trate was concentrated to dryness. The viscous, oily residue was dissolved in 25 ml of dioxane, treated with 1.65 g (7.3 mmoles) of dichlorodicyanoquinone, and stirred for 2 hr at room temperature. The precipitate which had formed was removed by filtration and washed with several portions of dioxane and the combined filtrate and washings concentrated to dryness. The residue was dissolved in methylene dichloride, washed with 2 *N* sodium hydroxide and water, and dried over powdered magnesium sulfate, then evaporated to dryness, and the oily residue was chromatographed on silica gel. Elution with 5% methanol in ether afforded 0.93 g of oil which was shown by thin layer chromatography on silica gel G (1:9 methanol–ether) to be mainly 12α,17β-dihydroxyandrost-4-en-3-one (**14**), but which could not be induced to crystallize from ethyl acetate. Acetylation of the crude oil with acetic anhydride and pyridine and purification of the product by recrystallization from ether–pentane containing a trace of methylene dichloride gave 0.60 g of **12α-17β-dihydroxyandrost-4-en-3-one diacetate** (**15**), mp 191–194°. The analytical sample was prepared by recrystallization from acetone–hexane: mp 194–196°; $[\alpha]D$ +130.2°; λ_{max} 240 mμ (ε 17,300); λ_{max} 5.73, 5.77, and 7.92 ($OCOCH_3$ at C-12 and C-17), 6.00 (conjugated CO at C-3), and 6.19 μ (C=C).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.84; H, 8.10.

17β-Hydroxy-12α-isopropoxyandrost-4-en-3-one (**17**).—To a stirred suspension of 3.45 g of lithium aluminum hydride in 300 ml of tetrahydrofuran was added dropwise a solution of 3.45 g (10.0 mmoles) of 12α-isopropoxyandrost-4-ene-3,17-dione (**11**) in 300 ml of tetrahydrofuran and the mixture heated under reflux for 18 hr. Water (7 ml) was added cautiously; the precipitate was removed by filtration through Celite and washed with tetrahydrofuran. The combined filtrate and washings were concentrated to dryness to furnish a white, crystalline residue which was dissolved in 50 ml of dioxane and treated with 3.0 g (13 mmoles) of dichlorodicyanoquinone. The resulting solution was stirred for 3 hr at room temperature and the precipitate which formed during that time was collected and washed with dioxane. The filtrate and washings were combined and concentrated under reduced pressure at <50°; the residue was dissolved in methylene dichloride, washed with 2 *N* sodium hydroxide and water, dried over powdered magnesium sulfate, then concentrated to dryness. The red, oily residue was crystallized from ether–pentane to produce 2.2 g of material, mp 94–99°. Two further recrystallizations from the same solvent mixture afforded 1.57 g (45% yield) of title compound **17**: mp 93–96°; $[\alpha]D$ +125.8°; λ_{max} 243 mμ (ε 14,800); λ_{max} 3.00 (OH at C-17), 5.96 (conjugated CO at C-3), 6.19 μ (C=C).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; PrO, 17.05. Found: C, 76.14; H, 9.80; PrO, 17.38.

Acknowledgment.—The author wishes to thank Dr. Robert L. Clarke and Dr. Sol J. Daum for helpful discussions during the course of this work. Spectral determinations were carried out by Dr. R. K. Kulling, Miss C. M. Martini, Mr. M. Priznar, and staff, and analyses by Mr. K. D. Fleischer and staff. Dr. Kulling and Miss Martini assisted in the interpretation of the nmr spectra.

17β Alkylation of a 17-Keto Steroid by Alkylmagnesium Halides

PHILIP E. SHAW

Sterling-Winthrop Research Institute, Rensselaer, New York

Received February 4, 1966

The reaction of a 12α-hydroxy-17-keto steroid with methylmagnesium bromide to give both epimeric 17-methyl derivatives and with allylmagnesium bromide to give only the 17β-allyl derivative is described. Chemical evidence for the configurations of these products is presented.

