the minor hydrocarbon obtained during hydrogenation of (+)-thujene at −20° and with the major hydrocarbon obtained during the hydrogenation of (+)-sabinene at −20° by glpc and nmr. This compound had $n^{20}\text{D}$ 1.4390; $[\alpha]^{28.5}\text{D}$ −10.05° (*c* 20, CCl_4).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.04; H, 12.86.

Hydroboration–Isomerization–Oxidation of (+)-α-Thujene.—After hydroboration of α-thujene (0.085 g) with diborane in tetrahydrofuran (0.2 ml, 2.43 *M* in BH_3), diglyme, 2 ml, was added and tetrahydrofuran was removed under vacuum. The reaction mixture was then heated at 170–175° for 2.5 hr, oxidized by alkaline hydrogen peroxide, and analyzed by glpc on column D which indicated the ratio of alcohol **A** to alcohol **B** to be 40:60.

Hydroboration–Isomerization–Oxidation of (+)-Sabinene.—To a mixture of (+)-sabinene (0.1 g) in diglyme (0.5 ml) and sodium borohydride solution in diglyme (1.0 *M*, 0.9 ml) was added at 0° boron trifluoride–diglymate (3.65 *M*, 0.33 ml). The solution was stirred for 2 hr. It was heated at 150–160° for 2.5 hr and oxidized as usual. When analyzed by glpc on column D, the ratio of alcohol **A** to **B** was 40:60.

Oxidation of 10-Thujanol with Chromic Acid.—10-Thujanol (0.1 g) was oxidized with chromic acid under the same conditions as described for thujyl alcohol. Glpc analysis on column A indicated 47% yield of the aldehydes, the ratio of 10-thujylaldehyde (**8**) (t_r 5.0 min) to 10-isothujylaldehyde (**9**) (t_r 4.1) being 97:3. 10-Thujylaldehyde was obtained by preparative glpc. Although a pure analytical sample of 10-thujylaldehyde was not obtained, it was characterized by reducing it back to 10-thujanol with sodium borohydride.

Oxidation of 10-Isothujyl Alcohol with Chromic Acid.—10-Isothujyl alcohol was oxidized under the same conditions as above. The compound gave back pure 10-isothujanol on reduction with sodium borohydride.

Equilibration of 10-Thujylaldehyde.—A mixture of 85% pure 10-thujylaldehyde and 15% 10-isothujylaldehyde (40 mg) was added to sodium ethoxide solution (0.5 *M*, 1 ml) in ethanol. It was stirred at 25° and the progress of the reaction was studied by removing aliquots and neutralizing it with 1% hydrochloric adid. The pentane extract of the neutralized reaction mixture was then analyzed by glpc on column D. The results are (time in minute and per cent thujylaldehyde) 0.85; 30, 76; 60, 63; 120, 59; 200, 59.

Registry No.—(+)-Sabinene, 2009-00-9; (−)-α-thujene, 3917-48-4; (+)-*trans*-thujane, 5523-91-1; (−)-*cis*-thujane, 4423-90-0; (+)-10-thujanol, 20-126-25-4; (+)-10-thujanol acetate, 20-126-26-5; (+)-10-isothujanol, 20-126-27-6; (+)-10-thujanol acid phthalate, 20147-89-1; (+)-10-isothujanol acetate, 20-126-28-7; (−)-3-thujanol, 20-126-29-8; (−)-3-thujanol acetate, 20-126-30-1; 3-thujanol tosylate, 20-126-31-2; (+)-α-thujene, 563-34-8; (−)-*trans*-thujane, 20126-20-9; (+)-*cis*-thujane, 7712-66-5.

The Preparation and Chemistry of 9β-Estr-4-en-3-ones

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Hydrogenation of 17α-substituted estra-4,9(10)-dien-3-ones gave the corresponding 9β-estr-4-en-3-one accompanied by the 10α isomer. Because of inherent strain, the 9β-estr-4-en-3-ones readily isomerized under mild acid or base conditions to yield the analogous 9β-estr-5(10)-en-3-ones; more vigorous conditions resulted in epimerization to the 9β,10α-estr-4-en-3-ones. Reduction of 17β-hydroxy-17α-methyl-9β-estr-4-en-3-one with Li-NH_3 yielded 17β-hydroxy-17α-methyl-5α,9β,10β-estran-3-one.

