Summary

1. Chlorogenin has been converted to tigogenin without altering the C-3 hydroxyl group. This proves that the C-3 hydroxyl has the β-configuration.

2. *epi*-Chlorogenin has been prepared.

3. Chlorogenin and its epimer are analogous to other *allo*-steroid carbinols epimeric at C-3 in behavior toward digitonin and sodium amylate.


Acetylenic Ethers. II. Ethoxy- and Butoxy-acetylene

BY THOMAS L. JACOBS, RICHARD CRAMER[1] AND JOHN E. HANSON

In the first paper of this series,[2] the synthesis and properties of phenoxyacetylene and substituted phenoxyacetylenes were described. It seemed likely that simple alkoxyacetylenes would show quite different properties. The following reactions have been employed to synthesize two such compounds

$$CH_2BrCH(OR)_2 \longrightarrow CHBr_2CH(OR)_2 \xrightarrow{Zn} \overline{C_2H_5OH}$$

$$BrCH=CHOR \xrightarrow{KOH} H-C\equiv C-OR$$
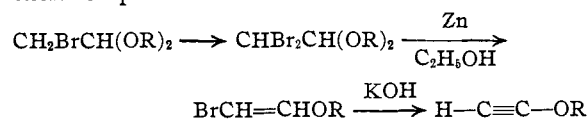
Bromoalkoxyethylenes were prepared by the action of zinc and alcohol on dibromoacetals in the same way that alkenes are obtained from β-bromoethers.[3] When the starting material was the dibutyl acetal, a mixed acetal of monobromoacetaldehyde, $BrCH_2CH(OC_2H_5)OC_4H_9$, was obtained as a by-product, apparently by the addition of a molecule of alcohol to bromobutoxyethylene. When a large run was attempted this mixed acetal was the principal product. No diethyl acetal was isolated in the preparation of bromoethoxyethylene, where the reaction with zinc was more rapid. The elimination of hydrogen bromide from the bromoalkoxyethylene by distillation from powdered potassium hydroxide corresponds to the final step in the synthesis of phenoxyacetylene.

Ethoxy- and butoxy-acetylene are colorless, mobile, evil-smelling liquids which must be distilled under reduced pressure. Their structures were proved by analysis, molecular weight determinations and hydrogenation to the corresponding saturated ethers. The observed molecular refractions showed only slight exaltations as compared with the values calculated from constants derived from saturated ethers and 1-alkynes.[4] Chalmers[5] found that the molecular refractions of aliphatic vinyl ethers were also normal.

While phenoxyacetylene gave a white silver salt which was sufficiently stable to permit analysis,[6] the alkoxyacetylenes gave only black precipitates probably containing metallic silver. These burned with a puff when dry, but showed no tendency to explode. When the freshly precipitated derivative was treated with dilute nitric or sulfuric acid, the odor of ethyl or butyl acetate was at once apparent, and these esters could be isolated in low yield. Ethoxyacetylene gave a white mercury derivative which rapidly turned brown. While no attempt has yet been made to synthesize such substituted acetylenic ethers as $RC\equiv CO$-Alkyl by the use of sodium or bromomagnesium derivatives of alkoxyacetylenes, ethoxyacetylene gave one mole of methane in the Grignard "machine"[7] and none of the reagent was used in other ways.

Although ethoxy- and butoxy-acetylene polymerize much less rapidly than phenoxyacetylene, they remained completely colorless only when sealed in glass and stored at minus eighty degrees. A yellow color developed in a few days at zero degrees or in a few hours at room temperature. When tubes containing the most carefully purified samples were opened at room temperature a yellow color appeared in a few minutes. As in the case of phenoxyacetylene, the moderately rapid heating of a small sample in a sealed tube to around 100° resulted in an explosion with the production of a black solid.
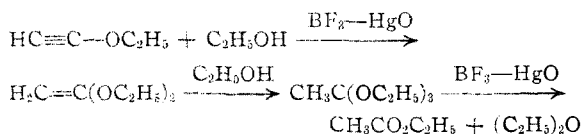
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(2) Jacobs, Cramer and Weiss, THIS JOURNAL, 62, 1849 (1940).

(3) Dykstra, Lewis and Boord, *ibid.*, 52, 3401 (1930).

(4) Eisenlohr values of the atomic refractivities from Landolt–Börnstein, "Physikalische Tabellen," 5th ed., Vol. II, 985. The revised constant for the triple bond was used, *ibid.*, Supp. Vol. IIIb, 1696.

