

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

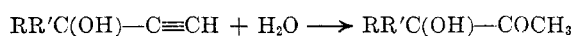
Reactions of α -Ketols Derived from Tertiary Acetylenic Carbinols. I. Preparation and Low Pressure Hydrogenation¹

G. F. HENNION AND E. J. WATSON²

Received October 18, 1957

A general procedure has been developed for the hydration of tertiary acetylenic carbinols and has been used for the preparation of six α -ketols in high yields from the corresponding commercially available carbinols. The ketols were easily converted to the *vic*-glycols by low pressure hydrogenation using a platinum oxide catalyst in the presence of alkali.

Acetylenic carbinols are converted to the corresponding α -ketols by hydration in acidic aqueous solution in the presence of dissolved mercuric salts.³ The reaction has been accomplished in various ways, sometimes in good yield and sometimes not, and no general procedure has yet been recom-



mended. Since assorted tertiary acetylenic carbinols are now commercially available and hold promise as intermediates for syntheses, especially in the pharmaceutical field, renewed interest in these compounds is evident in the current literature. The hydration reaction, for example, has been employed as the first step in the preparation of simple analogs of cortisone.⁴

Since acetylenic compounds (including most of the carbinols) commonly are not water soluble, experience in this laboratory has shown that the hydration reactions are best carried out in mixed aqueous solvents, notably well in aqueous methanol.⁵ It has now been found that use of aqueous methanol containing only a 50% excess of water over that required by theory, with sulfuric acid and mercuric oxide as catalysts, provides an excellent general procedure which permits easy recovery of the product in high yield. The reaction is best carried out at a temperature near the reflux point, usually self-maintained since it is very exothermic. Surprisingly, an induction period is frequently observed and it is therefore imperative that the acetylenic carbinol be added to the aqueous methanol-catalyst mixture in small amount at first, delaying further addition until reaction is

evident. Otherwise unreacted carbinol may accumulate so that the reaction finally becomes very vigorous and entirely uncontrollable.

The general procedure described below is a mild one and in special cases more strenuous conditions may be needed. Thus diisopropylethynylcarbinol did not respond to this method; in this case hydration may be achieved (in 40–50% yield) by boiling with 20% aqueous sulfuric acid containing mercuric oxide.⁶ When the acetylenic alcohol is particularly sensitive to acids, as in the case of phenylmethyl-ethynylcarbinol, control of acid concentration and temperature become more critical.^{5c}

α -Ketols have been converted to the corresponding glycols by reduction with sodium in ethanol,⁷ by hydrogenation⁸ in the presence of Raney nickel⁹ at high pressure,⁸ⁱ by reaction with lithium aluminum hydride,⁶ and, in a few cases, by low pressure hydrogenation with platinum oxide catalyst.^{4c} The low pressure method was chosen for further study.

When 1-acetylcyclohexanol was hydrogenated as previously described by Stacy and Mikulec,^{4c} reaction proceeded very slowly as reported. Addition of acid suppressed reaction completely. On the other hand, addition of a small amount of ethanolic sodium hydroxide resulted in the desired acceleration.

The ketols are described in Table I and the glycols in Table II.

EXPERIMENTAL

Hydration of acetylenic carbinols. A two-liter, three-neck flask was fitted with a mercury-sealed stirrer and a reflux condenser. In the flask was placed 15 grams of red HgO and a solution of 10 ml. of concd. H₂SO₄ in 135 ml. (7.5 moles) of water. The warm mixture was stirred for three to five min. and then 385 ml. of methanol was added. A bright yellow suspension formed. The third neck of the flask was closed with a stopper bearing a thermometer and an addition funnel. The catalyst mixture was heated to 60–65°.

(6) W. J. Hickenbottom, A. A. Hyatt, and M. B. Sparke, *J. Chem. Soc.*, 2529 (1954).

(7) (a) A. Favorski, *J. Russ. Phys. Chem. Soc.*, **44**, 1347 (1912); *Chem. Abstr.*, **7**, 984 (1913). (b) I. N. Nazarov and A. N. Elizarova, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 195 (1940); *Chem. Abstr.*, **36**, 742 (1942).