Grignard addition to a 17-keto steroid generally affords the 17β-hydroxy-17α-alkyl derivative as the only product isolated.[1] However, in the large-scale preparation of 17α-methyltestosterone involving the addition of methylmagnesium bromide to dehydroepiandrosterone, a small amount of the 17β-methyl isomer was isolated.[2]

We have found that addition of methylmagnesium bromide to 3α,12α-dihydroxy-5β-androstan-17-one (**1**)[3] afforded both the 17α- and 17β-methyl isomers (**2** and **3**), respectively, and the 17α-methyl isomer predominated. Unexpectedly, addition of allylmagnesium bromide to **1** furnished the **17β-allyl derivative 14** in 81% yield as the only product isolated. This paper reports the proof of structure for these products and some related transformations.

Treatment of 3α,12α-dihydroxy-5β-androstan-17-one (**1**) with excess methylmagnesium bromide in ether–tetrahydrofuran at reflux temperature for 40–96 hr afforded the 17α-methyl derivative **2** in 34–46% yield and the 17β-methyl derivative **3** in 4–15% yield. The best yield of both derivatives was obtained by crystallization of **2** from acetone followed by acetylation of the residue from the mother liquor and chromatography to give 17α-methyl-5β-androstane-3α,12α,17β-triol 3,12-diacetate (**4**) and, finally, hydrolysis of the noncrystalline chromatography fractions to a mixture from which **3** could be separated by crystallization.

The configuration at C-17 in products **2** and **3** was determined by preparation of the corresponding diacetates, **4** and **5**, respectively, followed by hydrolysis of each diacetate in aqueous methanolic potassium hydroxide at reflux temperature for 30 min. In the case of the 17α-methyl diacetate **4**, only the 3α-acetoxy group was hydrolyzed under the reaction conditions, and the 12α-monoacetate **6** was obtained. Resistance to hydrolysis by a 12α-acetate because of the hindrance provided by a 17α-methyl substituent has been encountered in other steroid derivatives.[4] Both acetoxy groups of the 17β-methyl diacetate **5** were hydrolyzed under the same conditions and triol **3** was formed. Hydrolysis of the 12α-acetate in **5** should be even faster than that of the 3α-acetate, since the 17α-hydroxyl group bears a 1,3-diaxial relationship to the 12α-substituent and thus can assist in its hydrolysis.[5]

(1) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 467; (b) A. Butenandt and D. Peters, *Chem. Ber.*, **71**, 2688 (1938); (c) H. Heusser, K. Eichenberger, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 370, 1088 (1950); (d) J. deFlines and W. F. Van der Waard, *Rec. Trav. Chim.*, **82**, 149 (1963); (e) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963); (f) D. Bertin and J. Perronnet, *Bull. Soc. Chim. France*, 564 (1964).

(2) K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1939).

(3) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 1825 (1954).

(4) C. R. Engel, K. F. Jennings, and G. Just, *J. Am. Chem. Soc.*, **78**, 6153 (1956).

(5) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

Corroborative evidence for the configurations assigned to the 17-substituents in triols **2** and **3** was obtained by treatment of each under acetonide-formative conditions.[6] Only the 17α-hydroxy derivative **3** formed an acetonide (**7**) when treated with acetone containing a trace of perchloric acid; a dehydration product (**8a**) was also isolated in smaller amount and was characterized as the 3α,12α-diacetate **8b**. On the other hand, the 17β-hydroxy derivative **2** underwent dehydration only, and **8a** was obtained and converted to the crystalline diacetate **8b**. The nmr spectrum of **8a** showed that the C-13 methyl group had not rearranged to the 17 position (C-16 vinyl proton at 5.37, C-17 vinyl angular methyl group at 1.72, and two methyl groups at 0.73 and 0.92 ppm) Examination of a Dreiding model of triol **2** revealed that the steric arrangement of the 12α- and 17β-hydroxyl groups would prohibit acetonide formation. The acetonide group in **7** was readily removed by treatment of this compound with aqueous acetic acid, and triol **3** was recovered.

Molecular rotation values for **2** and **3** are +155° and +95°, respectively, where the 17α-hydroxy compound has the more negative value, as would be expected.[7]

We converted the 3α-hydroxy-12α,17α-acetonide **7** to a Δ^4-3-keto analog (**10**) without hydrolyzing the acetonide linkage. N-Bromoacetamide oxidation of **7** afforded a 3-keto derivative (**9a**). When **9a** was treated with 1 equiv of bromine in dimethylformamide containing a trace of *p*-toluenesulfonic acid and the crude 4β-bromo derivative **9b**, thus formed, was heated overnight with lithium bromide and lithium carbonate in dimethylformamide at steam-bath temperature,[8] the Δ^4-3-keto compound **10** was obtained.

