ) of the minor isomer **5** is strikingly similar to that of 2-acetylcyclohexanone[7] in both neutral and basic solution, while that of the desired isomers **3** and **4** is shifted to 353 mμ and shows no bathochromic displacement on addition of base. Nuclear magnetic resonance spectra in carbon tetrachloride solutions revealed isomer **5** to be completely enolic, while the desired intermediate is a mixture containing 80% enol **4** (or its tautomer) and 20% diketone **3**.



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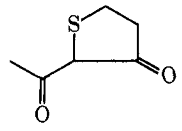

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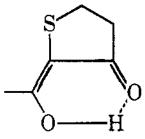

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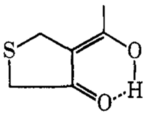

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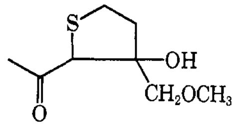

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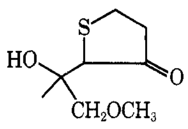

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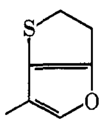

8

Before proceeding with a discussion of the synthesis, it should be pointed out that the preferential formation of the 2-acetyltetrahydrothiophenes **3** and **4** was anticipated because the intermediate carbanion leading to 2 substitution is stabilized by the 3d orbitals of the neighboring sulfur atoms[8,9] as well as by the carbonyl group. In analogy to the essentially quantitative alkali-catalyzed hydrolysis of 2-acetylcyclopentanone to δ-acetylvaleric acid,[10] we anticipated an organometallic reagent to preferentially add to the cyclic carbonyl function in **3**–**4**. In fact, the addition of methoxymethyl magnesium chloride[11] yielded a mixture of adducts containing two parts of the diastereomeric hydroxy ketones

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(1) M. Stoll, M. Winter, F. Gautschi, I. Flament, and B. Willhalm, *Helv. Chim. Acta*, **50**, 628 (1967). The isolation of kahweofuran is described on p 656.

(2) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, England, 1969, p 209.

(3) Reference 2, p 173.

(4) Reference 2, p 199.

(5) S. Rodmar, S. Forsen, B. Gestblom, S. Gronowitz, and R. A. Hoffman, *Acta Chem. Scand.*, **19**, 485 (1965).

(6) H. Wynberg, A. Logothetis, and D. Ver Ploeg, *J. Amer. Chem. Soc.*, **79**, 1972 (1957). The overall yield was improved substantially when the crude mixture of 2- and 4-carbomethoxy- and -carbethoxy-3-ketotetrahydrothiopenes was *not* purified by distillation.

(7) H. Smith, *J. Chem. Soc.*, 803 (1953).

(8) K. C. Bank and D. L. Coffen, *Chem. Commun.*, 8 (1969).

(9) A similar case was described by R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, **68**, 2229 (1946).

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(11) F. Runge, E. Taeger, C. Fiedler, and E. Kahlert, *J. Prakt. Chem.*, **19**, 37 (1963); H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959).

6 and one part of what we tentatively believe to be their isomers **7**. Separation of these unstable compounds was not possible, and the only evidence in favor of structure **7** is the presence of *C*-methyl signals in the nmr spectrum of the crude reaction mixture. Steam distillation in the presence of dilute sulfuric acid gave a single product in 15% yield whose infrared, ultraviolet, and mass and nuclear magnetic resonance spectra were indistinguishable from those of "natural" kahweofuran (**1**). The question as to whether the isomeric furan **8** derived from the minor Grignard adduct **7** was not formed or destroyed under the conditions used remains unanswered. In any event, the possibility that the synthesis described has actually given the furan **8** rather than **1** is excluded by the nmr evidence already discussed. Kahweofuran (**1**) in the pure state has a violent sulfury odor, but in high dilution it develops a pleasant roasted and smoky note.

Experimental Section

Microanalyses were performed in the laboratory of Dr. E. Palluy, Firmenich et Cie, Geneva. Boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a F & M 720 instrument, using a Carbowax 20M column. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian A-60 (TMS as internal standard); infrared (ir), Perkin-Elmer Model 237; ultraviolet (uv), Cary Model 14. Silicic acid Mallinckrodt 100 mesh and silica gel Merck 70–325 mesh were used for column chromatography.

2-Acetyl-3-ketotetrahydrothiophene (3 and 4).—Sodium hydride (1.31 g, 33 mmol, washed free of mineral oil) and 20 ml of dry 1,2-dimethoxyethane were placed in a three-necked flask fitted with a stirrer and a gas inlet tube. A slow stream of nitrogen was passed through the apparatus. The flask was immersed in an ice bath and 3.06 g (30 mmol) of 3-ketotetrahydrothiophene[6] was added to the stirred mixture over a period of 15 min. After hydrogen evolution had ceased (5–10 min), dry ethyl acetate (10 ml) was added over 5 min. Stirring was continued for 60 min at 5° and 60 min at room temperature. The mixture was decomposed with ice and 20 ml of $2N$ H_2SO_4 and extracted with ether. The organic layers were washed with saturated salt solution, dried (Na_2SO_4), and evaporated. Distillation of the residue yielded 865 mg (20%) of the yellow diketone, bp 43–47° (0.2 mm), containing 15–16% 4-acetyl-3-ketotetrahydrothiophene (**5**). Further purification was achieved by vpc collection: uv max (EtOH) 219 mμ (ε 7000), 353 (5200); uv max (EtOH + NaOH) 219 mμ (ε 7530), 353 (6830); ir ($CHCl_3$) 1740 (w), 1640 (s), 1600 cm^{-1} (s); nmr (CCl_4) enol form, δ 1.95 (s, 3 H), 2.71 (m, 2 H), 3.06 (m, 2 H), 12.6 (s, broad, 1 H) (disappears on exchange with D_2O); nmr (CCl_4) diketone form, δ 2.27 (s, 3 H), 2.71 (m, 2 H), 3.06 (m, 2 H), 3.96 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (89.8), 126 (23.2), 102 (50.2), 88 (100), 43 (81.6).