(8) (a) G. Bernard and J. Colonge, *Bull. soc. chim. France*, **12**, 356 (1945). (b) E. D. Bergmann, U. S. Patent **2,539,806** (1951); *Chem. Abstr.*, **45**, 6655 (1951). (c) E. D. Bergmann and D. F. Herman, *J. Appl. Chem.*, **3**, 42 (1953).

(1) Paper LXVIII on substituted acetylenes; previous paper, G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958).

(2) Eli Lilly Co. Fellow, 1954–1956. Abstracted in part from the Ph.D. Dissertation of E. J. W.

(3) For review and references see A. W. Johnson, *Acetylenic Compounds. Vol. I. The Acetylenic Alcohols*, Edw. Arnold Co., London, 1946, pp. 102–105.

(4) (a) J. D. Billimoria, N. F. Maclagan, *J. Chem. Soc.*, 3067 (1951); 2626 (1953); 3257 (1954); 1126 (1955). (b) D. Papa, H. F. Ginsberg, and F. J. Villani, *J. Am. Chem. Soc.*, **76**, 4441 (1954). (c) G. W. Stacy and R. A. Mikulec, *J. Am. Chem. Soc.*, **76**, 524 (1954).

(5) (a) G. F. Hennion, R. J. Thomas, K. N. Campbell, R. B. Davis, D. E. Maloney, and B. R. Fleck, *J. Am. Chem. Soc.*, **60**, 718 (1938); (b) **71**, 2813 (1949); (c) **77**, 3253 (1955).

TABLE I

 α -KETOLS, RR'C(OH)COCH₃, FROM TERTIARY ACETYLENIC CARBINOLS

R	R'	Yield (%)	B.P. (°C./Mm)	n_D^{25}	Reference
CH ₃	CH ₃	81	46-47/21	1.4129	^a
CH ₃	C ₂ H ₅	80	54-56/21	1.4198	^b
C ₂ H ₅	C ₂ H ₅	88	61-62/20	1.4231	^c
CH ₃	<i>i</i> -C ₄ H ₉	94	69-70/17	1.4260	^d
-CH ₂ (CH ₂) ₃ CH ₂ -		91	105-107/26	1.4660	^e
CH ₃	C ₆ H ₅	92 ^g	78-85/1.4 ^g	1.5180 ^g	^f

^a M. S. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1952), gives b.p. 137°, n_D^{25} 1.4176; E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3131 (1953), give b.p. 49-51°/17 mm., n_D^{25} 1.4158. ^b G. F. Hennion *et al.*, (ref. 5b), give b.p. 70-73°/50 mm., n_D^{25} 1.4200. ^c R. Locquin and W. Sung, *Compt. rend.*, **176**, 516 (1923), give b.p. 56-57°/13 mm., n_D^{15} 1.4303. ^d D. Papa *et al.*, (ref. 4b), give b.p. 68-70°/12 mm., n_D^{25} 1.4300. ^e G. W. Stacy and R. A. Mikulec (ref. 4c), give b.p. 92-94°/15 mm., n_D^{25} 1.4670. ^f G. F. Hennion and R. Fleck (ref. 5c), give b.p. 99-100°/3 mm., n_D^{25} 1.5215. ^g This ketol could be prepared in good yield only by applying the method of Hennion and Fleck.^{5c} The yield and physical constants are for once distilled product suitable for hydrogenation. In all other cases physical constants were determined after redistillation.

TABLE II

vic-GLYCOLS, RR'C(OH)CH(OH)CH₃, FROM α -KETOLS

R	R'	Yield (%) ^a	B.P. (°C./Mm.)	n_D^{25}	d_4^{25}	Ref.
CH ₃	CH ₃	88	173-174/ atm.	1.4361	0.9688	^b
CH ₃	C ₂ H ₅	94	63/0.5	1.4440	0.9638	^c
C ₂ H ₅	C ₂ H ₅	97	109/24	1.4503	0.9612	^d
CH ₃	<i>i</i> -C ₄ H ₉	99	111/21	1.4450	0.9285	^e
-CH ₂ (CH ₂) ₃ - CH ₂ -		96	87/1.4	1.4840		^f
CH ₃	C ₆ H ₅	78	106/1.6	1.5301		^g

