intense absorption below 215 mμ, 342 mμ (ε 7600); ν_{max} (KBr) 1715 (m), 1655 (m), 1605 (m), 1550 (s), 1455 (m), 1370 (s), 1250 (m), 1120 cm^{-1} (m); δ (dimethyl sulfoxide-d_6) 6.15 (s, area 0.8, =CH), 5.95 (broad singlet, area 0.2, =CH), 2.30–0.90 (complex multiplet with sharp peaks at 1.63, 1.27, 1.20, and 1.18, area 18, CH_2 and CH_3).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; mol wt, 220. Found: C, 76.07; H, 9.25; mol wt, 220 (mass spectrometric).

2,5,6,7,8,8a-Hexahydro-2,5,5,8a-tetramethyl-2-(3-oxobutyl)-1,3-naphthalenedione (16).—A mixture of 104 mg of **13** (0.47 mmole), 0.47 ml of methanol containing 1 mg of potassium hydroxide per milliliter (0.47 mg), 2.8 ml of methanol, and 0.086 ml of methyl vinyl ketone (72 mg, 1.08 mmoles) was heated at 80° in a sealed tube for 5.5 hr.[4] Extractive work-up with ether followed by evaporation gave 140 mg of yellow oil which was chromatographed on 3 g of silica gel. Elution with 1:1 petroleum ether–ether gave an initial 9 mg of red oil, which was discarded, followed by 127 mg (92%) of light yellow oil. An analytical sample was prepared by distillation in a microsublimation apparatus: λ_{max} 239 mμ (ε 14,300); ν_{max} 1710, 1665, 1610 cm^{-1}; δ 6.23 (broad singlet, area 1, =CHCO), 2.80–1.00 [complex multiplet with sharp peaks at 2.12 and 2.08 ($COCH_3$), 1.47, 1.35, 1.30, and 1.25, area 25, CH_2 and CH_3].

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02; mol wt, 290. Found: C, 74.37; H, 9.04; mol wt, 290 (mass spectrometric).

Attempts were made to carry out the cyclization of **16** with catalytic and molar amounts of sodium methoxide, potassium *t*-butoxide, pyrrolidine, and pyrrolidine acetate under a variety of conditions. With catalytic amounts of base **16** was recovered, while molar or excess base led to recovered **13**.

Registry No.—**7**, 13395-77-2; **8**, 13395-78-3; **9**, 13395-79-4; **10**, 13395-80-7; **10a**, 13395-82-9; **13**, 13428-02-9; **16**, 13395-81-8.

Acknowledgment.—We are grateful to the U. S. Public Health Service (GM-12595) for partial support of this work.

Dependence of the Rate, Reversibility, and Stereoselectivity of 17-Keto Steroid Alkynylation on the Alkyne and on the Alkali Metal

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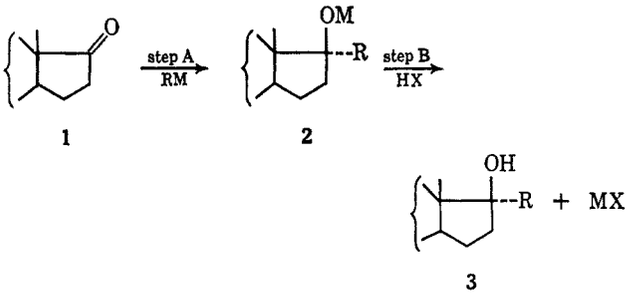
The alkynylation of estrone methyl ether (**4**) with the lithium, sodium, and potassium derivatives of propargyl alcohol, 3-butyn-1-ol, and propargylaldehyde diethyl acetal in pyridine and/or dioxane was studied. Every combination of alkali metal and alkyne tried but one gave the products of highly selective 17α attack of the keto group of **4**. That exception was the alkynylation of **4** with the potassium derivative of propargylaldehyde diethyl acetal in pyridine at room temperature, which produced a mixture containing appreciable amounts of both epimeric 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3-5(10)-trien-17-ol diethyl acetals (**9** and **10**). Nonstereoselectivity in this reaction and high stereoselectivity in the formation of 17-(3-hydroxy-1-propynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**5a**) were both found to be associated with reversibility of the alkynylations of **4** with the *potassium* derivatives of the alkynes. The rate of alkynylation of **4** depended on the structure of the alkyne in the order propargylaldehyde diethyl acetal > 3-butyn-1-ol > propargyl alcohol and on the alkali metal in the order potassium > sodium > lithium. Oxidation of **5a** produced 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17β-ol (**11**), which was also obtained by hydrolysis of **9**. Hydrolysis of **10** gave the C-17 epimer (**12**) of **11**. Assignment of the configurations at C-17 of **5a** and its epimer **6**, **9** and its epimer **10**, **11** and its epimer **12**, and 17-(4-hydroxy-1-butynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**7**) was made on the basis of their optical rotations.