The preparation of steroids having natural configurations at various ring juncture carbons continues to be a challenge to the synthetic chemist.[1] Although the 9β C_{19} steroid analogs have been prepared,[2] the corresponding 19-nor compounds have not been reported. In an earlier study, the hydrogenation of 17β-hydroxyestra-4,9(10)-dien-3-one to give unnatural 10α,19-nor steroids was described.[1c] As the C_{17} substituent of the dienone was varied, increasing amounts of a new isomer were obtained; changes in catalyst and in solvent also resulted in increased yields of this new isomer.

As an example, when 17β-hydroxy-17α-methylestra-4,9(10)-dien-3-one[3] was hydrogenated in EtOH with Pd–$SrCO_3$ catalyst,[4] there was obtained after fractional crystallization a 26% yield of 17β-hydroxy-17α-methyl-10α-estr-4-en-3-one (**1**) and an 18% yield of the new isomer, 17β-hydroxy-17α-methyl-9β-estr-4-en-3-one (**2**). The structure of **2** was assigned on the basis of spectral studies and chemical transformation. The presence of an α,β-unsaturated ketone was indicated by the uv and ir data. Also, the nmr supported the assignment as an isomeric 19-nor-4-en-3-one, since it revealed the presence of the 4 proton as a broadened singlet at δ 5.86 and the 17- and 18-methyl protons as singlets at δ 1.23 and 1.00, respectively. The 18-methyl proton resonance of the isomeric ketone **1** was at δ 0.82.

Examination of molecular models indicates that the 9β stereochemistry necessitates the presence of a boat conformation in one of the rings; the B ring is generally assigned this conformation since the flexible terminal A ring can assume a conformation which will minimize some of the resultant strain interactions. This conformation is consistent with the nmr data, since the C_{18} angular methyl group would be expected to be deshielded because it is situated on the convex β surface of the molecule.

The circular dichroism (CD) spectrum of **2** exhibits a positive Cotton effect in the long-wavelength region and a negative Cotton effect in the π–π^* region. This curve is similar to the CD spectrum of 17β-hydroxy-9β,10α-estr-4-en-3-one, except that the short-wavelength Cotton effect is less intense.[5] Because of this lower intensity, the chirality of the chromophore appears to be more nearly planar in the predominant conformer, a situation similar to that with the 9α,10α-estr-4-en-3-

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(1) (a) P. Crabbe, A. Cruz, and J. Iriarte, *Can. J. Chem.*, **46**, 349 (1968); (b) M. Uskokovic, J. Iacobelli, R. Philion, and T. Williams, *J. Amer. Chem. Soc.*, **88**, 4538 (1966); (c) E. Farkas, J. M. Owen, M. Debono, R. M. Molloy, and M. M. Marsh, *Tetrahedron Lett.*, 1023 (1966); (d) R. Bucourt, D. Hainait, J. C. Gase, and G. Nomine, *ibid.*, 5093 (1968), and references cited therein.

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(3) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Amer. Chem. Soc.*, **82**, 2402 (1960).

(4) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

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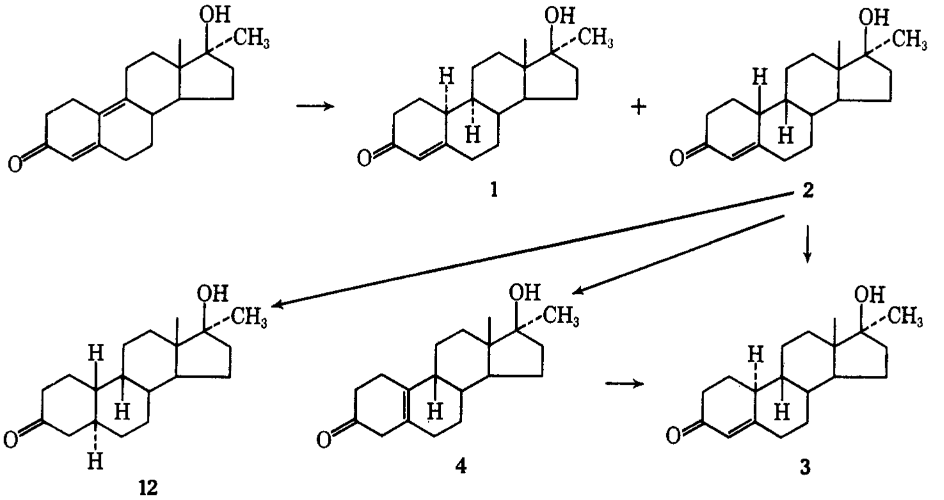
SCHEME I



ones.[1c] Unlike the 9α,10α isomer, the 9β,10β isomer experiences no change in the sign of the Cotton effect in the π–π* region on changing solvent from dioxane to methanol.