(5) Chalmers, *Can. J. Research*, 7, 464 (1932).

(6) Slimmer, *Ber.*, 36, 289 (1909).

(7) Kohler, Stone and Fuson, THIS JOURNAL, 49, 3181 (1927); Kohler and Richtmyer, *ibid.*, 52, 3736 (1930).

Considerable interest attaches to the possibility of comparing more closely the carbon–carbon double and triple bonds in analogous, highly reactive molecules. It is well known that the presence of oxygen on a double bond increases its reactivity[3] and the same appears to be true for the triple bond.

The rapid hydrolysis of vinyl ethers in dilute acid solutions has been followed quantitatively by a dilatometric method.[9] At the same temperature (25°) and acid concentration (0.05 M) the hydrolysis of ethoxyacetylene to ethyl acetate was too rapid to measure. Butoxyacetylene was hydrolyzed rapidly by dilute acids and was completely converted to butyl acetate and polymer by refluxing with distilled water. The hydrolysis with distilled water at room temperature was slow. Ethoxyacetylene did not react with ethyl alcohol under simple refluxing, but at 0° in the presence of the boron trifluoride-mercuric oxide catalyst developed by Nieuwland and his co-workers[10] the products were ethyl acetate and diethyl ether. Under similar conditions ethyl orthoacetate yielded the same products. The reaction may therefore be formulated as the addition of alcohol to ethoxyacetylene.

$$HC{\equiv}C{-}OC_2H_5 + C_2H_5OH \xrightarrow{\ BF_3{-}HgO\ }$$

$$H_2C{=}C(OC_2H_5)_2 \xrightarrow{\ C_2H_5OH\ } CH_3C(OC_2H_5)_3 \xrightarrow{\ BF_3{-}HgO\ }$$

$$CH_3CO_2C_2H_5 + (C_2H_5)_2O$$

The intermediate ketene diethylacetal[11] is known to add either water or alcohol spontaneously with the evolution of heat. With respect to these addition reactions the relative reactivity is

$$H_2C{=}CHOC_2H_5 < HC{\equiv}COC_2H_5 < H_2C{=}C(OC_2H_5)_2$$

Two acetylenic ethers have been tested as anaesthetics by Dr. Chauncey D. Leake of the Medical School of the University of California. Ethoxyacetylene, especially interesting because of its similarity to diethyl and ethyl vinyl ethers, was found to have some anesthetic action, but the compound was quite poisonous and killed mice even on short exposure to low concentrations. Phenoxyacetylene had no anesthetic action but was quite poisonous.

Experimental

Bromoacetals were prepared by brominating an acetal,[12] from vinyl acetate,[13] or by the action of a sodium alcoholate on an α,β-dibromoethyl alkyl ether. The last method was unsatisfactory for the diethyl acetal of bromoacetaldehyde, but gave excellent yields of the corresponding dibutyl acetal. Butyl α-chloroethyl ether was prepared from paraldehyde, n-butyl alcohol and anhydrous hydrogen chloride and converted to butyl α,β-dibromoethyl ether without purification.[5,14] Using a procedure similar to that for the preparation of dibutyl acetal from butyl α-chloroethyl ether,[15] 90 g. (0.34 mole) of the crude dibromo ether was added during fifteen minutes with shaking and cooling to a solution of 12 g. (0.52 mole) of sodium dissolved in 160 g. of butyl alcohol. The reaction mixture was heated at 70-80° for thirty minutes, cooled, washed with water, dried over sodium sulfate and distilled under reduced pressure from a modified Claisen flask. The yield of bromodibutyl acetal, b. p. 139-140° (33 mm.), was 78 g. (89%). The over-all yield was 84%. This compound was also obtained in 54% yield by the method of Filachione.[13]

Dibromoacetals were prepared by brominating the bromoacetals.[11,16] Dibromodibutylacetal was obtained in 40-50% yield, b. p. 131-134° (10 mm.), molecular weight (cryoscopically in benzene) 314 (calcd. 332). Butyl bromoacetate and butyl bromide were the principal by-products in this synthesis. The ester was isolated in yields as high as 44%. Magnani and McElvain[17] have observed that the two hydrogens of dibromoacetal are replaced with about equal ease, ethyl bromide and ethyl dibromoacetate being produced from the decomposition of $CHBr_2CBr(OC_2H_5)_2$. In dibutyl bromoacetal the hydrogen on the carbon bearing the butoxyl groups appears to be as readily replaced as the hydrogens on the bromine-bearing carbon. The replacement of the hydrogen on the alkoxyl-bearing carbon of acetals is a rather general reaction, for bromination produced 12% ethyl bromoacetate from bromoacetal and 16% ethyl acetate from acetal. The esters were identified by conversion to amides.