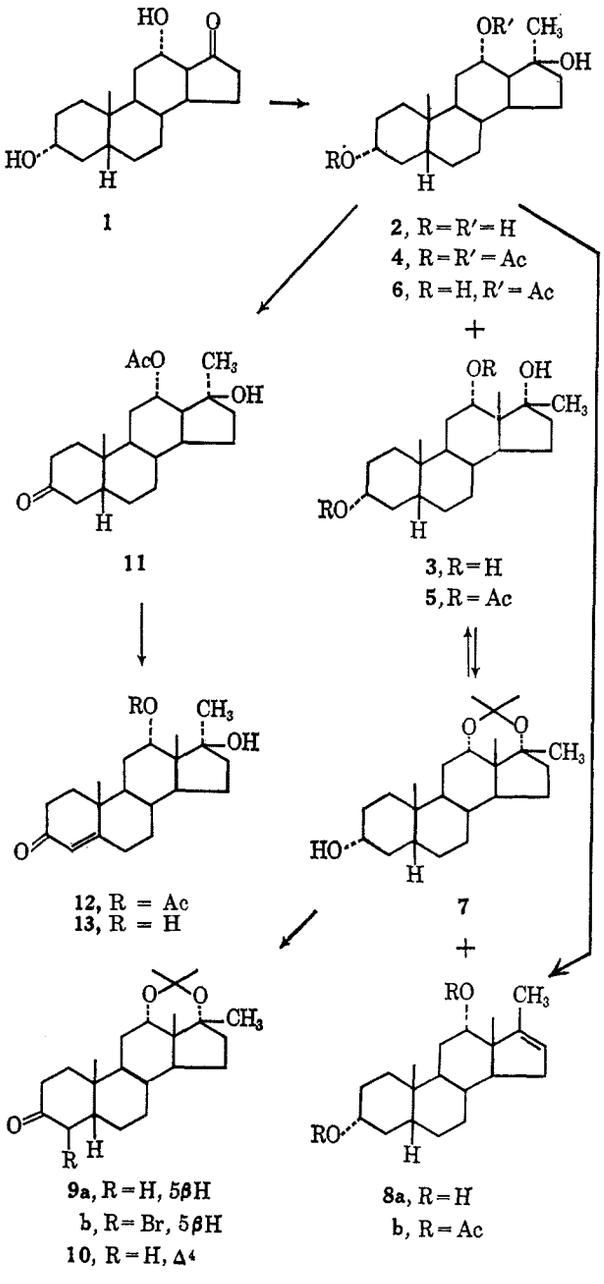
12α-Hydroxy-17α-methyl testosterone (**13**), as yet unknown, was synthesized in four steps from the monoacetate **6**. Oxidation of **6** with N-bromoacetamide in aqueous acetone produced the 3-keto derivative **11**. Bromination of **11** afforded the amorphous 4β-bromo compound which was dehydrobrominated[8] without further purification by treatment with lithium bromide and lithium carbonate in dimethylformamide to give 12α-acetoxy-17α-methyltestosterone (**12**). Hydrolysis of the hindered 12α-acetate was accomplished by treatment of **12** with aqueous methanolic potassium hydroxide at reflux temperature for 4.5 hr, and a 76% yield of 12α-hydroxy-17α-methyltestosterone (**13**) was obtained. (See Scheme I.)

Addition of allylmagnesium bromide[1b] to 3α,12α-dihydroxy-5β-androstan-3-one (**1**) resulted in β addition to the 17-ketone, and the 17β-allyl derivative **14** could be isolated in 81% yield. Attempts to isolate the 17α-allyl epimer of **14** from the mother liquor either by crystallization or by acetylation and then chromatography were unsuccessful.

Assignment of configuration at C-17 in Grignard product **14** was based on the same arguments used above. Triol **14** was acetylated with acetic anhydride and pyridine to give a diacetate (**15**), which could be hydrolyzed back to triol **14** in dilute aqueous methanolic potassium hydroxide solution at reflux temperature for 30 min. Catalytic hydrogenation of **14** to the 17β-propyl derivative **16** and acetylation

(6) J. J. Brown and S. Bernstein, *J. Org. Chem.*, **26**, 5033 (1961).
(7) Reference 1a, p 179.
(8) R. Joly, J. Warnant, G. Nomine, and D. Bertin, *Bull. Soc. Chim. France*, 366 (1958).