^a Yields are for once distilled products; physical constants were determined after redistillation. ^b I. N. Nazarov and A. N. Elizarova, (ref. 7b), give b.p. 170-176°, n_D^{17} 1.4290. *Cf.*, Beilstein, 4th ed., Vol. I, p. 482. ^c H. van Risseghem, *Bull. soc. chim. France*, **177** (1952), gives b.p. 93°/15 mm., d_4^{15} 0.9750. ^d D. Gauthier, *Compt. rend.*, **152**, 1100 (1911), gives b.p. 105°/17 mm. ^e E. D. Bergmann (refs. 8b,c), gives b.p. 84-85°/7 mm., n_D^{25} 1.4455, d_4^{25} 0.9157. ^f G. W. Stacy and R. A. Mikulec, (ref. 4c), give b.p. 120-121°/10 mm., n_D^{25} 1.4843, d_4^{25} 1.0422. ^g T. I. Temnikova, *J. Gen. Chem. U.S.S.R.*, **8**, 1022 (1938); *Chem. Abstr.*, **33**, 3777 (1939), gives b.p. 153.5-154.5°/17 mm.

The acetylenic carbinol (5 moles) was placed in the funnel and about 5 to 10 ml. was admitted to the flask after the heat source had been removed. Either immediately or after a short induction period, the reaction mixture became clear and nearly colorless and the temperature began to rise.

When the initial portion of the acetylenic carbinol had reacted, a white cloudy suspension formed and the temperature began to drop slowly. The remainder of the acetylenic carbinol then was added dropwise at such a rate as to maintain the temperature at about 65°. It is important to ascertain that the reaction actually has started by observing the rise in temperature and the appearance of the cloudy suspension. If these are not observed, the reaction mixture is refluxed for 5 to 10 min., allowed to cool to 60-65° and the procedure repeated. The reaction mixture gradually becomes darker during the reaction and metallic mercury appears (grey sludge). The addition requires about 4 hr. The reac-

tion mixture was allowed to cool overnight and the next day was refluxed for 0.5 hr. After allowing the reaction mixture to cool, 100 grams of anhydrous sodium carbonate was added to neutralize the acid and to absorb most of the excess water. Although the reaction mixture can be filtered immediately, it is best to allow the solids to settle overnight.

As much of the liquid as possible was decanted through a Büchner funnel. The reaction flask and the solid material were washed with about 30 ml. of methanol and this was poured through the filter. The filtrate was transferred to a two-liter flask for distillation. Anhydrous potassium carbonate (5 g.) was added to suppress acidification due to the thermal decomposition of small amounts of organomercury compounds. Methanol was removed by distillation through a helix-packed column at atmospheric pressure and the residual liquid was distilled at an appropriate pressure. Some water and a small amount of organic material usually distilled over before the desired product and all such fore-runs were discarded. The ketol was then redistilled.

2-Methyl-2,3-butanediol. 3-Hydroxy-3-methyl-2-butanone (25.5 g., 0.25 mole) in 100 ml. of ethanol was hydrogenated in the Parr low pressure apparatus using 0.25 g. of PtO₂ as catalyst. Hydrogen uptake (0.25 mole) was complete in one hour. A second run was carried out under the same conditions. The reaction mixtures were filtered and each hydrogenation vessel was rinsed twice with 10 ml. portions of ethanol, the solvent then being poured through the filter. The combined filtrates were placed in a dropping funnel and gradually admitted to a heated 100-ml. Claisen flask in order to remove the ethanol. The residual liquid was distilled to give 46.1 g. (88% yield) of 2-methyl-2,3-butanediol, b.p. 169-172°, n_D^{25} 1.4345.

2-Methyl-2,3-butanediol monophenylurethane. 2-Methyl-2,3-butanediol (2.08 g., 0.02 mole) in a 50-ml. Erlenmeyer flask was treated with 2.38 g. of phenyl isocyanate overnight at room temperature. The clear, hard glass which formed was induced to crystallize by scratching. One recrystallization from CCl₄ gave 2.8 g. (63% yield) of crystals, m.p. 128-130° (lit.⁹ m.p. 125.5°).