Alkylations of 17-keto steroids (**1**) by organometallic reagents (RM) generally proceed by attack of the reagent at the sterically less hindered α side of the keto group (17α attack), producing **2**, which after neutralization gives the 17-alkyl steroid 17β-ol **3**.[1] Products resulting from 17β attack have been obtained in small proportion from these alkylations[2,3] and in significant proportion from alkylations with allylic Grignard reagents[4–6] and from alkylations[5] and alkynylations[7,8] in which 17α attack was sterically hindered by nearby α substituents. Concerning alkynylations in particular, little is known about factors other than nearby substituents which affect the rate, reversibility, and stereoselectivity of step A, such as the structure of the alkynyl group R and the metal M. The concern of this paper is several interesting clarifications of these relationships and their synthetic implications arising from a study of the alkynylation of estrone methyl ether (**4**) with the lithium, sodium, and potassium derivatives of propargyl alcohol, 3-butyn-1-ol, and propargylaldehyde diethyl acetal in pyridine and/or dioxane.



Results

The results of these alkynylations are summarized in Tables I–III. They were carried out in two ways. In method A the metal alkyne was prepared by adding the alkyne to a solution of the alkali metal in liquid ammonia. The solvent and **4** were added either as a solution or separately, the ammonia was allowed to evaporate, and the reaction was allowed to proceed

(1) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 467.
(2) K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1939).
(3) See ref 1, p 556.
(4) G. Muller, J. Mathieu, A. Petit, and L. Velluz, *Bull. Soc. Chim. France*, 747 (1951).
(5) P. E. Shaw, *J. Org. Chem.*, **31**, 2119 (1966).
(6) S. H. Pines, R. A. Firestone, L. Re, M. A. Kozlowski, and M. Sletzinger, *Steroids*, **8**, 877 (1966).
(7) J. Hannah and J. H. Fried, *J. Org. Chem.*, **29**, 3739 (1964).
(8) N. W. Atwater, R. H. Bible, Jr., E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *ibid.*, **26**, 3077 (1961).

TABLE I

ALKYNYLATIONS WITH PROPARGYL ALCOHOL

Expt no.	Method	Metal	Solvent	Temp, °C	Time, hr	Yield of 5, %	Yield of 6, %
1	A	K	Pyridine	25–30	7[a]	77[b]	<2[c]
2	A	K	Pyridine–dioxane	25–30	15	65[b]	...
3	A	K	Dioxane	25–30	15	52[b]	<2[c]
4	A	Na	Pyridine	25–30	24	3[b]	0[c]
5	A	Li	Pyridine–dioxane	25–30	22	0[d]	...
6	B	Li	Dioxane	Reflux	2	25[b]	...

[a] An arbitrary reaction time not meant to express rate. [b] Isolated. [c] Estimated by thin layer chromatography of column chromatographic fractions. [d] Starting material recovered quantitatively.

TABLE II

ALKYNYLATIONS WITH 3-BUTYN-1-OL

Expt no.	Method	Meta	Solvent	Temp, °C	Time, hr	Yield of 7, %
7	A	K	Pyridine	25–30	4[a]	74[b]
8	A	Na	Pyridine	25–30	24	67[b]
9	B	Li	Dioxane	Reflux	3	50[b]

[a] An arbitrary reaction time not meant to express rate. [b] Isolated.

TABLE III

ALKYNYLATIONS WITH PROPARGYLALDEHYDE DIETHYL ACETAL

Expt no.	Method	Metal	Solvent	Temp, °C	Time, hr	Yield of 9, %	Yield of 10, %
10	A	K	Pyridine	25–30	4[a]	32–36[b]	24–28[b]
11	A	Na	Pyridine	25–30	5	89[c]	0[d]
12	A	Li	Pyridine	25–30	45	73[c]	0[d]

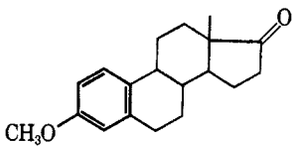
[a] An arbitrary reaction time not meant to express rate. [b] Estimated by thin layer chromatography of column chromatographic fractions. [c] Isolated. [d] Estimated by thin layer chromatography.

at room temperature. Alternatively, in method B, the lithium derivatives of propargyl alcohol and 3-butyn-1-ol were prepared by refluxing a suspension of lithium amide and the alkyne in dioxane, adding **4**, and letting the reaction take place at the reflux temperature.

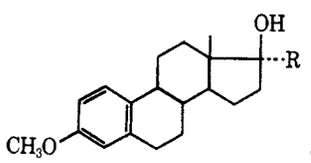
Alkynylation of **4** by method A with the reagent prepared from 4 g-atom equiv of potassium and 4 mole equiv of propargyl alcohol in pyridine at room temperature during 7 hr afforded, after hydrolysis, 17-(3-hydroxy-1-propynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**5a**),[9-11] the product of 17α attack, in 77% yield (experiment 1). These conditions proved to be optimum for the preparation of **5a** as shown by the variations given in Table I. In subsequent runs a reaction time of 4 hr sufficed without sacrifice in yields.

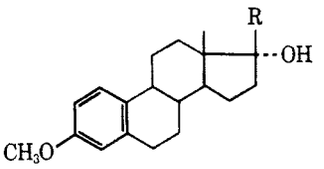
Besides **5a**, this alkynylation produced **6**, the C-17 epimer of **5a**, and several other unidentifiable and unisolable minor products, as shown by qualitative thin layer chromatography. Little or no unchanged **4** was indicated. Careful column chromatography of the mother liquors of another alkynylation (experiment 3) permitted the isolation of **6** in 0.53% yield.