SCHEME I

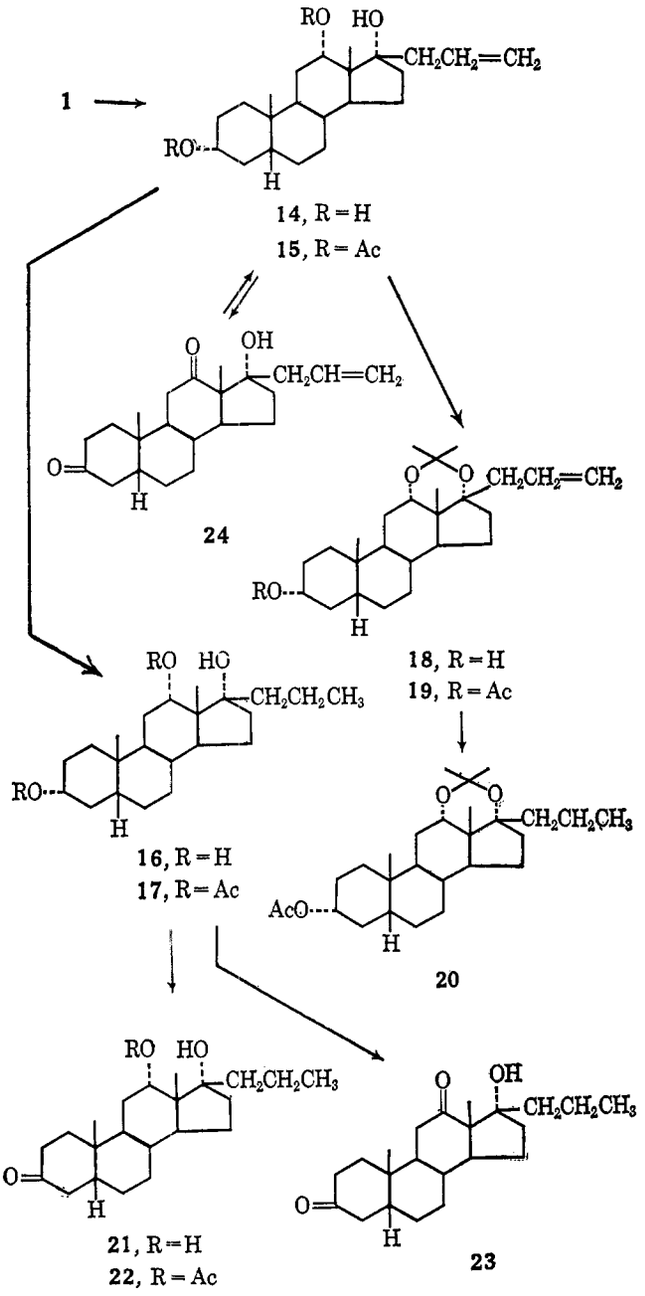


of this product gave a diacetate (**17**) which was hydrolyzed back to triol **16** under the same conditions used to hydrolyze **15** to the corresponding triol. By analogy with the epimeric 17-methyl 3α,12α-diacetates **4** and **5** above, only the epimer possessing a 17β-alkyl substituent should be completely hydrolyzed in the 30-min reaction time employed. Treatment of triol **14** under acetonide-formative conditions[6] furnished the corresponding acetonide **18** as an oil which was acetylated to form a crystalline acetyl derivative (**19**). Catalytic hydrogenation of **19** produced the corresponding 17β-propyl compound **20**. Acetonide formation from triol **14** would be possible only if the 17-hydroxy substituent were α.

Selective oxidation of the 17β-propyl-3α,12α,17α-triol **16** with N-bromoacetamide furnished the 3-keto derivative **21** in 46% yield, a selectivity previously observed in the case of 3α,12α,17α-trihydroxy-5β-pregnan-20-one.[3] Chromium trioxide–pyr-

idine oxidation of triol **16** resulted in the oxidation of both secondary hydroxyl groups, and a 3,12-diketone (**23**) was obtained. Similarly, chromium trioxide–pyridine oxidation of triol **14** gave the 3,12-diketo derivative **24**. Sodium borohydride reduced the latter diketone (**24**) back to triol **14** in 35% yield. (See Scheme II.)