Treatment of **2** in methanolic HCl gave the isomeric ketone 17β-hydroxy-17α-methyl-9β,10α-estr-4-en-3-one (**3**) (Scheme I). Its CD spectrum was similar to that reported for the analogous C_{19} retro (9β,10α) compounds.[5] Further, the chemical stability of this compound, as evidenced by its method of preparation, favors the all-chair retro assignment.[6] Interestingly, the 18-methyl proton resonance is at δ 0.95; the natural 9α,10β isomer has the chemical shift of these protons at δ 0.91.

Of the four isomeric estr-4-en-3-ones (at C_9 and C_{10}), only the 9β isomer experiences a disappearance of the uv maximum at 243 mμ upon the addition of a few drops of aqueous base. On acidification of this solution, the chromophore does not reappear. These changes can be used as a semiquantitative assay to determine the purity of the 9β isomer. An approximate duplication of these reaction conditions on a preparative scale led to the isolation of 17β-hydroxy-17α-methyl-9β-estr-5(10)-en-3-one (**4**). The 9β assignment can be made by a comparison of physical properties with those of the 9α isomer and also by examination of the rotatory dispersion (RD) spectrum, which shows a Cotton effect minimum in the long-wavelength region while the 9α isomer displays a maximum.[7] In addition, the nmr spectrum does not contain any vinyl protons, and it has the 17-methyl proton resonance at δ 1.13 compared with δ 1.26 for the 9α isomer. This upfield shift is in agreement with the assigned structure, since the double bond at 5(10) in the 9β series could be expected to shield the 17-methyl group protons. The ready deconjugation under these mild conditions reflects the severe strain existing in the molecule. Further, the α face of the dienolate is hindered to protonation at C_{10}, and this situation also favors the formation of the deconjugated ketone.[8]

The ketone **2** can also be deconjugated using dilute mineral acid; this change too can be readily observed in the uv. More concentrated acid or longer reaction time leads to the retro (9β,10α) compound mentioned previously. This 9β,10β-estra-4-en-3-one system, under acidic conditions, leads to a dienol which is protonated at C_4, leading to the deconjugated ketone. In the normal androstenone series, the dienol is protonated with mineral acid at C_6 and with AcOH at C_2.[8] This difference in the site of protonation can again be attributed to the strain inherent with the 9β,10β stereochemistry and to the severe hindrance of the α face of the dienol.

Several other 9β-estra-4-en-3-ones have been prepared by direct hydrogenation. Although it is not clearly the result of steric factors, best yields of the 9β,10β isomer were obtained by hydrogenation of 17α-hydroxyestra-4,9(10)-dien-3-one (**5**). This latter compound was readily prepared[8] from the corresponding 17α-hydroxyestr-5(10)-en-3-one.[9] Hydrogenation of dienone **5** gave almost exclusively 17α-hydroxy-9β-estra-4-en-3-one (**6**) with traces of the 9α,10α isomer (**7**). It is worthy of comment that allylic alcohols, on catalytic hydrogenation, direct the hydrogen to approach the molecule *cis* to the alcohol group.[10] In the present nonallylic situation, the 17α alcohol directs the hydrogen to approach predominantly from the opposite side. The conformation of the D ring undoubtedly contributes to the stereochemical course of this reaction.[11] Compound **6** is extremely sensitive to acid, and even spectral grade CDCl$_3$ results in partial isomerization to the 5(10)-en-3-one compound, necessitating the use of pyridine as solvent for nmr studies. Once again the nmr spectrum of this 9β isomer has the 18-methyl proton resonance considerably farther downfield when compared to the spectra of the other 9,10-isomeric compounds.