When 3-butyn-1-ol was substituted for propargyl alcohol under the conditions of experiment 1, 17-(4-hydroxy-1-butynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol (**7**)[12] was produced in 73% yield (Table II, experiment 7). Examination of the mother liquor by qualitative thin layer chromatography revealed only more **7** (no indication of C-17 epimer) and unchanged **4** (10–20%). When sodium was substituted for potassium under the conditions of experiment 1, the reaction was much slower (Table I, experiment 4). Besides **5a** (3% yield), column chromatographic separation of the product mixture afforded unchanged **4** (30% yield) plus a mixture of products of similar R_f values (thin layer chromatography) intermediate between those of **4** and **5**. Estradiol methyl ether (**8**) was isolated in 3% yield by crystallization from this mixture. It was probably formed by transfer of hydride ion from sodium propargylate or the sodium salt of **5a** to **4**. Contrastingly, under otherwise identical conditions, alkynylation of **4** with the sodium salt of 3-butyn-1-ol gave **7** in 67% yield (Table II, experiment 8).



4





5a, R = C≡CCH$_2$OH
b, R = C≡CCH$_2$OCOCH$_2$CH$_2$C$_6$H$_5$
7, R = C≡CCH$_2$CH$_2$OH
8, R = H
9, R = C≡CCH(OC$_2$H$_5$)$_2$
11, R = C≡CCHO

6, R = C≡CCH$_2$OH
10, R = C≡CCH(OC$_2$H$_5$)$_2$
12, R = C≡CCHO

Starting material was recovered quantitatively from the attempted alkynylation of **4** with the lithium instead of the potassium derivative of propargyl alcohol and with pyridine–dioxane (1:1) instead of pyridine alone (Table I, experiment 5). A lithium derivative of propargyl alcohol or unknown lithium content was capable of alkynylating **4** at higher temperature. The reaction of **4** with the reagent formed from 4 mole equiv of lithium amide and 2 mole equiv of propargyl alcohol in refluxing dioxane by method B produced **5a**

(9) Compound **5a** was required for the preparation of its hydrocinnamate ester **5b**, of biological interest for the relative separation of its estrogenic and serum cholesterol lowering effects: A. Arnold, G. O. Potts, J. P. McAuliff, R. G. Christiansen, and T. C. Miller, *Proc. Soc. Exptl. Biol. Med.*, **121**, 122 (1966).

(10) After it was prepared for the present work, **5a** was reported by G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963).

(11) Earlier methods for the 17α-(3-hydroxy-1-propynylation) of 17-keto steroids consisted in treating the ketone with propargyl alcohol and potassium *t*-amyloxide in *t*-amyl alcohol (V. Wenner and T. Reichstein, *Helv. Chim. Acta*, **27**, 24 (1944), in 38% yield and S. P. Barton, G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 5094 (1957), in undisclosed yield) or with the Grignard derivative of propargyl tetrahydropyranyl ether followed by hydrolysis of the ether (S. P. Barton, *et al.*, *ibid.*, 5094 (1957), in 35% yield and ref 10 in undisclosed yield).

(12) G. D. Searle Co., British Patent 843,155 (Aug 4, 1960).

in 25% yield (Table I, experiment 6). The same conditions gave **7** in 50% yield from 3-butyn-1-ol and **4** (Table II, experiment 9).

The conditions of experiment 1 were altered by decreasing the amount of propargyl alcohol from 4 to 2.40 mole equiv while still using 4 g-atom equiv of potassium (experiment 13). Unchanged **4** was recovered in 48% yield and the yield of **5a** decreased to 32%. Little or no **6** was indicated by thin layer chromatography. The recovery of unchanged **4** suggested reversibility of step A of the alkynylation under these conditions. Reversibility of the formation of **5a** with potassium as the metal was demonstrated by subjecting **5a** to the influence of 4 mole equiv of potassium amide in pyridine at room temperature (experiment 14). Quantitative thin layer chromatography of an aliquot of the product indicated an 83% yield of **4** and an 11% yield of unchanged **5a**. No **6** was indicated.

Application of the conditions of experiment 1 to the alkynylation of **4** with propargylaldehyde diethyl acetal (Table III) in an attempt to prepare **9** gave the products of both 17α and 17β attack, 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17β-ol diethyl acetal (**9**) and 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3,5-(10)-trien-17α-ol diethyl acetal (**10**) (experiment 10).[13] In this experiment, the reagent was formed from 4 g-atom equiv of potassium and 4 mole equiv of propargylaldehyde diethyl acetal. Column chromatography permitted only a partial separation of **9** and **10**. Pure samples were obtained by recrystallization of the head and tail fractions.

Reversibility of step A in this alkynylation was suggested by the recovery of **4** in 6% yield and was confirmed by treating **9** with 1 mole equiv of the potassium derivative of propargylaldehyde diethyl acetal in pyridine at room temperature for 4 hr (experiment 15). Quantitative thin layer chromatography of an aliquot of the product allowed complete separation of **9** in 58% yield, **10** in 23% yield, and **4** in 12% yield.

