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THE SYNTHESIS OF SECOSTEROID ACETYLENIC KETONES

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The fragmentation of cyclic α,β-epoxyketones by reaction with p-toluenesulfonylhydrazine to yield acetylenic ketones has recently been described (1,2). The reaction proceeds readily to yield terminal and internal acetylenes. Medium size and large ring ketones containing an acetylene function are also available by this method.

This report presents application of this reaction to several steroidal α,β-unsaturated ketones, along with modifications of the original fragmentation process.

Reaction of a representative group of 3-keto-4,5-epoxysteroids (A) with p-toluenesulfonylhydrazine in ethanol at 50° yielded the 4,5-secosteroid acetylenic ketones (B) (Table I). The 4,5-epoxysteroids (A) are available by the action of alkaline hydrogen peroxide on the Δ^4-3-ketones (3). An epimeric mixture of epoxides is obtained in which the 4β,5β-epoxide predominates (4). This mixture was utilized for the fragmentation reaction without further separation.

The 4,5-secosteroid acetylenic ketones(B) were hydrated with trifluoroacetic acid and catalytic traces of mercuric oxide to afford 4,5-secosteroid-3,5-diketones (C). Cyclization of the 4,5-seco-derivatives to the parent 3-keto-Δ^4-steroids (D) was effected with potassium t-butoxide in t-butanol. This sequence of reactions proved to be extremely useful for the preparation of a variety of C_6- and C_{10}-substituted steroids via the alkylation of either the $\Delta^{5,6}$-enolate or the $\Delta^{5,10}$-enolate derivatives of some C_5-ketones. The alkylation of these ketones will be the subject of a forthcoming publication.

The fragmentation reaction was also accomplished with some modifications. One procedure consisted of the initial preparation of the p-toluenesulfonylhydrazone of the α,β-unsaturated ketone. Treatment of the α,β-unsaturated p-toluenesulfonylhydrazone with m-chloroperbenzoic acid yields the fragmented ketone via the 4,5-epoxy-3-tosylhydrazone. Testosterone, when reacted with p-toluenesulfonylhydrazine, was converted to its 3-p-toluenesulfonylhydrazone, mp 124-139° (dec); λ_{max}^{MeOH} 259 mμ (ε = 17,500). Reaction of the 3-p-toluenesulfonylhydrazone

Table I*
4,5-SECO-ACETYLENIC KETONES**

Compound	Yield %	M.p.	$\alpha]D$ ($CHCl_3$)	NMR $\tau(CDCl_3)$***
IB -17β-hydroxy-4,5-seco-3-androstyn-5-one	85	74-78°	+ 29°	6.4 (C_{17}-H) 8.90 (C_{19}-3H) 9.20 (C_{18}-3H)
IIB - 17β-hydroxy-4,5-seco-3-estryn-5-one	65	89-90°	- 1°	6.4 (C_{17}-H) 9.17 (C_{18}-3H)
IIIB - 17α,20;20,21-bis-methylene-dioxy-4,5-seco-3-pregnyne-5,11-dione	57	149-150°		4.81, 4.93, 5.00 (BMD-4H) 6.04 (C_{21}-2H) 8.73 (C_{19}-3H) 9.17 (C_{18}-3H)
IVB - 17α,20;20,21-bis-methylene-4,5-seco-3-pregnyn-5-one	66	101-102°	- 75°	4.83, 4.87 (BMD-4H) 6.02 (C_{21}-2H) 8.90 (C_{19}-3H) 9.12 (C_{18}-3H)
VB - 17α-hydroxy-4,5-seco-3-pregnye-5,20-dione	76	185-188°		7.77 (C_{21}-3H) 8.88 (C_{19}-3H) 9.28 (C_{18}-3H)
VIB - 17α,20-isopropylidene-dioxy-4,5-seco-3-pregnyn-5-one	70	110-112	+ 24°	5.9 (C_{20}-H q) 8.68 (C_{21}-2H d, J = 6 cps) 8.60, 8.73 (isopropylidene-dioxy 6H) 8.90 (C_{19}-3H) 9.32 (C_{18}-3H)

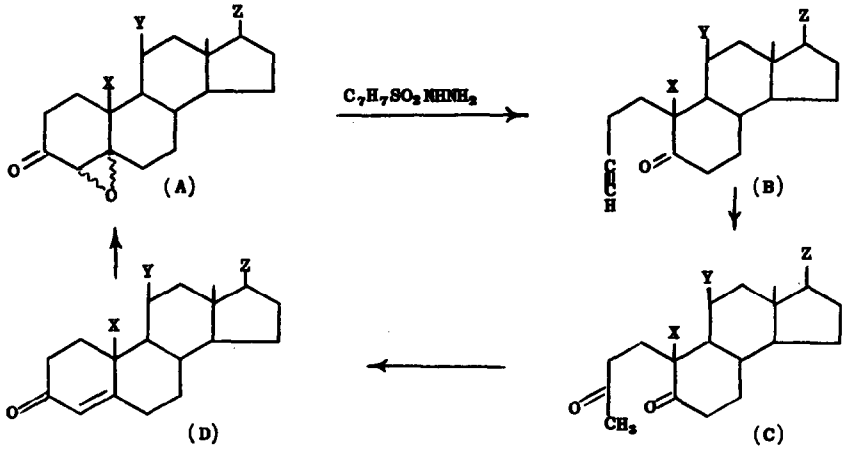
*Satisfactory analyses were obtained for all new compounds reported in this paper.
**All of the terminal acetylenic ketones exhibited bands in the infrared spectrum at 3.0 μ (≡C-H), 4.65-4.74 μ (C≡C), and 5.85 μ (> C=O).
***The nmr spectra were determined on a Varian A-60 spectrometer.

of testosterone with 1.1 equivalents of m-chloroperbenzoic acid in methylene chloride solution yielded 34% of 17β-hydroxy-4,5-seco-3-androstyn-5-one.