Hydrogenation of the epimeric 17β-hydroxyestra-4,9(10)-dien-3-one did not yield any detectable amounts of the 9β isomer under a variety of conditions.[1c] In sharp contrast, it was recently shown that the presence of either a 17α- or a 17β-hydroxyl group, albeit with a different catalyst, results in hydrogenation of a 14(15) double bond from the α face.[12] Thus, in the present

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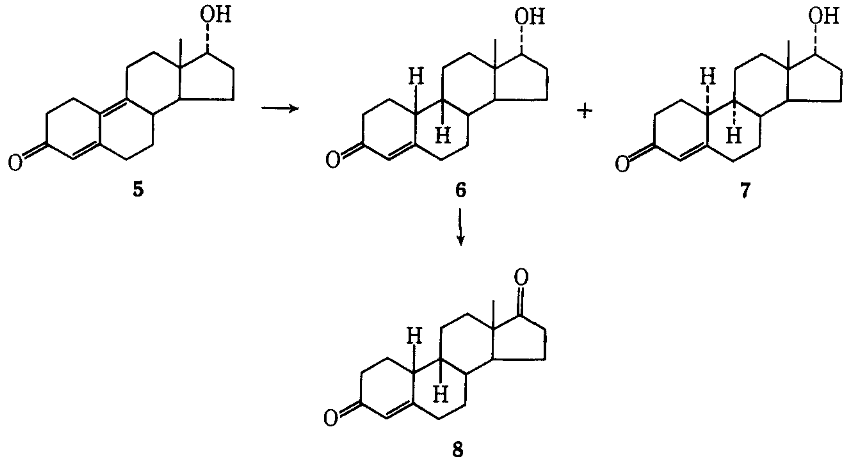
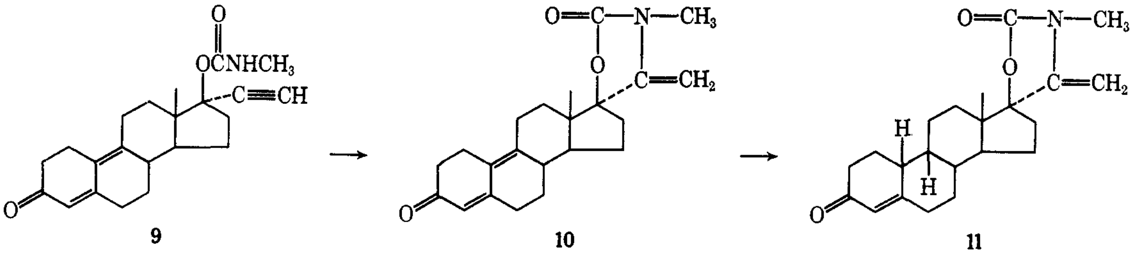
SCHEME II



SCHEME III



study, the 17α-hydroxy compound is of value, because it can be used as an intermediate for the preparation of a variety of other 17-substituted analogs. Using chromic anhydride–pyridine, 17α-hydroxy-9β-estra-4-en-3-one (**6**) can be oxidized in good yield to 9β-estr-4-ene-3,17-dione (**8**) (Scheme II). Chemical transformations of this 17-one compound are currently underway.

Added insight into the steric requirements of β-face hydrogenation was obtained on hydrogenation of N-methyl-N-{1-[17β-hydroxyestra-4,9(10)-dien-3-one-17α-yl]vinyl}carbamic acid γ-lactone (**10**). **10** was readily obtained by cyclization of the methyl carbamate **9**[13] (Scheme III). Hydrogenation using Pd–BaSO_4 catalyst led to a 25% yield of the 9β,10β isomer (**11**) as the sole crystalline product. Many of the reaction mixtures from the hydrogenations being reported are composed of mixtures of isomers which appear as a single component in a variety of tlc systems; to date these mixtures have only been resolved by fractional crystallization. The structural assignment of **11** was made on the basis of the disappearance of the uv chromophore with the addition of base and also because the 18-methyl proton resonance occurs farthest downfield when compared with its 9,10 isomers.

In addition to the reactions of the 9β-estra-4-en-3-one system already described, metal–NH_3 reduction was also studied. Compound 2 was readily converted in good yield into 17β-hydroxy-17α-methyl-5α,9β,10β-estran-3-one (**12**). This structural assignment was supported by the RD spectrum of **12**, which was nearly identical in sign and amplitude of its Cotton effect with that of the analogous cholestanone.[14] Once again the nmr spectrum revealed that the chemical shift of the 18-methyl protons again occurs further downfield than the related isomeric estranes. The A/B *trans* protonation of the radical anion obtained during the course of the reduction is consistent with current views of this reaction.[15]

Additional transformations of this novel system are currently underway.

Experimental Section

Melting points are uncorrected. The uv spectra were obtained using a Cary 15 spectrophotometer, while a Perkin-Elmer 21 was used for the ir spectra. Nmr spectra were obtained on a Varian HR-60 with TMS as internal standard. The CD and RD spectra were recorded on a Cary 50 spectropolarimeter.