The use of sodium instead of potassium provided the optimum conditions for the stereospecific preparation of **9** (Table III, experiment 11). Neither **10** nor **4** could be detected in the product. Alkynylation of **4** with the lithium derivative of propargylaldehyde diethyl acetal also produced **9** stereospecifically, but the reaction was appreciably slower and the yield was lower (Table III, experiment 12). The reaction was followed by thin layer chromatography and was not quite complete after 45 hr. No **10** could be detected in the product.

The configurational assignments of **5a**, **6**, **9**, and **10** at C-17 were correlated by the following transformations. Manganese dioxide oxidation of **5a** afforded 3-methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17β-ol (**11**), which was also obtained by hydrolysis of **9** in dilute acetic acid. Hydrolysis of **10** in dilute acetic acid afforded the C-17 epimer of **11**. Optical rotations also served to correlate the assignments. Compounds **5a**, **7**, **9**, and **11** had molecular rotation values of -20, 0, -36, and $-91°$, respectively. The 17β-alkynyl-17α-ols **6**, **10**, and **12**, on the other hand, showed high positive molecular rotation values of $+225$, $+256$, and $+256°$, respectively. Ethynylestradiol methyl ether[14] had a molecular rotation of $+14°$. The chemical shifts of the C-18 protons in the proton magnetic resonance spectra of **5a** and **6** and of **9** and **10** differed by 1 cps for each pair.

(13) Alkynylation of 3-methoxyestra-2,5(10)-dien-17-one with propargylaldehyde diethyl acetal and potassium *t*-butoxide in *t*-butyl alcohol was claimed to produce a mixture of C-17 epimers, but the experiment was not documented.[12]

Discussion

A problem of general significance in organic synthesis is the choice of a reagent which will produce the desired reaction at the desired rate and with the desired stereoselectivity. The results of this study bear importantly on this problem as it applies to the alkynylation of ketones.

The relative rates of the alkynylation of **4** in pyridine at room temperature with the sodium derivatives of the three alkynes were related to the structures of the alkynes in the order propargylaldehyde diethyl acetal > 3-butyn-1-ol > propargyl alcohol. This may be seen by examination of the reaction times for experiments 4, 8, and 11 in the tables. In these experiments, the disappearance of **4** was followed by thin layer chromatography. The data for the other two metals did not permit comparison of the rates. This order of rates reflects the balance between the relative concentrations and reactivities of the effective alkynylating reactants. The structures of these reactants may be inferred as **13**, **15**, and **17** in order of their decreasing rates of addition to **4**. These inferences may be drawn by recalling that each reactant was formed from 4 g-atom equiv of sodium and 4 mole equiv of alkyne/mole of **4** and by considering the expected relative acidities of alcoholic and acetylenic functions.[15] Thus, the two alcohols would form mostly **14** and **16** which would equilibrate with small amounts of **15** and **17**. Assessments of the relative concentrations and reactivities of **13**, **15**, and **17** must take into account electronic factors, particularly the influence of the acetal function in **13** and the proximity of the two anionic centers in **15** and in **17**, and steric factors. The latter would be influenced by the extent of solvation and aggregation of each reactant. Comparing experiments 1, 4, and 5, 7 and 8,

$$\underset{\mathbf{13}}{NaC{\equiv}CCH(OC_2H_5)_2}$$

$$\underset{\mathbf{14}}{HC{\equiv}CCH_2CH_2ONa} \rightleftharpoons \underset{\mathbf{15}}{NaC{\equiv}CCH_2CH_2ONa}$$

$$\underset{\mathbf{16}}{HC{\equiv}CCH_2ONa} \rightleftharpoons \underset{\mathbf{17}}{NaC{\equiv}CCH_2ONa}$$

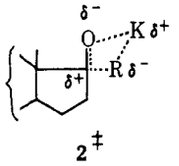
and 10–12 in the tables reveals that relative rates of *alkynylation* of **4** with the three alkynes showed a dependence on the alkali metal in the order potassium > sodium > lithium for each alkyne. Since both the length and the degree of ionic character of both metal–alkoxide and metal–alkyne bonds would be expected to vary in the same order, these results suggest that the loose bonding permitted by potassium in the transition state represented by $2^{\ddagger}$ would be most favorable for alkynylation. The relative rates of the cleavage of tertiary carbinols by alkali metal *t*-butoxides (reversal of ketone *alkylation*) have been determined.[16] In

(14) 3-Methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol, a commercial sample from G. D. Searle Co.

(15) D. J. Cram, "Fundamentals of Carbanion Chemsitry," Academic Press Inc., New York, N. Y., 1965, Chapter 1.

(16) See ref 15, pp 32–33 and 146.

dimethyl sulfoxide, the rates varied with the metal in the order potassium >> sodium >> lithium whereas in *t*-butyl alcohol they varied only slightly with the metal.



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Nonstereoselectivity in the alkynylation of **4** by the potassium derivative of propargylaldehyde diethyl acetal (experiment 10) brings to three the number of reported cases of appreciable amounts of 17β attack by organometallic reagents on 17-keto steroids not having substituents near the keto function. In experiment 10, about 40% of the alkynylation product resulted from 17β attack. In the addition of 3-methyl-2-butenylmagnesium bromide to 3β-hydroxyandrost-5-en-17-one acetate, 80% of the products were derived from 17β attack.[4] About 15% of 17β attack occurred in the addition of allylmagnesium chloride to 3β-hydroxyandrost-5-en-17-one.[6] The generality of the rule of 17α attack by organometallic reagents has thus been seriously challenged.