3-Methyl-2,3-pentenediol. 3-Hydroxy-3-methyl-2-pentanone (29.0 g., 0.25 mole) in 60 ml. of ethanol was hydrogenated as previously described using 0.25 g. of PtO₂ and 1 ml. of 0.1N NaOH in ethanol. The theoretical amount of hydrogen was absorbed in 100 min. In another experiment, identical except for the addition of 3 ml. of 0.1N base, hydrogen uptake was complete in 45 min. The reaction mixtures were filtered, all filtrates and washings combined, and the ethanol distilled off. The residual liquid, upon distillation at reduced pressure, gave 55.8 g. (94% yield) of 3-methyl-2,3-pentenediol, b.p. 68-70° at 2.7 mm., n_D^{25} 1.4438. Without the addition of base, the hydrogenation required 5 hr.

3-Methyl-2,3-pentenediol monophenylurethane. When the glycol was treated with phenyl isocyanate as previously described, there was obtained, after one recrystallization from CCl₄, a 55% yield of white crystals, m.p. 131-133°. An additional recrystallization from CCl₄ raised the m.p. to 134-136°.

Anal. Calcd. for C₁₃H₁₉NO₃: C, 65.80; H, 8.07. Found: C, 65.64; H, 8.09.

3-Ethyl-2,3-pentenediol. 3-Hydroxy-3-ethyl-2-pentanone (39.1 g., 0.3 mole) in 75 ml. of ethanol was hydrogenated using 0.30 g. of PtO₂ and 10 ml. of 0.1N base, 3 hr. 40 min. being required. The time required for hydrogenation was not shortened in another run using 20 ml. of base. 3-Ethyl-2,3-pentenediol was obtained from the two runs in 90% and in 97% yield, respectively, b.p. 105-109° at 24 mm., n_D^{25} 1.4498 and 1.4490.

No crystalline phenylurethane or α -naphthylurethane could be prepared.

3,5-Dimethyl-2,3-hexanediol. When 3-hydroxy-3,5-dimethyl-2-hexanone (43.3 g., 0.3 mole) was hydrogenated using

(9) L. S. Dedusenko, *J. Gen. Chem. U.S.S.R.*, **9**, 1294 (1939); *Chem. Abstr.*, **34**, 715 (1940).

75 ml. of ethanol, 0.30 g. of PtO₂ and 20 ml. of 0.1N base, hydrogen uptake was complete in 40 min., and upon distillation 43.5 g. (99% yield) of 3,5-dimethyl-2,3-hexanediol was obtained, b.p. 110–113° at 23 mm., n_D^{25} 1.4446.

1-(1'-Hydroxyethyl)cyclohexanol. Hydrogenation of 1-acetylcyclohexanol (42.6 g., 0.3 mole) using 75 ml. of ethanol, 0.30 g. of PtO₂, and 5 drops of 0.1N ethanolic NaOH took 30 min. (without base, 2 runs required 3 hr. each). Upon distillation there was obtained 41.7 g. (96% yield) of 1-(1'-hydroxyethyl)cyclohexanol, b.p. 75–85° at 0.8 mm., n_D^{25} 1.4828.

No phenylurethane or α -naphthylurethane could be prepared. However, esterification with 3,5-dinitrobenzoic acid using the method of Brewster¹⁰ gave the monoester in 94% yield, m.p. 122–125° after one recrystallization from ethanol (lit.⁴⁰ m.p. 122.5–123.5°).

2-Phenyl-2,3-butanediol. Hydrogenation of 25.3 g. (0.15 mole) of 3-hydroxy-3-phenyl-2-butanone in 50 ml. of ethanol

using 0.20 g. of PtO₂ and 10 drops of 0.1N NaOH in ethanol required 1 hr. 40 min. and gave 19.9 g. (78% yield) of 2-phenyl-2,3-butanediol, b.p. 106–113° at 2.0 mm. When no base was used, hydrogenation required 5.5 hr. Because of the possibility of hydrogenolysis a sample was submitted for analysis.