17β-Hydroxy-17α-methyl-10α- and 17β-Hydroxy-17α-methyl-9β-estr-4-en-3-one (1 and 2).—Using a calibrated atmospheric hydrogenation apparatus, 0.42 g of 2% Pd–$SrCO_3$ in 30 ml of 3A EtOH was prereduced, and then 1 g of 17β-hydroxy-17α-methylestra-4,9(10)-dien-3-one in 30 ml of EtOH was added. The hydrogenation was allowed to proceed until 1.08-equiv uptake occurred (9 min). The catalyst was filtered off, the solvent was evaporated *in vacuo*, and the residue was recrystallized from Et_2O. The first crop (0.26 g), mp 177–183°, was found by uv to be the 10α isomer. Recrystallization gave mp 188–190°; uv λ_{max} (EtOH) 242 mμ (ε 15,300). There was no appreciable depression in melting point upon addition of OH^-.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.05; H, 9.64.

The second crop of material (0.18 g) was found to be the 9β isomer, mp 168–174°. Recrystallization from Et_2O gave an analytical sample, mp 186–188°; CD (*c* 0.00097, MeOH) $[\Delta\epsilon]_{365}$ ±0, $[\Delta\epsilon]_{325}$ +1.26, $[\Delta\epsilon]_{285}$ ±0, $[\Delta\epsilon]_{244}$ −8.7, $[\Delta\epsilon]_{223}$ ±0; uv λ_{max} (EtOH) 243 mμ (ε 15,500), λ_{max} (EtOH, OH^-) 235 mμ (ε 2430).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.84; H, 9.91.

Hydrogenation studies using 5% Pd–$BaSO_4$ in EtOAc in portions indicated above gave similar results.

Acid Isomerization to 17β-Hydroxy-17α-methyl-9β,10α-estr-4-en-3-one (3).—To a solution of 8 ml of MeOH and 0.04 g of 2 was added four drops of concentrated HCl. The course of the reaction was followed by removing aliquot samples and examining their uv spectra. After 20 min, the 243-mμ extinction had almost

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[14] C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

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disappeared, while, after 4.5 hr, the extinction had returned to approximately its original magnitude. Much of the solvent was removed *in vacuo*, without heat, and the solution was diluted with iced H_2O. The mixture was extracted with several portions of Et_2O, and this combined solution was washed with $NaHCO_3$ and NaCl solutions. After drying (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was recrystallized from Et_2O to give 0.022 g of **3**, mp 162–164°; CD (*c* 0.00053, MeOH) $[\Delta\epsilon]_{360}$ ±0, $[\Delta\epsilon]_{317}$ +1.89, $[\Delta\epsilon]_{273}$ ±0, $[\Delta\epsilon]_{242}$ −11.6; uv λ_{max} (EtOH) 242 mμ (ε 16,350); nmr ($CDCl_3$) δ 0.95 (s, 3 H, C-18 Me), 1.30 (s, 3 H, C-17 Me), 5.85 (s, 1 H, C-4).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.37; H, 9.70.

Nmr analysis of the noncrystalline residue showed this to be an approximately 1:1 ratio of **3** and **4** (see below).

Base Deconjugation to 17β-Hydroxy-17α-methyl-9β-estr-5(10)-en-3-one (**4**).—To a solution of 0.15 g of **2** in 25 ml of MeOH which was flushed with N_2 was added 30 drops of a 0.4 *N* solution of $NaOCH_3$ in MeOH. The resultant solution was let stand under a N_2 atmosphere for 1.5 hr. Much of the solvent was then removed *in vacuo* without heating and the solution was poured into iced H_2O which had been acidified with AcOH. This mixture was extracted with several portions of CH_2Cl_2. The combined solution was washed with NaCl solution and dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. Nmr analysis of the crude residue showed this to be predominately **4**. The residue was dissolved in a small volume of 4:1 C_6H_6/Skelly F and was chromatographed over 10 g of grade III neutral alumina. Taking 40-ml fractions, the fractions 8–30 were combined; the solvent was evaporated to dryness *in vacuo;* and the residue was crystallized from Et_2O–Skelly B to give 0.062 g, mp 121–122°; no uv; ORD (*c* 0.0011, dioxane) $[\phi]_{317}$ −3878, $[\phi]_{308}$ −4063; nmr ($CDCl_3$) δ 0.92 (s, 3 H, C-18 Me), 1.14 (s, 3 H, C-17 Me).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.54; H, 10.01.