SCHEME II



Experimental Section[9]

3α,12α-Dihydroxy-5β-androstan-17-one (1).—Of the two procedures described (without yields) by Adams, *et al.*,[3] for the preparation of **1** from 3α,12α-diacetoxy-5β-pregnan-20-one,[10] the procedure involving performic acid oxidation of the intermediate enol acetate was the more direct one and gave **1** in an overall yield of 45%.

Reaction of Methylmagnesium Bromide with 3α,12α-Dihydroxy-5β-androstan-17-one (1).—A solution of 10.36 g (34.1 mmoles) of 3α,12α-dihydroxy-5β-androstan-17-one (**1**) in 500 ml of tetrahydrofuran was stirred as 400 ml of a 3 *M* methylmagnesium bromide solution in ether[11] was added dropwise in 30 min. The resulting solution was refluxed for 36 hr and then cooled to room temperature. The complex was decomposed by adding 400 ml of saturated ammonium chloride solution. More ether and water were added and the layers were separated. The aqueous layer was extracted with two portions of ether and the combined organic layers were washed with saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The residue was recrystallized from acetone to give 4.5 g of material which melted at 217–222°. Concentration of the mother liquor afforded 7.1 g of a viscous, brown oil, $\lambda_{max}^{CHCl_3}$ 5.79 μ (see below). The crystalline portion of the product, upon two further recrystallizations from acetone, afforded 2.25 g of **17α-methyl-5β-androstane-3α,12α,17β-triol** (**2**), mp 224–228°. Concentration of the combined mother liquors from the last two recrystallizations afforded an additional 1.27 g of **2**, mp 220–224° (32% yield for the two crops). One recrystallization of the first crop from ethyl acetate afforded the analytical sample, mp 225–228°, $[\alpha]_D$ +48.2° (*c* 1, ethanol).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.62; H, 10.37.

The 7.1 g of oil was recycled by dissolving it in 350 ml of tetrahydrofuran and refluxing for 72 hr with 275 ml of methylmagnesium bromide solution following the above procedure. The product was an oil which was combined with the residue from the mother liquor of the second crop of **2**, and the resulting 7.6 g of residue was acetylated with acetic anhydride and pyridine at room temperature for 24 hr. The product (about 10 g of oil) was dissolved in 30% ether–70% pentane and chromatographed on 300 g of silica gel. Elution with 50% ether–50% pentane and 80% ether–20% pentane solvent mixtures afforded crystalline material which was combined and recrystallized from acetone–hexane to give 2.0 g (14% yield) of **17α-methyl-5β-androstane-3α,12α,17β-triol 3,12-diacetate** (**4**), mp 166–168°. One further recrystallization from acetone–hexane afforded the analytical sample, mp 166–168°, $[\alpha]_D$ + 101.2°.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.94; H, 9.42.

A sample of **2**, mp 225–228.5°, was acetylated with acetic anhydride and pyridine to give 17α-methyl-5β-androstane-3α,12α,17β-triol 3,12-diacetate (**4**), mp 165–167°, undepressed upon admixture with a sample of that prepared above.

Early chromatograph fractions eluted with 50% ether–50% pentane which were noncrystalline were combined with the residue obtained upon concentration of the mother liquor from the crystallization of **4** and the resulting 5.5 g of oil was hydrolyzed by refluxing it for 30 min with 4.4 g of potassium hydroxide and 11 ml of water in 225 ml of methanol. The reaction mixture was treated with 5 ml of acetic acid and the bulk of the methanol was removed by warming *in vacuo*. Ether (500 ml) was added followed by the minimum amount of water needed to dissolve all ether-insoluble material. The layers were separated and the organic layer was washed with salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The white, crystalline residue was recrystallized from methylene dichloride–ether to give 1.5 g (14% yield) of **17β-methyl-5β-androstane-3α,12α,17α-triol** (**3**), mp 207–214°. The analytical sample was prepared by recrystallization from methylene dichloride–acetone: mp 210–214°, $[\alpha]_D$ +29.2° (*c* 1 ethanol).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.25; H, 10.40.

The 3,12-diacetate 5 was prepared with acetic anhydride and pyridine and recrystallized from ether–pentane: mp 121–124°, $[\alpha]_D$ + 108.4°.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.04; H, 9.31.

