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Preparation of Some $\Delta^{4,7}$ - and $\Delta^{1,4,7}$ -3-Keto Steroids by Deconjugation

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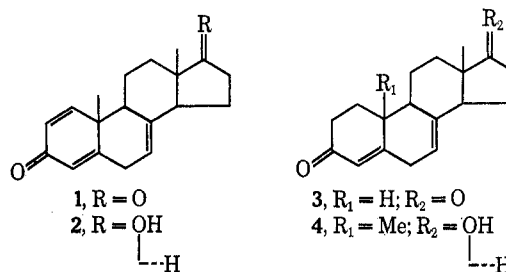
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Deconjugation of unsaturated ketones can be achieved by deprotonation with strong bases followed by acid treatment of the enolate anions formed. Thus Ringold and Malhotra¹ have recently deconjugated steroidal Δ^4 -3-ketones to the corresponding Δ^5 -3-ketones, using potassium *t*-butoxide in *t*-butyl alcohol for the deprotonation and aqueous acetic acid for the subsequent protonation, while Shapiro, Legatt, Weber, and Olivetto² converted $\Delta^{1,4}$ -3-ketones into the corresponding $\Delta^{1,5}$ -3-ketones using basic reagents, such as potassium *t*-butoxide, sodium acetylde, sodium amide, and sodium hydride, in aprotic solvents for the deprotonation and weak acids such as acetic acid and boric acid for the subsequent protonation. In some of their experiments the authors used potassium *t*-butoxide as the base and dimethyl sulfoxide as the aprotic solvent. We wish to report the preparation of some $\Delta^{4,7}$ - and $\Delta^{1,4,7}$ -3-ketones by treatment of the fully conjugated ketones with sodium methoxide in dimethyl sulfoxide and subsequent reprotonation with strong aqueous acids, such as aqueous 2 *N* hydrochloric acid. When weak acids were used for the final protonation inferior yields of the desired $\Delta^{4,7}$ - or $\Delta^{1,4,7}$ -3-ketones were obtained and this was attributed to the intermediate formation of the isomeric $\Delta^{5,7}$ - and $\Delta^{1,5,7}$ -3-ketones. Thus, when in the deconjugation of 17 β -hydroxyandrosta-4,6-dien-3-one the basic mixture was poured into aqueous 2 *N* acetic acid, ultraviolet analysis on the ether extract showed two sharp absorption peaks at 270 and 275 $m\mu$ which were considered to derive from 17 β -hydroxyandrosta-5,7-dien-3-one and which disappeared on shaking the ether extract with 2 *N* aqueous hydrochloric acid with concomitant increase in absorption at 239 $m\mu$, indicating additional formation of the desired $\Delta^{4,7}$ -3-ketone.

Generally, the conjugated ketones were treated with two parts of sodium methoxide in ten parts of dimethyl sulfoxide at room temperature and in an atmosphere of nitrogen. The basic reaction mixture was poured into excess 2 *N* hydrochloric acid; ultraviolet analysis on a small sample of reaction mixture, acidified with 2 *N* hydrochloric acid, indicated the presence of only trace amounts of starting material. For the isolation of

4 in the pure form it was found necessary to resort to chromatography.

The preparation of **4** has previously been achieved³ by allylic bromination of the ethylene ketal of testosterone benzoate, dehydrobromination to the corresponding 5,7-diene, alkaline hydrolysis of the benzoate in the 17 position, and acid hydrolysis of the 3-ketal with dilute sulfuric acid in alcohol, while **3** has been prepared⁴ by conversion of 17 β -hydroxy-4,6-estradiene-3,17-dione into the corresponding 3,17 β -diacetoxy-3,5,7-triene, sodium borohydride reduction to the 3 β ,17-dihydroxy-5,7-diene, and subsequent Oppenauer oxidation.