Base Isomerization to 17β-Hydroxy-17α-methyl-9β,10α-estr-4-en-3-one (**3**).—A solution of 10 ml of MeOH and 0.1 g of **2** was flushed with N_2 and then 0.85 ml of a 0.4 *N* $NaOCH_3$ in MeOH solution was added. The resultant solution was heated at reflux under N_2 overnight. Much of the solvent was removed *in vacuo* and the solution was poured into iced H_2O. This mixture was extracted with Et_2O in several portions and the combined ethereal solution was washed in turn with $NaHCO_3$ and NaCl solutions and dried (Na_2SO_4). The solvent was evaporated *in vacuo*. Nmr analysis of the residue indicated that it was composed largely of the 9β,10α isomer. Recrystallization of the residue from Et_2O–Skelly B gave 0.041 g, mp 161–163°. This was identical with material described above.

Acid Deconjugation to 4.—To a solution of 0.2 g of **2** in 80 ml of 2 B EtOH was added 4 drops of 0.1 *N* HCl. After 2.25 hr, uv analysis of the solution indicated that the maximum at 243 mμ had diminished 95%. The solution was concentrated *in vacuo* without heat, and this concentrate was poured into iced H_2O. The mixture was extracted with several portions of Et_2O, the ethereal solution was washed with NaCl solution and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was dissolved in a small volume of 4:1 C_6H_6–hexane, and this was chromatographed over 25 g of activity III neutral alumina. Individual fractions of 10 ml were collected and the fractions between 30 and 40 were combined. The solvent was evaporated and the residue was recrystallized from Et_2O to give 0.031 g of **4**, mp 119–122°. The nmr spectrum of this material was identical with material obtained by base deconjugation.

17α-Hydroxyestra-4,9(10)-dien-3-one (**5**).—A solution of 10 g of 17α-hydroxyestra-5(10)-en-3-one[8] and 275 ml of dry pyridine was cooled in an ice bath, and then 11.7 g of pyridine perbromide hydrobromide was added in portions with swirling. The mixture was let stand in the cold for 1 hr and at room temperature for 3 hr. The mixture was poured into excess iced H_2O, and this was extracted thoroughly with CH_2Cl_2. This latter combined solution was washed eight times with 200-ml portions of 5% HCl solution and with aqueous NaCl solution and dried. The solvent was evaporated *in vacuo* and the residue was crystallized from Et_2O–Skelly F to give 6.9 g of diene, mp 127–129°; uv λ_{max} (EtOH) 304 mμ (ε 20,200).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.85.

17α-Hydroxy-9β-estr-4-en-3-one (**6**) **and 17α-Hydroxy-10α-estr-4-en-3-one** (**7**).—The hydrogenation was carried out as described above, using 0.21 g of 2% Pd–$SrCO_3$ in 35 ml of 3 A EtOH and 0.5 g of diene. There was a 1.1-equiv uptake in 5 min. After the usual treatment, the residue was crystallized from Et_2O to give 0.13 g of crystals, mp 139–140°; CD (c 0.00103, dioxane) $[\Delta\epsilon]_{385}$ ±0, $[\Delta\epsilon]_{362}$ +0.64, $[\Delta\epsilon]_{348}$ +1.15, $[\Delta\epsilon]_{334}$ +1.14, $[\Delta\epsilon]_{324}$ + 0.815, $[\Delta\epsilon]_{295}$ ± 0, $[\Delta\epsilon]_{262}$ ± 0, $[\Delta\epsilon]_{239}$ − 7.82, $[\Delta\epsilon]_{220}$ ± 0; uv λ_{max} (EtOH) 244 mμ (ε 15,500), λ_{max} (EtOH, OH^-) 240 mμ (ε 4900); nmr (pyridine-*d*$_5$) δ 0.82 (s, 3 H, C-18 CH_3) and 5.96 (br s, 1 H, C-4 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 79.01; H, 9.71.

A second crop of 0.031 g was obtained, which on recrystallization from Et_2O gave the 10α isomer, mp 177–179°; uv λ_{max} (EtOH) 243 mμ (ε 15,300); nmr (pyridine-*d*$_5$) δ 0.63 (s, 3 H, C-18), 5.94 (br s, 1 H, C-4 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 78.65; H, 9.51.