Bromoethoxyethylene.—To 138 g. (0.5 mole) of dibromoacetal and 170 cc. of 95% alcohol in a 500 cc., 3-necked flask fitted with a mercury-sealed stirrer and condenser and preheated to refluxing in a water-bath was added 65 g. (1 mole) of zinc dust in small portions so that refluxing continued without further heating. The zinc dust was activated by treatment with 3 N hydrochloric acid and careful washing with water and alcohol. Usually thirty minutes were required for the addition, and after thirty minutes of further refluxing, the mixture was cooled, filtered with suction, the precipitate carefully washed with alcohol and the filtrate treated with 750 cc. of N ammonium chloride solution containing ice. The bromoethoxyethylene layer was separated, washed with 50 cc. of cold N ammonium chloride solution, then with 30 cc. of ice water and dried over calcium chloride. The aqueous washings were extracted with three 100-cc. portions of ether and the

(8) Meyer and Lenhardt, *Ann.*, **398**, 66 (1913).

(9) Skrabal and Skrabal, *Z. physik. Chem.*, **181**, 449 (1938); Skrabal, *ibid.*, **185**, 81 (1939).

(10) Hennion, Killian, Vaughn and Nieuwland, THIS JOURNAL, **56**, 1130 (1934).

(11) Beyerstedt and McElvain, *ibid.*, **58**, 529 (1936).

(12) Hartung and Adkins, THIS JOURNAL, **49**, 2520 (1927).

(13) Filachione, *ibid.*, **61**, 1705 (1939).

(14) Swallen and Boord, *ibid.*, **52**, 651, 654 (1930).

(15) Henze and Murchison, *ibid.*, **55**, 4255 (1933).

(16) Beyerstedt and McElvain, *ibid.*, **59**, 2266 (1937).

(17) Magnani and McElvain, *ibid.*, **60**, 2210 (1938).

ether was washed with ice water and dried over calcium chloride. The product was distilled through a small column, b. p. 41–44° (19 mm.), yield 38 g. (50%).

Bromobutoxyethylene was similarly prepared, but the reaction on addition of zinc was less vigorous so that the mixture was heated with a water-bath at 70–80° at all times, and stirring was continued for three hours after the addition was complete. Yields varied from 55 to 78% on 0.3 mole runs. It was also possible to isolate a compound, b. p. 95–96° (4 mm.), which had the composition of a mixed butyl ethyl acetal of bromoacetaldehyde. The yield was usually about 6%, but in one instance using 1 mole of dibutyl dibromoacetal this product was obtained in 65% yield, n^{20}D 1.4459. *Anal.* Calcd. for $C_8H_{17}O_2Br$: C, 42.70; H, 7.64. Found: C, 42.77; H, 7.42. The purified by-product did not absorb bromine in carbon tetrachloride, and was not oxidized by dilute, cold permanganate.

The bromoalkoxyethylenes absorb bromine rapidly and are rapidly oxidized by dilute, cold permanganate.

Ethoxyacetylene was prepared by mixing bromoethoxyethylene with twice its weight of powdered potassium hydroxide in a distilling flask and heating at atmospheric pressure in an oil-bath. A vigorous reaction occurred when the bath was at 90–100° and the ethoxyacetylene distilled very rapidly. The receiver was a U-tube in dry-ice. The product was dried over sodium sulfate and distilled through a small column, b. p. 27.5–28.5° (300 mm.), yield 50–55%. The receivers were cooled in dry-ice and the samples were sealed at the end of the distillation after reducing the pressure to a few millimeters. The distillation of ethoxyacetylene from an ordinary flask at atmospheric pressure resulted in considerable decomposition and no definite boiling point was observed.

Molecular weight (cryoscopically in benzene). Calcd. for C_4H_6O: 70.1. Found: 75.9.

Butoxyacetylene was similarly prepared, but a Claisen flask was used for the reaction and the pressure was reduced to 370 mm. After most of the product had distilled, starting material could be recovered by reducing the pressure to a few millimeters. The yield of redistilled butoxyacetylene, b. p. 50.5° (110 mm.), was 34–56% and 30–40% of the starting material was recovered.