Partial Hydrolysis of Diacetate 4.—To 16.0 g (39.3 mmoles) of 17α-methyl-5β-androstane-3α,12α,17β-triol 3,12-diacetate (**4**) in 650 ml of methanol was added 32 ml of 30% aqueous potassium hydroxide and the resulting solution was refluxed for 30 min. The reaction mixture was acidified with acetic acid (15 ml) and the bulk of the methanol removed *in vacuo* at <45°. Ether and methylene dichloride were added and the organic solution was

(9) Melting points are corrected unless otherwise stated. Except as noted, specific rotations were measured in chloroform solution (1%) at 25°, ultraviolet spectra in 95% ethanol (Cary), infrared spectra in potassium bromide disks (Perkin-Elmer 21), and nmr spectra in deuteriochloroform solution (20%) with tetramethylsilane as an internal standard (Varian A-60).

(10) Canada Packers Ltd., Toronto, Canada.

(11) Arapahoe Chemicals, Inc., Boulder, Colo.

washed with saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The residue was crystallized from ether to produce 13.0 g (90% yield) of **17α-methyl-5β-androstane-3α,12α,17β-triol 12-acetate** (**6**) as a solvate, mp 118–122° (bubbling), which was suitable for N-bromoacetamide oxidation without further purification (see below). Thin layer chromatography revealed that a trace of more polar material was present and so the analytical sample was prepared by chromatography of 0.50 g of the solvate on 15 g of silica gel. Elution with 1:9 methylene dichloride–ether afforded an oil which was crystallized from ethyl acetate to give 0.32 g of **6**, mp 162.5–163°, $[\alpha]D$ + 74.4°.

Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.34; H, 9.88.

Hydrolysis of Diacetate 5.—A sample of 17β-methyl-5β-androstane-3α,12α,17α-triol 3,12-diacetate (**5**), mp 123–124.5°, hydrolyzed in the same manner, gave a 57% yield of triol **3**, mp 210–215°, and undepressed upon admixture with the sample from the Grignard reaction described above. The infrared spectra of the two samples were identical.

12α,17α-Isopropylidenedioxy-17β-methyl-5β-androstan-3α-ol (**7**).—A solution of 3.65 g (11.3 mmoles) of 17β-methyl-5β-androstane-3α,12α,17α-triol (**3**) in 440 ml of acetone containing 20 drops of 72% perchloric acid was kept for 3.5 hr at room temperature. The reaction mixture was treated with 220 ml of water and then sufficient saturated sodium bicarbonate solution (about 15 ml) was added to neutralize the acid present. The acetone was removed by concentration *in vacuo* at <50° and the aqueous residue was extracted twice with ether. The ether extracts were combined and washed with saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The residue was taken up in 1:9 methylene dichloride–ether and poured into a column containing 120 g of silica gel. The first 1000 ml of eluate afforded crystalline material which was recrystallized from ether–pentane to give 1.8 g (44% yield) of acetonide **7**, mp 166–169°. Two further recrystallizations from the same solvent mixture afforded the analytical sample, mp 168.5–170°, $[\alpha]D$ + 13.6°.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.49; H, 10.78.

Elution of the chromatograph column with methanol followed by recrystallization of the eluted solid from acetone gave 0.25 g (7% recovery) of starting material **2**, mp 211–216°.

In a larger run (8.5 g), there was obtained about 11 g of oily product which was chromatographed on 275 g of silica gel. Elution of the chromatographic column with 1:3:6 methylene dichloride–ether–pentane produced 5.0 g of acetonide **7**. Elution with 1:9 methylene dichloride–ether afforded 2.1 g of **8a** as an oil: nmr vinyl H at C-16, 5.37 ppm; two *t*-CH_3, 0.73 and 0.92 ppm; vinyl *t*-CH_3 at C-17, 1.72 ppm. Elution with 1:19 methanol–ether furnished 0.8 g of starting material **3**.

17-Methyl-5β-androst-16-ene-3α,12α-diol Diacetate (**8b**).—A 2.0-g portion of **8a** prepared in the above experiment was acetylated with acetic anhydride and pyridine and the product purified by recrystallization from methanol to give 1.50 g of the diacetate (**8b**), mp 139–143°. One further recrystallization from the same solvent afforded the analytical sample: mp 143–146°; $[\alpha]D$ + 110.9°; λ_{max} 3.35 (w), 5.81 (s), 6.17 (w), 8.02 (s), 8.11 μ (s).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.12.