9β-Estr-4-ene-3,17-dione (**8**).—To a mixture of 0.2 g of CrO_3 in 2 ml of pyridine in an ice bath, a solution of 0.2 g of **6** in 4 ml of pyridine was added, and the mixture was let stand at room temperature for 2 days. The reaction mixture was then poured into excess iced H_2O and extracted with several portions of Et_2O. The solvent was removed from the combined solution *in vacuo* without excessive heat, and the residue was dried using a vacuum pump until the pyridine was removed. The residue was crystallized from Et_2O–Skelly F to give 0.052 g of **7**, mp 174–176°; uv λ_{max} (EtOH, OH^-) 243 (ε 16,050) and 239 mμ (ε 2,700); ir ($CHCl_3$) 1655 and 1727 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.21; H, 8.87.

17α-Ethynyl-17β-hydroxyestra-4,9(10)-dien-3-one Methyl Carbamate (**9**).—To a solution of 80 ml of CH_3NCO and 0.4 g of Dabco was added 4.0 g of 17α-ethynyl-17β-hydroxyestra-4,9(10)-dien-3-one[3] and the solution was heated at reflux overnight. The solvent was evaporated *in vacuo* and the residue was recrystallized from Et_2O to give 2.1 g of product, mp 158–160°.

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.72; H, 7.90; N, 3.99.

N-Methyl-N-{1-[17β-hydroxyestra-4,9(10)-dien-3-on-17α-yl]-vinyl}carbamic Acid γ-Lactone (**10**).—A solution comprised of 2.0 g of **9**, 100 ml of MeOH, and 8 ml of 0.4 *N* $NaOCH_3$–MeOH was heated at reflux overnight. After removal of about 1/3 of the solvent *in vacuo*, the solution was poured into excess iced H_2O. The mixture was extracted with several portions of CH_2Cl_2; this combined nonaqueous solution was washed with NaCl solution, dried over anhydrous Na_2SO_4, and evaporated to dryness *in vacuo*.

The residue did not crystallize readily and thus was chromatographed on 200 g of neutral activity III alumina using C_6H_6 as solvent. Fractions 30–100 were found to be one spot by tlc analysis and were combined. Recrystallization using Et_2O as solvent gave 0.51 g of **10**, mp 201–203°.

Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.78; H, 7.64; N, 3.78.

N-Methyl-N-[(17β-hydroxy-9β-estr-4-en-3-on-17α-yl)vinyl]-carbamic Acid γ-Lactone (**11**).—Following the procedure described for **2**, 0.21 g of 5% Pd–$BaSO_4$ in 15 ml of EtOAc was prereduced with hydrogen and then 0.5 g of **10** was added. The hydrogenation was carried out until 1.06-equiv uptake (11 min) and the catalyst was filtered. The solvent was removed *in vacuo* and the residue was recrystallized from Et_2O to give 0.149 g of **11**, mp 173–175°; uv λ_{max} (EtOH) 240 mμ sh (ε 13,600, disappears on addition of OH^-); nmr ($CDCl_3$) δ 1.10 (s, 3 H, C-18 Me), 5.90 (s, 1 H, C-4 H).

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.05; H, 8.47; N, 4.31.

17β-Hydroxy-17α-methyl-5α,9β,10β-estran-3-one (**12**).—To 200 ml of redistilled NH_3 was added 0.4 g of Li while the mixture was cooled in a dry ice bath. A solution of 0.2 g of **2** in 35 ml of dry THF was added with stirring. The reaction mixture was stirred for an additional 20 min and excess NH_4Cl was slowly added. The NH_3 was allowed to evaporate overnight and the residue was taken up with CH_2Cl_2–H_2O. The aqueous solution was further washed with CH_2Cl_2. The combined nonaqueous solution was washed with NaCl solution and dried, and the solvent was evaporated *in vacuo*. The residue was dissolved in a small volume of 3:2 Skelly F–C_6H_6 and this solution was chromatographed over 15 g of activity III neutral alumina. The fractions 10–49 were combined and again the solvent was evaporated *in vacuo*. The residue was crystallized from Et_2O–Skelly F to give 0.127 g of **11**, mp 177–178°; ORD (c 0.00207, dioxane) $[\phi]_{313}$ +2994, $[\phi]_{291}$ ±0, $[\phi]_{272}$ −1768; nmr δ 1.1 (s, 3 H, C-18 CH_3) and 1.25 (s, 3 H, C-17 CH_3).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.29; H, 10.35.