Hydrogenation.—One mole-equivalent of hydrogen was very rapidly absorbed by ethoxyacetylene at room temperature in the presence of either platinum or palladium, but the second mole equivalent was only incompletely absorbed even after forty-five hours. Addition of new catalyst did not greatly accelerate absorption of the second equivalent. When a total of 0.14 g. of Adams platinum oxide catalyst was added (two portions) to 0.7 g. of ethoxyacetylene in 30 cc. of ethyl alcohol, 82% of the theoretical amount of hydrogen (for two mole equivalents) was absorbed in forty-five hours. With 0.38 g. of palladium on barium sulfate and 0.8 g. of ethoxyacetylene, absorption was 70% complete in the same time. Diethyl ether was isolated from the first run by careful fractionation, and identified by boiling point, odor and refractive index. While the vapor phase hydrogenation of ethyl vinyl and divinyl ethers was rapid and complete,[18] Ruigh and Major[19]

found that the liquid phase hydrogenation of divinyl ether with a platinum catalyst was very slow.

When 0.8 g. of butoxyacetylene in 50 cc. of alcohol was shaken with 0.06 g. of Adams catalyst and hydrogen at atmospheric pressure, 98.5% of the theoretical amount (two mole equivalents) was absorbed in an hour, and no more was then taken up. The second mole equivalent was absorbed more rapidly than the first (this was checked in a second run). It was found that butyl ethyl ether and ethyl alcohol form an azeotropic mixture boiling at 73–74° which contains roughly 59 mole % alcohol. Mixtures of 95% alcohol and butyl ethyl ether boiled at 72–73° indicating a ternary azeotropic mixture with water. Butyl ethyl ether was isolated from the reduction mixture by fractionating to obtain the constant boiling mixture and washing out the alcohol with water. The pure ether was identified by b. p., refractive index and density.

Hydrolysis of butoxyacetylene was accomplished by refluxing 3.55 g. with 10 cc. of distilled water for two hours. The acetylene layer turned reddish-brown. The product was taken up in ether, dried over sodium sulfate and fractionated at 110 mm. There was no evidence for butoxyacetylene, but 2.8 g. (67%) of butyl acetate, b. p. 70–71° (110 mm.), was obtained and identified by refractive index, density and saponification equivalent. A dark brown, viscous residue in the distilling flask accounted for the rest of the starting material.

Addition of Alcohol.—When it was found that ethoxyacetylene could be recovered with almost no loss after refluxing for three hours with twice its volume of absolute alcohol, an attempt was made to add alcohol to the triple bond by the use of boron trifluoride and mercuric oxide.[10] Ethyl alcohol was used in the hope that ethyl orthoacetate could be isolated, notwithstanding the published statement[20] that addition of alcohols other than methyl to the triple bond occurred rapidly, but the products were to a large extent polymeric. The catalyst was prepared as described,[10] but on a small scale (0.4 g. of mercuric oxide) and using absolute ethyl alcohol. This was diluted with 1.1 cc. of absolute alcohol, the mixture cooled in ice and 3.45 g. of ethoxyacetylene dissolved in 3.4 cc. of absolute alcohol was added with stirring during two and one-half hours. Stirring was continued for two hours. The material was protected from moisture at all times by calcium chloride tubes. Filtration left a grey solution apparently due to colloidal catalyst. The filtrate was distilled through a small, efficient column at 300 mm. Separation was poor, but there was no odor of ethoxyacetylene in the low boiling fraction, nor was a precipitate obtained with ammoniacal silver nitrate. Refractionation at atmospheric pressure gave 1.72 g. (47% yield) of diethyl ether, identified by b. p., refractive index and density and 3.14 g. of ethyl alcohol-ethyl acetate azeotrope, b. p. 71–72°. Since the mixture contains 69.2% by weight of ethyl acetate this corresponds to 2.17 g. (50% yield) of the ester. There was some polymeric material as a flask residue, and some loss in manipulation. The *azeotrope* was identified by refractive index ($n^{24.2}$D 1.3670) and boiling point. The alcohol was removed by washing an ether solution with water, and a little pure ethyl acetate was isolated.

Exactly similar treatment of 1.8 g. of ethyl orthoacetate

(18) Dolliver, Gresham, Kistiakowsky, Smith and Vaughan, THIS JOURNAL, **60**, 440 (1938).

(19) Ruigh and Major, *ibid.*, **53**, 2662 (1931).

(20) Killian, Hennion and Nieuwland, *ibid.*, **56**, 1384 (1934).