The association of nonstereoselectivity and reversibility in the alkynylation of **4** by the potassium derivative of propargylaldehyde diethyl acetal (experiments 10 and 13) is not without precedent. Reversibility of the formation of alkynylcarbinols by base treatment is well documented.[17,18] Pertinently, 17-ethynyl steroid 17β-ols reverted to 17-keto steroids by treatment with potassium *t*-butoxide in *t*-butyl alcohol.[18] Formation of the cyanohydrins of 17-keto steroids from potassium cyanide was nonstereoselective.[19] Cyanohydrin formation is known to occur by reversible addition of cyanide ion to a ketone or an aldehyde.[20,21] In cyanohydrin formation, however, the role of the metal has not been examined.

While experiments 10 and 13 did associate nonstereoselectivity and reversibility in the formation of **9** and **10**, they did not demonstrate the equilibrium product composition nor did they show which, if either, was the product of kinetic control of stereoselectivity. These and the question whether extended time or elevated temperature in the alkynylation of **4** with the sodium and lithium derivatives of propargylaldehyde diethyl acetal would also produce a mixture of **9** and **10** under thermodynamic control await future experimentation.

Contrastingly, high stereoselectivity was associated with reversibility in the formation and reversal of the formation of **5a** with potassium as the metal (experiments 1, 14, and 15). 17α-Ethynylation of 3β-hydroxy-5α-androstan-17-one with potassium acetylide in pyridine–ammonia at below −15°, conditions similar to those used in the present work, was also highly stereoselective.[22] In these cases, there also remain the unanswered questions whether thermodynamic control of stereoselectivity was operative and, if it was, what other factors operated in producing these contrasting stereoselectivities.

Future experimentation must provide these answers. It must also determine the effects of other solvents and the effects of further structural variations of the alkyne on the rate, reversibility, and stereoselectivity of these alkynylations.

(17) A. W. Johnson, "The Chemistry of Acetylenic Compounds," Vol. 1, Edward Arnold and Co., London, 1946, pp 131–133.

(18) H. J. Ringold in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engel, Ed., The Macmillan Co., New York, N. Y., 1961, p 218.

(19) H. Heusser, P. Th. Herzig, A. Fürst, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

(20) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp 676–678.

(21) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1956, pp 251–252.

Experimental Section

General.—Reagent-grade solvents were used for reactions. Melting points were taken in capillaries and are corrected. Qualitative and quantitative thin layer chromatographic plates were coated with silica gel supplied by Merck AG (GF_{254}). The spots were brought out on the qualitative plates (5 cm × 20 cm and 2.5 cm × 8 cm) by spraying with 20% ethanolic sulfuric acid, then heating on a hot plate. The bands on the quantitative plates (20 cm × 40 cm) were visualized by ultraviolet light. Infrared spectra were determined on 0.75% potassium bromide pellets (unless otherwise noted) on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer on 95% ethanol solutions. Proton magnetic resonance spectra were determined on heptadeuteriodimethylformamide solutions unless otherwise noted on a Varian Model A-60 spectrometer using tetramethylsilane as an internal reference. Optical rotations were determined on 1% chloroform solutions.

Experiment 1. 17-(3-Hydroxy-1-propynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol[10] (5a).—This experiment illustrates method A. Propargyl alcohol (4.54 g, 0.0810 mole) was added dropwise to a solution of potassium (3.13 g, 0.0800 g-atom) in liquid ammonia (100 ml), held under reflux by a Dry Ice condenser, and protected from atmospheric moisture by a drying tube. Pyridine (100 ml) was added, then estrone methyl ether (**4**) (mp 171–173°, 5.69 g, 0.0200 mole) as a solid. The Dry Ice condenser was removed, the ammonia was allowed to evaporate, and the mixture was blanketed with nitrogen and stirred at room temperature for 7 hr. The solid (6.6 g) obtained by quenching the reaction mixture in 0.1 *N* hydrochloric acid was triturated with methylene dichloride, affording 5.23 g of **5a**, mp 171–173°, in two crops, 76.9% yield.

An analytical sample obtained from experiment 6 showed mp 173–174° (lit.[10] mp 173–175°), $[\alpha]^{25}D$ −5.9° (lit.[10] $[\alpha]^{25}D$ 0°), λ_{max} 278 mμ (ϵ 2510) and 287 mμ (ϵ 2180). The infrared spectrum showed no acetylenic bond-stretching absorption. The proton magnetic resonance spectrum showed a two-proton singlet at 258 cps (with added deuterium oxide, $-CH_2OD$) and a three-proton singlet at 51 cps (C-18 H_3).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.83; H, 8.09.

Experiment 2 was carried out similarly with 2.84 g (0.0100 mole) of **4**, pyridine (25 ml), dioxane (25 ml), and proportional amounts of other materials. The reaction time was 15 hr.