Anal. Calcd for $C_6H_8O_2S$: C, 49.98; H, 5.60. Found: C, 49.93; H, 5.66.

4-Acetyl-3-ketotetrahydrothiophene (5).—This substance was also obtained by collection: uv max (EtOH) 286 mμ (ε 6500); uv max (EtOH + NaOH) 306 mμ (ε 17,000); ir ($CHCl_3$) 1710 (w), 1640 (s), 1600 cm^{-1} (s); nmr (CCl_4) δ 2.07 (s, 3 H), 3.58 (m, 2 H), 3.69 (s, 2 H), 14.2 (s, broad, 1 H) (disappears on exchange with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 144 (93.4), 102 (31.4), 70 (50.4), 55 (39.8), 43 (100).

Grignard Adducts 6 and 7.—Magnesium (2.58 g, 0.106 g-atom) was placed in a three-necked flask and activated by heating with a trace of iodine. A slow stream of nitrogen was passed through the apparatus, and 20 ml of freshly distilled methylal and some crystals of mercuric chloride were added. Several minutes after the addition of a few drops of 8.75 g (0.106 mol) of freshly distilled chloromethyl methyl ether, an exothermic reaction commenced, the flask was then immersed in a Dry Ice–acetone bath and the rest of the chloromethyl methyl ether was slowly added at −5° (60 min) with vigorous stirrring. The mixture was stirred for a further 60 min at −5°. A solution of 3.8 g (26.4 mmol) of diketone **3** and **4** in 35 ml of dry methylal was added dropwise at such a rate that the temperature remained between −40 and −50° (30 min). Stirring was continued for 2 hr while the temperature was allowed to rise to room temperature. The reaction product was then poured into cold saturated NH_4Cl solution and extracted with ether twice, washed with saturated salt solution, dried (Na_2SO_4), and evaporated. Distillation gave a yellow oil (3.6 g), bp 80–100° (0.05–0.07 mm), which was chromatographed on 100 g of silicic acid. Elution with chloroform–ethanol (98:2) followed by distillation gave a colorless oil (3.0 g, 60%), bp 64–66° (0.03 mm). Nmr spectroscopy indicated that this material was a 2:1 mixture of the epimers of 2-acetyl-3-hydroxy-3-methoxymethyltetrahydrothiophene (**6**) and 2-(1-hydroxy-1-methoxymethyl)ethyl-3-ketotetrahydrothiophene (**7**), respectively. The spectrum (CCl_4) had bands at δ 1.15 (s), 1.25 (s), 2.15 (s), 2.25 (s), 3.3–3.4 (four-overlapping singlets); ir ($CHCl_3$) 3530 (broad), 1710, 1110 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.52; H, 7.42. Found: C, 50.70; H, 7.24.

Kahweofuran (1) (2-Methyl-3-oxa-8-thiabicyclo[3.3.0]-1,4-octadiene).—The mixture of carbinols **6** and **7** (1.6 g) was added dropwise during 30 min to 50 ml of 1 *N* H_2SO_4 while steam distilling. After 1 hr, the distillate (150 ml) was extracted twice with ether, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The remaining orange oil was chromatographed on 20 g of silica gel using hexane–ethyl acetate (9:1) as eluent. Distillation gave kahweofuran as a colorless oil (177 mg, 15%): bp 105–107° (20 mm); uv max (EtOH) 245 mμ (ε 3100); ir ($CHCl_3$) 1630, 1575, 1100, 1075, 920 cm^{-1}; nmr (CCl_4) δ 2.17 (s, 3 H), 2.81 (t, 2 H, $J = 7$ Hz with fine splitting of 1.5 Hz), 3.57 (t, 2 H, $J = 7$ Hz with small fine splitting), 6.91 (t, 1 H, $J = 1.5$ Hz); mass spectrum (70 eV) *m/e* (rel intensity) 140 (100), 139 (28.4), 111 (37.9), 97 (29.2). The mass spectrum, ir, nmr, and uv spectra of synthetic kahweofuran were indistinguishable from those of the natural product.

Anal. Calcd for C_7H_8OS: C, 60.00; H, 5.75. Found: C, 60.32; H, 5.96.

Registry No.—**1**, 26693-24-3; **3**, 26693-25-4; **4**, 26693-26-5; **5**, 26693-27-6; **6**, 26693-28-7; **7**, 26693-29-8.

Acknowledgment.—We (G. B. and P. D.) are indebted to Firmenich et Cie., Geneva, for generous financial support.

The Effect of Pressure on Acetal Equilibria[1]

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Received March 19, 1970

The influence of pressure upon the rates of chemical reactions in solution continue to be widely investigated.[4-6] Far less interest has been generated for studies concerned with the influence of pressure on chemical equilibria in the solution.[4,6] This general lack of research interest is surprising because (1) pressure remains as a physical variable which can be changed

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[1] We gratefully acknowledge support for this work under Grant No. AM-11244 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

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[3] Undergraduate Research Participant, summer, 1969. We wish to acknowledge help given by Mr. Thomas S. Davis with the experimental work.

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