Experimental Section⁵

1,4,7-Androstatriene-3,17-dione (1).—To a solution of 10.0 g of 1,4,6-androstatriene-3,17-dione⁶ in 100 ml of dimethyl sulfoxide, 20 g of sodium methoxide was added in one portion. The mixture was stirred for 5 min in an atmosphere of nitrogen and then poured into a stirred solution of 600 ml of ice-cold, aqueous 2 *N* hydrochloric acid. Filtration and recrystallization of the precipitate from methanol-ethyl acetate (1:1) gave 5.5 g of 1,4,7-androstatriene-3,17-dione, mp 160–170°. Two further recrystallizations gave material of mp 168–170° (softening at 161°), $\lambda_{\text{max}}^{\text{EtOH}}$ 241 $m\mu$ (ϵ 15,800), $\nu_{\text{max}}^{\text{CHCl}_3}$ 1735 and 1663 cm^{-1} (17- and 3-ketones). The nmr spectrum showed maxima for 4 olefinic protons as multiplets between 6.0 and 7.3 (1, 2, and 4 positions) and 5.3 and 5.6 (7 position), 2 allylic protons (6 position) as a multiplet between 2.8 and 3.8, 3 protons (19 position) as a singlet at 1.28, and 3 protons (18 position) as a singlet at 0.82 ppm.

Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_2$: C, 80.81; H, 7.85. Found: C, 80.56; H, 7.99.

17 β -Hydroxy-1,4,7-androstatrien-3-one (2) was prepared as above in 60% yield from 17 β -hydroxy-1,4,6-androstatrien-3-one⁶ or from the 17-acetate, which was completely hydrolyzed under the reaction conditions: mp 185–186°; $\lambda_{\text{max}}^{\text{EtOH}}$ 242 $m\mu$ (ϵ 17,800); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3,640 (OH), 3450 (OH), and 1661 cm^{-1} (3-ketone). The nmr spectrum showed maxima for 4 olefinic protons as multiplets between 6.0 and 7.2 (1, 2, and 4 positions) and 5.15 and 5.4 (7 position), 1 proton as a broad triplet between 3.6 and 3.95 (17 position), 2 protons (6 position) as a multiplet between 2.8 and 3.5, 3 protons as a singlet at 1.25 (19 position), and 3 protons as a singlet at 0.70 ppm (18 position).

Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2$: C, 80.24; H, 8.51. Found: C, 80.13; H, 8.21.

4,7-Estradiene-3,17-dione (3) was prepared as above in 46% yield from 4,6-estradiene-3,17-dione,⁴ mp 147–148° (lit.⁴ mp 148–149°), $\lambda_{\text{max}}^{\text{EtOH}}$ 238 $m\mu$ (ϵ 15,100). The nmr spectrum showed maxima for 2 olefinic protons as a singlet at 5.9 (4 position) and as a multiplet between 5.28 and 5.48 (7 position), 2 allylic protons as a multiplet between 2.8 and 3.7 ppm (6 position), and 3 protons as a singlet at 0.80 ppm (18 position). Its infrared spectrum was identical with that of an authentic sample.

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(5) Melting points were determined with a Thomas-Hoover apparatus and are corrected. Ir spectra were determined with a Perkin-Elmer spectrophotometer, Model 21; nmr spectra were determined in deuteriochloroform with a Varian A-60 spectrometer; and chemical shifts are reported in parts per million downfield from tetramethylsilane.

(6) Productos Esteroides, Naucalpan, Mexico.

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17 β -Hydroxyandrosta-4,7-dien-3-one (4).—To 1.0 g of 17 β -hydroxyandrosta-4,6-dien-3-one,⁷ dissolved in 10 ml of dimethyl sulfoxide, was added 1.5 g of sodium methoxide. The mixture was stirred under nitrogen at room temperature for 1 hr and then added to 66 ml of ice-cold, aqueous 2 *N* hydrochloric acid with stirring. The precipitate was filtered, dissolved in methylene chloride, and then, after drying with sodium sulfate, chromatographed on Davidson silica gel, which had previously been deactivated by treatment with wet ether for 2 hr. Elution with methylene chloride-methanol 50:1 gave 400 mg of a yellow crystalline material which, after treatment with charcoal and recrystallization from methanol-ethyl acetate (1:1), gave 280 mg of white crystalline material: mp 162–164° (mp lit.³ 161–163°); $\lambda_{\text{max}}^{\text{OH}}$ 239 m μ (ϵ 15,400); and $\nu_{\text{max}}^{\text{CHCl}_3}$ 3638 (OH), 3465 (OH) and 1662 (3 ketone) cm⁻¹. The nmr spectrum showed maxima for 1 olefinic proton as a doublet ($J = 2$ Hz) centered at 5.79 (4 position), 1 olefinic proton as a multiplet between 5.1 and 5.3 (7 position), 1 proton as a broad triplet between 3.6 and 4.0 (17 position), 1 proton as a broad triplet between 3.6 and 4.0 (17 position), 2 allylic protons as a multiplet between 2.6 and 3.5 (6 position), 3 protons as a singlet at 1.19 (19 position), and 3 protons as a singlet at 0.68 ppm (18 position).