Registry No.—**1**, 5670-57-5; **2**, 20708-78-5; **3**, 4258-76-8; **4**, 20708-79-6; **5**, 20790-83-4; **6**, 20708-80-9; **7**, 20708-81-0; **8**, 6827-75-4; **9**, 20708-83-2; **10**, 20708-84-3; **11**, 20708-85-4; **12**, 20708-86-5.

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Selective Transglycosylation of Methylated 2-Acetamido-2-deoxy-β-D-glucopyranosides on a Microscale

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When heated at 125° in butyl acetate solution and in the presence of butyl alcohol and zinc chloride, methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (β **1**) is converted into a mixture of the anomeric butyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (**2**), the β anomer preponderating. Under these conditions, α **1** is not attacked and the anomeric forms of methyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranoside (**3**) are attacked to only a minor extent, and thus it appears that methylated 2-acetamido-2-deoxy-β-D-glucopyranosides may be selectively transglycosylated by this mixture of reagents. Since the anomeric forms of **2** are readily detected by gas–liquid partition chromatography (glpc) and thin layer chromatography (tlc), the method is applicable on a microscale. To explore the method further, it was applied to the chitobiose derivative **4**; the β linkage in this disaccharide was readily cleaved to give **2** and a second product which showed the chromatographic behavior expected of a butyl 2-acetamido-2-deoxy-3,6-di-*O*-methyl-β-D-glucopyranoside (**5**).

We have recently shown[2] that acetylated 2-acetamido-2-deoxy-β-D-glucopyranosides readily undergo a transglycosylation reaction when heated with benzyl alcohol at 125° in the presence of zinc chloride, giving benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside. An acetylated, β-linked disaccharide, "α-chitobiose octaacetate," was also, in part, cleaved under these conditions, and, since neither methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside nor methyl β-D-glucopyranoside tetraacetate was attacked under the transglycosylation conditions used, it is possible that a method of selective solvolysis is actually or potentially available here to cleave oligosaccharide chains at those points where a 2-acylamido-2-deoxyaldose is linked by a *trans* glycosidic bond. We have explored this reaction further, and will now describe the development of a modified transglycosylation procedure which is designed to be used on 1–5-mg quantities of material and which ought, in principle, to yield information regarding the point of attachment of the cleavage-susceptible sugar moiety.

In the earlier paper,[2] we suggested that the relative susceptibility of acetylated 2-acetamido-2-deoxy-β-D-glucopyranosides to transglycosylation arises through anchimeric assistance provided by the acetamido group in cleaving the *trans*-disposed glycosidic linkage. On the basis of evidence[3] obtained in this laboratory, it was assumed that an oxazoline was formed and that this, in turn, was attacked by the benzyl alcohol to form benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucoside. The *O*-acetyl groups were not deemed to be an essential feature of the reaction, except insofar as they masked hydroxyl groups. In adapting the process to small-scale work, gas–liquid partition chromatography of cleavage mixtures was contemplated and *O*-methyl, rather than *O*-acetyl, derivatives were used inasmuch as they would not only give products susceptible to glpc, but also the nature of these products should indicate the points of linkage in an oligosaccharide. Finally, substituted benzyl 2-acetamido-2-deoxy-D-glucopyranosides proved somewhat unsuitable for glpc examination, and we have turned to the more volatile butyl glycosides; this is a fortunate circumstance, since the medium of choice for the transglycosylation is butyl acetate, which, unless carefully purified, frequently contains a significant proportion of butyl alcohol.

At the outset, authentic samples of the anomeric butyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-D-glucopyranosides (α and β **2**) were synthesized *via* a conventional glycosylation of 2-acetamido-2-deoxy-D-glucose, followed by methylation and separation of the anomers by chromatography on silica gel; both proved to be readily crystallizable substances.

Turning now to the transglycosylation reaction, the behavior of methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (β **1**) with butyl alcohol and zinc chloride in butyl acetate solution was first examined. After 4 hr at 125°, the reaction mixture was cooled and freed of zinc chloride. Glpc as well as tlc showed that only *ca.* 2.5% of β **1** remained, the bulk of the product being β **2**, along with some α **2**. While the immediate objective here was the development of a microanalytical method, the reaction described above was repeated on a preparative scale and β **2** was isolated in 82% yield.

That α **2** is formed from β **1** was somewhat unexpected in view of the presumed mechanisms involved. Glycosides such as α **1** (as well as α and β **3**) were not anomerized under the transglycosylation conditions,

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