Experiment 3. 17-(3-Hydroxy-1-propynyl)-3-methoxyestra-1,3,5(10)-trien-17α-ol (6).—The use of **4** (28.44 g, 0.100 mole) and dioxane (400 ml) instead of pyridine and proportional amounts of other materials according to method A (experiment 1) produced 17.17 g (52.3% yield) of **5a**, mp 171–173°, after a 15-hr reaction time. Chromatography of the residue from the mother liquor on a column of alumina (Merck, 480 g) afforded 0.66 g of **6** essentially free of **5a** in the ether–methanol (96:4) eluates. Two recrystallization, from ethyl acetate gave 0.18 (0.53% yield) of pure **6**, mp 153–155°, $[\alpha]^{25}D$ +66.1°. Its infrared spectrum showed no acetylenic bond-stretching absorption. Signals were observed at 256 cps (with added deuterium oxide, two protons, singlet) and at 52 cps (three protons, singlet) in the proton magnetic resonance spectrum.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.52; H, 8.33.

Experiment 4.—Experiment 1 was carried out with sodium (1.84 g, 0.0800 g-atom) instead of potassium. The reaction time

(22) E. P. Oliveto, L. Weber, and E. B. Herschberg, *J. Am. Chem. Soc.*, **76**, 4482 (1954).

was 24 hr. Chromatography of the entire crude product on a column of silica gel (Davison, 180 g) gave unchanged **4** (1.73 g, mp 164–170°, undepressed with authentic **4**) in the pentane–ether (4:1) eluates. Manual separation of the colorless rods obtained by trituration with hexane and recrystallization of them from ether–hexane gave 0.15 g (2.6% yield) of estradiol methyl ether (**8**, mp 93–94°, an allotrope of authentic material of mp 118–119°, whose melting point **8** did not depress). Compound **8** was also identified by proton magnetic resonance spectral comparison with authentic **8**.

Experiment 5.—Experiment 1 was carried out substituting lithium (0.56 g, 0.080 g-atom) for potassium and pyridine (50 ml) and dioxane (50 ml) for pyridine alone. The reaction time was 22 hr. The crude product was unchanged **4**, 5.69 g, 100%, mp 167–171°, undepressed on admixture with authentic **4**.

Experiment 6 illustrates method B. A mixture of lithium amide (3.67 g, 0.160 mole) and propargyl alcohol (4.48 g, 0.0800 mole) in dioxane was refluxed for 2 hr under nitrogen. Estrone methyl ether (**4**, 11.38 g, 0.0400 mole) was added and refluxing was continued for 2 hr. After the addition of glacial acetic acid (20 ml), the mixture was concentrated on the steam bath under reduced pressure to an amorphous yellow solid, which was partitioned between water (500 ml) and methylene dichloride (300 ml). After having been dried over sodium sulfate, filtered, and concentrated to about 100 ml, the methylene dichloride layer afforded colorless plates of **5a**, 3.46 g, 25.4% yield, mp 171–173°. Recrystallization of this material from ethyl acetate gave **5a**, mp 173–174°, 2.94 g, 21.6% yield.

Experiment 7. 17-(4-Hydroxy-1-butynyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol[12] (**7**).—Substitution of 3-butyn-1-ol (5.68 g, 0.0810 mole) for propargyl alcohol in experiment 1 (reaction time 4 hr) resulted in two crops of **7**, 5.24 g, 74.1% yield, mp 185–187°. An analytical sample from experiment 9 had mp 188–189° (lit.[12] mp 187–188°), $[\alpha]^{25}D$ 0.0°. It showed no absorption owing to the acetylenic bond in the infrared spectrum.

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.85; H, 8.74.

Experiment 8.—Experiment 7 was repeated with sodium (1.84 g, 0.0800 g-atom) instead of potassium. The yield of **7** in two crops was 4.78 g, 67.4%, mp 184–186°.

Experiment 9.—The conditions of experiment 6 with 3-butyn-1-ol (5.61 g, 0.0800 mole) substituted for propargyl alcohol produced analytically pure **7** in 44.3% yield, after recrystallizations of the crude product first from acetone, then from methylene dichloride, and finally from acetone again.

Experiment 10. 3-Methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17β-ol Diethyl Acetal (**9**).—Method A (experiment 1) was used with the following amounts of materials: liquid ammonia (200 ml), potassium (3.13 g, 0.0800 g-atom), propargylaldehyde diethyl acetal[23] (bp 75–76° (72 mm), $n^{25}D$ 1.410) (10.25 g, 0.0800 mole), pyridine (200 ml), and **4** (10.81 g, 0.0380 mole). The reaction time was 4 hr. The reaction mixture was quenched in water (1 l.) containing ammonium chloride (4.27 g, 0.0800 mole). The quench was extracted with one 100-ml and four 10-ml portions of chloroform and the combined chloroform extracts were washed with water, dried over sodium sulfate, filtered, and concentrated to a brown oil, which was chromatographed on a column of alumina (Merck, 800 g). Fractions of about 800 ml were cut. Estimates of the composition of each fraction were made by qualitative thin layer chromatography (Table IV). Two recrystallizations of fractions 28–30 from hexane gave pure **9** as colorless needles, 3.22 g, mp 99–100°, $[\alpha]^{25}D$ −8.8°. The infrared spectrum (carbon tetrachloride) of **9** showed a weak–medium absorption at 4.50 μ owing to the acetylenic bond. A one-proton singlet at 320 cps ($CH(OR)_2$) and a three-proton singlet at 51 cps (C-18 H_3) were observed in the proton magnetic resonance spectrum.