TABLE I

Compound	B. p. °C.	mm.	$n^{20}D$	d^{20}	MR_D obs.	MR_D calcd.	Empirical formula	Calcd. C	Calcd. H	Found C	Found H
BrCH₂CH(OC₄H₉)₂	86.5	1	1.4477	1.1511	58.85	59.44	C₁₀H₂₁O₂Br	47.43	8.36	47.42	8.53
Br₂CHCH(OC₄H₉)₂	104	1	1.4750	1.3937	67.09	67.20	C₁₀H₂₀O₂Br₂	36.16	6.07	36.44	6.20
										36.56	6.57
BrCH=CHOC₂H₅	41	14	1.4725	1.4237	29.73	29.61	C₄H₇OBr	31.81	4.67	32.10	4.93
BrCH=CHOC₄H₉	60	8	1.4660	1.2744	38.92	38.85	C₆H₁₁OBr	40.23	6.19	40.34	6.34
HC≡COC₂H₅	28	300	1.3812	1.3785²⁵	0.7929	0.7874²⁵	20.53	20.25	C₄H₆O		
HC≡COC₄H₉	50.5	110	1.4053	1.4033²⁵	0.8129	0.8078²⁵	29.06	29.49	C₆H₁₀O	73.41	10.27	73.19	10.28

with the boron trifluoride catalyst gave 0.33 g. of diethyl ether (40% yield) and 1.1 g. of the alcohol-ethyl acetate azeotrope, which corresponds to 0.75 g. of ethyl acetate (77% yield).

The table gives the physical constants and analyses of the new compounds prepared.

Summary

Ethoxy- and butoxy-acetylene have been prepared from the corresponding bromoalkoxyethylenes. They are rather poisonous liquids which give unstable copper, silver and mercury derivatives. Their structures were proved by hydro-genation to the corresponding saturated ether and by hydrolysis to esters. They polymerize slowly at room temperature, but explode when heated in a sealed tube. Water adds more readily than to vinyl ethers, but less readily than to ketene acetal. Ethoxyacetylene may be refluxed with ethyl alcohol without reaction, but at 0° in the presence of a boron trifluoride–mercuric oxide catalyst and alcohol the products are diethyl ether and ethyl acetate. Ethyl orthoacetate gives the same products under like conditions.

A Kinetic Study of the Reactions of n-Butyl Bromide with the Sodium Salts of Phenol, Thiophenol and n-Butyl Mercaptan[1]

BY OSBORNE R. QUAYLE AND E. EARL ROYALS[2,3]

The reaction of sodium phenolate with n-butyl bromide in boiling alcohol requires from three to four hours for completion, while the corresponding reactions of sodium thiophenolate and sodium n-butyl mercaptide are essentially complete in a few seconds. There appears to be no previous quantitative work on these reactions, although similar reactions have been extensively studied. The reaction between methyl iodide and sodium ethylate was studied by Hecht, Conrad and Bruchner[4] who observed that the bimolecular rate constant is decreased by increasing initial concentrations of reactants. Segaller[5] made an extended study of the reactions of a series of normal and branched-chain alkyl iodides with sodium phenolate and observed the effects of temperature, con-

centration and solvent on the bimolecular rate constants. The rate constants were found to decrease with increasing initial concentrations of reactants, and no correlation was observed between reactivity and dielectric constant of the solvent. It was concluded that the reactions are "not ionic." The work of Hecht, Conrad and Bruchner and that of Segaller on the reaction of propyl iodide with sodium phenolate was repeated by Schroeder and Acree[6] as a test of their "dual hypothesis," according to which both ionic and molecular reactions proceed simultaneously and independently. The observed concentration effect was explained by this hypothesis. Lauer and Shingu[7] have recently studied the kinetics of the etherification reaction of allyl bromide with sodium phenolate with particular interest in concentration and solvent effects and conclude that the reaction is entirely ionic. Concentration effect is explained as due to a varying degree of solvation of the phenolate ion.

The object of this investigation was to deter-

(1) The authors wish to express their gratitude to Dr. E. Emmet Reid, research consultant to the department, for suggesting the problem and for his continued interest and aid during its investigation.

(2) Abstracted from a thesis submitted by E. Earl Royals to the Graduate Faculty of Emory University in partial fulfillment of the requirements for the degree of Master of Science.

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(4) Hecht, Conrad and Bruchner, Z. physik. Chem., 49, 329 (1904).

(5) Segaller, J. Chem. Soc., 103, 1154 (1913); 103, 1421 (1913); 105, 106 (1914).

(6) Schroeder and Acree, ibid., 105, 2582 (1914), and previous papers.

(7) Lauer and Shingu, Ber., 69, 273 (1936).