Testosterone, which was isolated from the reaction mixture, probably arises from the reaction of the 3-p-toluenesulfonylhydrazone derivative with m-chloroperbenzoic acid to yield the 3-hydroxy-N-p-toluenesulfonylazo derivative (E) along with the 4,5-oxide (F). The intermediate E decomposes to testosterone, p-toluenesulfinic acid, and nitrogen. The oxide F decomposes, via the fragmentation mechanism, to the seco-acetylenic ketone (B).

This modification is a convenient alternate method for the preparation of seco-acetylenic ketones in steroids when the direct epoxidation of the α,β-unsaturated ketone is difficult or unsuccessful.

Scheme 1



I: X = CH_3, Y = H_2, Z = β-OH, H

II: X = H, Y = H_2, Z = β-OH, H

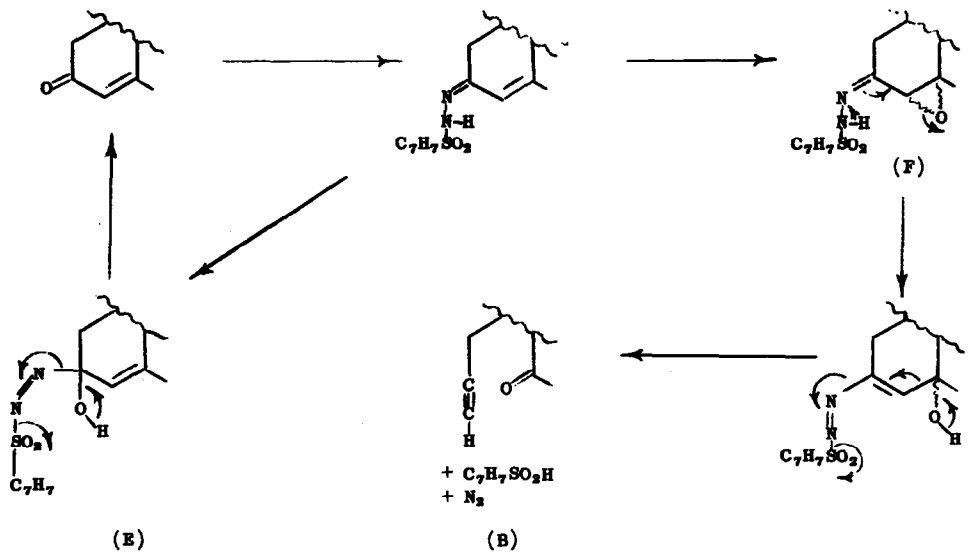
III: X = CH_3, Y = O=, Z = 17α,20;20,21-bismethylenedioxy (BMD)

IV: X = CH_3, Y = H_2, Z = BMD

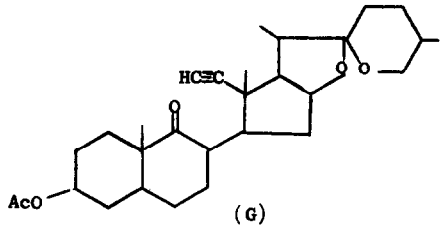
V: X = CH_3, Y = H_2, Z = α-OH, β-C(=O)-CH_3

VI: X = CH_3, Y = H_2, Z = α-OH, β-C(H)(OH)-CH_3 (17α,20-acetonide)

Scheme 2



Another illustration of the alternate method is the formation of 3β-acetoxy-9,11-seco-22α,25a,11-spirostyn-9-one (G). The parent ketone did not form a 9,11-oxide under the usual alkaline hydrogen peroxide conditions (3). Reaction of $\Delta^{9(11)}$dehydrohecogenin acetate with p-toluenesulfonylhydrazine in ethanol yields the 12-p-toluenesulfonylhydrazone, mp 270-273° (dec); λ_{max}^{Nujol} 3.05 (NH), 5.83 (OAc), 6.23, 8.25, 8.65, and 12.4 μ ($C_7H_7SO_2$). The p-toluenesulfonylhydrazone was treated with 1.2 equivalents of m-chloroperbenzoic acid in methylene chloride solution to yield G, 5%; λ_{max}^{Nujol} 3.05 μ (C≡C-H), 4.65 μ (C≡C), 5.80 μ (O-C(=O)-CH_3), and 5.85 μ (C=O); mp 203-207°; $[\alpha]_D^{23}$ -94° (dioxane).



(G)

The fragmentation reaction is not limited to the use of aromatic sulfonylhydrazine derivatives. Methanesulfonylhydrazine (1.1 equivalents) with 17β-hydroxy-4,5-epoxy-androstan-3-one in absolute ethanol gives, after nine hours at room temperature, an 80% yield of 17β-hydroxy-4,5-seco-3-androstyn-5-one. An intermediate N-methylsulfonylazo derivative can thus also function as a leaving group in the fragmentation process.

Several nonsteroidal examples of this reaction are given in Table II (2).

Table II

ACETYLENIC KETONES

Epoxyketone	Acetylenic Ketone	I.R. λ_{max}	B.P.
9,10-epoxy-1-decalone	5-cyclodecynone	5.85μ(C=O)	75-80°/2mm
10 methyl-1,9-epoxy-2-decalone	2-(1-butynyl)-2-methyl-cyclohexanone	3.0μ(C≡C-H) 4.5μ(C≡C) 5.85μ(C=O	76-80°/1mm
isophorone oxide	4,4-dimethylheptyn-6-one	3.0μ(C≡C-H 4.72μ(C≡C-H) 5.85 μ(C=O)	75-80°/14mm

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