TABLE IV

Fraction	Eluent	Wt, g	Estd compn	
1–25	Pentane–ether (8:2)	0.66	100% **4** (6.1% yield)	
26	Pentane–ether (7:3)	0.25	90–100% **10**	(59.7% yield)
27	Pentane–ether (7:3)	2.41	70–80% **10**	
28	Pentane–ether (7:3)	3.34	40–50% **10**	
29	Pentane–ether (7:3)	1.65	20% **10**	
30	Pentane–ether (7:3)	0.76	10% **10**	
31	Pentane–ether (7:3)	0.62	10% **10**	
32	Pentane–ether (7:3)	0.33	100% **9**	
33–40	Pentane–ether (7:3)	0.27	...	

(23) O. H. Johnson and J. R. Holum, *J. Org. Chem.*, **23**, 738 (1958).

Anal. Calcd for $C_{26}H_{34}O_4$: C, 75.69; H, 8.80. Found: C, 75.40; H, 8.60.

3-Methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17α-ol diethyl acetal (**10**) was isolated by two recrystallizations of fraction 27 from hexane as colorless blades, 0.85 g, mp 94–95°, $[\alpha]^{25}D$ +62.2°. The infrared spectrum of **10** also exhibited the 4.50-μ band and the proton magnetic resonance spectrum showed corresponding signals at 320 and 52 cps.

Anal. Calcd for $C_{26}H_{34}O_4$: C, 75.69; H, 8.80. Found: C, 75.72; H, 8.95.

Experiments 11 and 12 were conducted like experiment 10 with the appropriate metal. The crude product was recrystallized directly from hexane and the crystals identified as **9** by mixture melting point and infrared spectral comparisons.

Experiment 13 was carried out like experiment 1 with 2.66 g (0.0475 mole) instead of 4.54 g of propargyl alcohol. The reaction time was 4 hr. Quantitative thin layer chromatography of an aliquot of the crude product (6.30 g) afforded 0.130 g (45.8% yield) of **4** (mp 163–166°) and 0.109 g (32.2% yield) of **5a** (mp 164–168°). Both were identified by mixture melting point and qualitative thin layer chromatographic comparisons. The latter indicated no **6**.

Experiment 14. Reversal of the Formation of 5a.—A solution of **4** (6.81, 0.0200 mole) in pyridine (100 ml) was added to a solution of potassium amide in liquid ammonia (100 ml) prepared from potassium (3.13 g, 0.0800 g-atom) and ferric chloride hexahydrate (0.05 g, 0.002 mole).[24] After evaporation of the ammonia, the mixture was stirred for 4 hr at room temperature under nitrogen and quenched in dilute hydrochloric acid (1. *N*, 1 l.). Quantitative thin layer chromatography of an aliquot (0.305 g) of the resulting solid (5.96 g) afforded 0.243 g (83.4% yield) of **4** (mp 166–169°) and 0.038 g (11% yield) of **5a** (mp 158–169°). Both were identified by mixture melting point and qualitative thin layer chromatographic comparisons. Although **5a** contained other impurities, no **6** was indicated.

Experiment 15. Reversibility in the Formation of 9 and 10.—A solution of **9** (8.25 g, 0.0200 mole) in pyridine (100 ml) was added to a solution of the potassium derivative of propargylaldehyde diethyl acetal in liquid ammonia (100 ml), prepared from potassium (0.78 g, 0.0200 g-atom) and the acetal (2.69 g, 0.0210 mole). After evaporation of the ammonia, the mixture was stirred for 4 hr at room temperature under nitrogen. The mixture was quenched in water (0.5 l.) containing ammonium chloride (2.2 g, 0.040 mole) and the quench was extracted with one 50-ml and three 10-ml portions of methylene dichloride. The combined methylene dichloride extracts were washed with water, dried with stirring over sodium sulfate, filtered, and concentrated to a red-brown oil (8.3 g). Quantitative thin layer chromatography of an aliquot (0.216 g) of the oil produced 0.018 g (12% yield) of **4** (mp 160–166°), 0.125 g (58% yield) of **9** (mp 92–96°), and 0.049 g (23% yield) of **10**. All were identified by mixture melting point and qualitative thin layer chromatographic comparisons.

3-Methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17β-ol (**11**). **A.**—A solution of **5a** (6.77 g, 0.0200 mole) in chloroform (300 ml) was stirred with manganese dioxide[25] (33.8 g) for 6 hr at room temperature. Filtration of the mixture, evaporation of the filtrate, and chromatography of the residue on a column of silica gel (Davison, 190 g) afforded the product (4.81 g) in the pentane–ether (1:1) eluates. Two recrystallizations of the solid from acetonitrile gave **11** as beige prisms, 2.62 g, 38.7% yield, mp 140–141.5°, $[\alpha]^{25}D$ −26.8°. Its infrared spectrum showed a medium–strong acetylenic group absorption at 4.54 μ and a very strong, broad carbonyl group absorption at 5.99–6.06 μ. Its ultraviolet spectrum showed λ_{max} 222 mμ (ε 10,200), 279 mμ (ε 2200), and 288 mμ (ε 2000). A one-proton singlet at 564 cps (–CHO) was seen in the proton magnetic resonance spectrum (deuteriochloroform).

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.33; H, 7.67.