Anal. Calcd. for C₁₀H₁₄O₂: C, 72.26; H, 8.49. Found: C, 71.90; H, 8.77.

Acknowledgments. The authors express their sincere thanks to Dr. C. O. Herman, Air Reduction Chemical Co., New York, and to Dr. F. E. Cislak, Reilly Tar and Chemical Co., Indianapolis, for generous gifts of acetylenic alcohols. Special thanks are due G. M. Maciak of the Lilly Research Laboratories, Indianapolis, for the analyses reported and to the Eli Lilly Co. for a fellowship award to E. J. W.

NOTRE DAME, IND.

(10) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

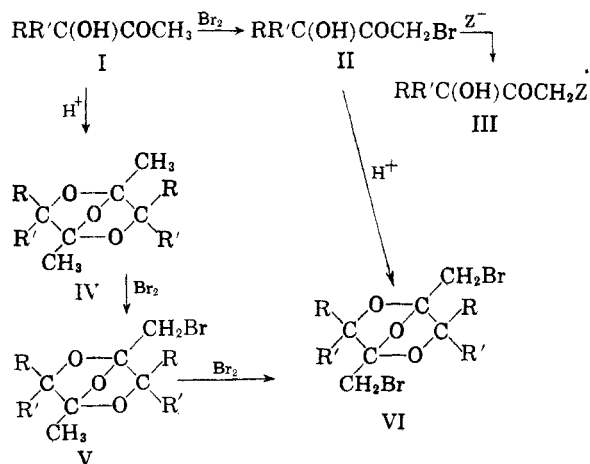
Reactions of α -Ketols Derived from Tertiary Acetylenic Carbinols. II. Bromination and Bimolecular Transannular Dehydration¹

G. F. HENNION AND E. J. WATSON²

Received October 18, 1957

α -Ketols, RR'C(OH)COCH₃, derived from tertiary acetylenic carbinols, have been found to be susceptible to a bimolecular condensation reaction in the presence of acid leading to 1,4-dimethyl-3,3,6,6-tetraalkyl-2,5,7-trioxabicyclo[2.2.1]heptanes (IV). This reaction often intervenes seriously in the bromination of the ketones so that most of the bromination product is the corresponding 1,4-bis(bromomethyl)trioxabicycloheptane (VI) rather than the anticipated bromomethyl ketone (II).

Since a variety of α -ketols are readily accessible in high yield from commercially available tertiary acetylenic carbinols,³ efforts are under way in this laboratory to develop syntheses from the ketols. One obvious approach to this end is provided by



(1) Paper LXIX on substituted acetylenes; previous paper, ref. (3).

(2) Eli Lilly Co. Fellow, 1954–1956. Abstracted from a portion of the Ph.D. Dissertation of E. J. W.

(3) G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 656 (1958).

bromination followed by various nucleophilic displacement reactions, I \rightarrow II \rightarrow III, as shown below (Z = –OH, –OCOR, –NR₂, etc.) We wish to report now our experience with the bromination step, I \rightarrow II.

At the outset of this work interest focused chiefly on dihydroxyacetone-type end products (III, Z = –OH; simple analogs of cortisone) since a significant amount of similar work had been reported by Billimoria and Maclagen,⁴ especially in the case of 1-acetylcyclohexanol [I, R and R' = –(CH₂)₅–]. The latter compound was found to brominate readily in carbon tetrachloride solution. When the solvent was removed and the residue subjected to hydrolysis under mild conditions (with sodium formate in methanol), a crystalline product, m.p. 101–111°, was recovered. Several crystallizations raised the melting point to 115–118°, indicating immediately that the product was not 1-hydroxyacetylcyclohexanol,⁴ m.p. 86–87°, but rather an unidentified dimeric bromination product mentioned by Billimoria.⁴ This substance surpris-

(4) J. D. Billimoria and N. F. Maclagen, *J. Chem. Soc.*, 3067 (1951); 3257 (1954). See also D. Papa, H. F. Ginsberg, and F. J. Villani, *J. Am. Chem. Soc.*, **76**, 4441 (1954) and G. W. Stacy, R. A. Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, **76**, 524 (1954); **79**, 3587 (1957).