Registry No.—1, 14532-68-4; 2, 24099-37-4; 3, 13209-46-6; 4, 13386-25-9.

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(7) Prepared from testosterone acetate by the method of S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

Reaction of α Olefins with Aqueous Formaldehyde

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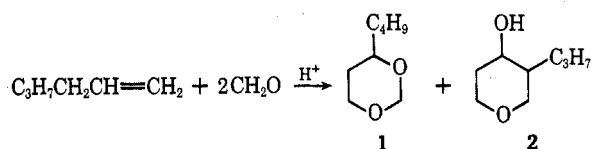
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The mineral acid catalyzed condensation of formaldehyde with olefins is commonly known as the Prins reaction.¹ It is well established that straight-chain 1-olefins are much less reactive than are substituted R(R')C=CHR'' types;² 1-olefins require either elevated temperatures with high catalyst concentrations^{2a} or the use of acetic acid solvent³ with substantial quantities of strong acid catalysts. This reaction generally leads to a rather complex mixture of products, mainly composed of 1,3-dioxanes, 1,3-glycols, and tetrahydropyranols,^{2,3} along with minor amounts of tetrahydrofuran derivatives^{2b,3,4} and the alcohol derived from hydration of the starting olefin.³

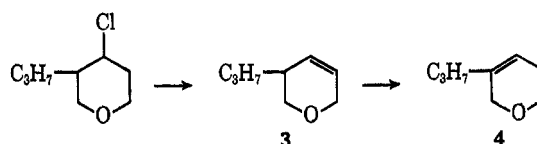
During the course of an investigation of modifications of the Prins reaction,⁵ we have also studied the

condensation of 1-olefins with aqueous formaldehyde (formalin) solutions at elevated temperatures and have developed useful synthetic procedures for the preparation of 4-alkyl-1,3-dioxanes and 3-alkyltetrahydropyran-4-ols from representative olefins from 1-pentene through 1-dodecene.

Initial studies were carried out by heating 2.0 mol of 1-hexene with 4.9 mol of 37% formalin and 8 ml of sulfuric acid at 175° in an autoclave for 5 hr. Complete conversion of the starting olefin was attained at these conditions; after distillation from a small amount of heavy residue the resulting product was analyzed by glpc and found to contain 5% of 2-hexanol, 44% of 4-butyl-1,3-dioxane (1), 45% of *cis,trans*-3-propyltetrahydropyran-4-ol (2), 6% of a mixture of dihydropyrans, and traces of other materials.



Pure 1 and 2 were obtained by fractional distillation. Structures were confirmed by elemental and spectral analysis, and in the case of 2 (a *cis-trans* mixture) by comparison with an authentic sample.⁵ 2-Hexanol and other minor products were separated by preparative glpc and identified by comparison with authentic samples (ir spectra, glpc retention times). 3,6-Dihydro-3-propyl-2H-pyran (3) and 5,6-dihydro-3-propyl-2H-pyran (4) were identified in approximately 2:1 proportions by glpc comparison with a 3:2 mixture synthesized by dehydrochlorination of *cis,trans*-4-chloro-3-propyltetrahydropyran⁵ with potassium hydroxide in ethylene glycol.



A study of variations in reaction parameters was carried out in an attempt to define optimum conditions for more selective production of either 1 or 2 from 1-hexene. A number of experiments were conducted in which the sulfuric acid concentration was varied between 0.24 and 0.40 *M*. In general, the higher acid concentrations provided increased reaction rates but also increased by-product formation. Replacement of the sulfuric acid by phosphoric acid decreased the reaction rate considerably; in addition, autoclave corrosion was markedly accelerated. Substitution of paraformaldehyde-water mixtures for the commercial formalin (stabilized with ca. 12% methanol) did not appreciably affect either the yield or product distribution nor did rather substantial variation in the olefin/formaldehyde ratio. A recycle of coproduct 4-butyl-1,3-dioxane did not affect the selectivity; the same relative distribution of products was obtained. Variation in temperature between 125 and 225° gave the expected results. At the lower end of the range reactions were slower and often incomplete while the higher temperatures gave faster reaction rates and more by-products (principally dihydropyrans). Indeed, at 225° the condensation proceeded slowly in the absence of added

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