(24) C. R. Hauser and W. R. Dunnavant, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 962.

(25) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

B.—A solution of **9** (0.41 g, 1.0 mmole) in acetic acid (9.0 ml) and water (1.0 ml) was allowed to stand for 24 hr, then diluted to 100 ml with water. The resulting solid (0.33 g, mp 139–141°, 98% yield) was identified by mixture melting point and qualitative thin layer chromatographic and infrared spectral comparisons with **11** prepared by the other method.

3-Methoxy-17-(3-oxo-1-propynyl)estra-1,3,5(10)-trien-17α-ol (12).—A solution of **10** (0.62 g, 1.5 mmole) in acetic acid (13.5 ml) and water (1.5 ml) was allowed to stand for 24 hr at room temperature, then diluted to 100 ml with water. The resulting solid (0.51 g, 100% yield, mp 93–98°) crystallized from acetonitrile as colorless microscopic crystals, 0.37 g, 73% yield, mp 94–98°, $[\alpha]^{25}D$ +75.5°. Its infrared spectrum showed absorption bands at 4.55 and 6.03 μ.

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.36; H, 7.50.

Registry No.—**4**, 1624-62-0; **5a**, 2848-92-2; **6**, 13491-22-0; **7**, 3966-17-4; **8**, 1035-77-4; **9**, 13389-55-4; **10**, 13389-56-5; **11**, 13389-57-6; **12**, 13389-58-7.

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The Preparation of α-Ketoaldehyde Derivatives from β-Keto Sulfoxides

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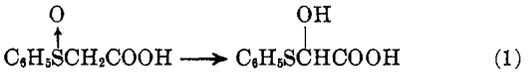
A novel preparation of α-keto acetals and α-ketoaldehyde hydrates from β-keto sulfoxides is described. Excellent yields of aliphatic as well as aromatic α-keto acetals are obtained by refluxing β-keto sulfoxides with 1 equiv of iodine in methanol. The rearrangement of β-keto sulfoxides to α-keto acetals occurs readily with a large variety of acid catalysts, but an equilibrium mixture of products is obtained (*cf.* eq 3) which strongly resists resolution into individual components by the usual methods of separation. Iodine forces the equilibrium toward the α-keto acetal by converting methyl mercaptan to dimethyl disulfide, removing it from the equilibrium system. Thus, iodine serves both as a source of acid catalyst (hydrogen iodide) and as an oxidant to remove methyl mercaptan. Support for an enolization mechanism is also presented.

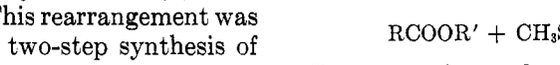
The action of acidic reagents on aromatic α-sulfinyl carboxylic acids to form hemithioacetals or other derivatives of glyoxylic acid was first reported by Pummerer[2] (eq 1). The reaction has been generalized by other



$$C_6H_5\overset{\uparrow}{\underset{O}{S}}CH_2COOH \longrightarrow C_6H_5S\overset{|}{\underset{OH}{C}}HCOOH \qquad (1)$$

workers[3,4] to include β-carbethoxy sulfoxides, β-keto sulfoxides, and β-disulfoxides. This rearrangement was also the key step in the elegant two-step synthesis of ninhydrin.[5]

No definitive study of the mechanism of the Pummerer reaction has been presented. It has been suggested[3] that a multistep dissociation–recombination mechanism initiated by attack of a proton on sulfur occurs, while several authors have suggested an intramolecular transfer of hydroxyl from sulfur to oxygen.[4-6] Evidence has been presented for an intermolecular attack of solvent or other nucleophile on a reactive intermediate[7,8] and for a carbonium ion mechanism.[9] It appeared to us that, if this reaction could be generalized for aliphatic as well as aromatic β-keto sulfoxides, it would represent a very valuable synthetic procedure for preparation of α-ketoaldehydes or their derivatives. There are few good general syntheses of α-ketoaldehydes; a good but more complex reaction sequence utilizing α-diazo ketones has recently been summarized.[10] The preparations of aliphatic[11] and aromatic[4] β-keto sulfoxides in good yield from reaction of the methylsulfinyl carbanion with the corresponding esters (eq 2) have been recently reported.



$$RCOOR' + CH_3SO\bar{C}H_2 \longrightarrow R\overset{\|}{\underset{O}{C}}CH_2\overset{\uparrow}{\underset{O}{S}}CH_3 \qquad (2)$$

Consequently we have investigated the scope of the Pummerer reaction and the conditions necessary to direct it to formation of single products in good yields.

Results

The β-keto sulfoxides were prepared by standard methods.[4,11] Structure determinations of the new compounds were based on their chemical analysis (Table I) and their infrared and nmr spectra (the methylene protons between ketone and sulfoxide in the aliphatic β-keto sulfoxides usually exhibited nonequivalence in nonpolar solvents, appearing as an AB quartet centered at τ 6.22).

Various acids in aqueous solvent systems cause the rearrangement. However, in contrast to the cases where R is aromatic and a crystalline product can be isolated, the variety of products (eq 3) possible in this equilibrium system are oils when R is aliphatic. No specific member of the equilibrium is formed exclusively and separation is very difficult. The mercaptal sulfur could not be completely removed by any of several pro-

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