Dehydration of 17α-Methyl-5β-androstane-3α,12α,17β-triol (**2**).—A solution of 5.0 g (15.5 mmoles) of triol **2** in 500 ml of acetone containing 20 drops of 70% perchloric acid was kept for 2 hr at room temperature and then 50 ml of 2 *N* sodium hydroxide was added and the acetone removed by warming *in vacuo*. The aqueous residue was extracted with ether, the layers were separated, and the organic layer was washed with water and salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The 5.15 g of oily residue was chromatographed on 150 g of silica gel and the 2.50 g of oily material (**8a**) which was eluted with 1:6:3 methylene dichloride–ether–pentane was acetylated with acetic anhydride and pyridine. Purification of the acetylated material by recrystallization from methanol produced 1.0 g of diacetate **8b**, mp 139–145°. A second crop of 0.34 g, mp 137–144°, was obtained by concentration of the mother liquor. Recrystallization of the first crop from methanol afforded a sample of 0.65 g, mp 143–145°, identical by mixture melting point and infrared spectral comparison with a sample prepared in the previous experiment.

Cleavage of the Acetonide Linkage of 7.—To 0.05 g of acetonide derivative **7** in 28 drops of acetic acid was added 7 drops of water and the solution was kept at room temperature for 2.5 hr. The precipitate which had formed was collected and washed with water and hexane and dried to give 0.03 g of 17β-methyl-5β-androstane-3α,12α,17α-triol (**3**), mp 208–212°. Recrystallization from acetone–hexane afforded a sample, mp 208–214°, undepressed upon admixture with the sample obtained from the Grignard reaction described above. The infrared spectra of the two samples were identical.

12α,17α-Isopropylidenedioxy-17β-methyl-5β-androstan-3-one (**9a**).—A solution of 0.15 g (0.41 mmole) of 12α,17α-isopropylidenedioxy-17β-methyl-5β-androstan-3α-ol (**7**) and 0.17 g (1.2 mmoles) of N-bromoacetamide in 1 ml of pyridine, 1 ml of water, and 10 ml of *t*-butyl alcohol was allowed to stand overnight at room temperature in the dark and then poured into 25 ml of water containing 0.25 g of sodium sulfite. The aqueous mixture was extracted with four portions of ether and the combined ether extracts were washed with saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The residue was recrystallized from ether–pentane to give 92 mg (62% yield) of title compound (**9a**), mp 164–168°. The analytical sample was prepared by recrystallization from the same solvent mixture: mp 162.5–165°, $[\alpha]D$ + 13.1°, λ_{max} 5.86 μ.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.51; H, 9.81.

12α,17α-Isopropylidenedioxy-17β-methylandrost-4-en-3-one (**10**).—To a solution of 2.95 g (8.2 mmoles) of the 3-keto compound **9a** in 60 ml of dimethylformamide containing 0.03 g of *p*-toluenesulfonic acid was added in one portion a solution of 1.31 g (8.2 mmoles) of bromine in 15 ml of dimethylformamide. The reaction mixture was kept for 2.5 hr at room temperature; during this period the solution gradually lightened in color until it became almost colorless. It was poured into 75 ml of saturated sodium bicarbonate solution in 750 ml of water and the aqueous mixture was extracted with two portions of ether. The ether extracts were combined, washed with saturated salt solution, and dried over powdered magnesium sulfate, then concentrated to dryness, affording bromo ketone **9b** as a white, crystalline solid, mp 135–144°. A 0.10-g portion of this solid was recrystallized twice from acetonitrile to give a small amount of material melting at 167–169° which was not analytically pure (bromine analysis 1% low), λ_{max} 5.79 μ.

The bulk of the crude bromo ketone was dehydrobrominated without further purification by dissolving it in 60 ml of dimethylformamide, adding 3.0 g of lithium carbonate and 3.2 g of lithium bromide, and heating the mixture for 18 hr on a steam bath with stirring. The reaction mixture was cooled and poured into water, then extracted with two portions of ether. The extracts were combined, washed with water and salt solution, and dried over powdered magnesium sulfate, then concentrated to a small volume and cooled. The precipitate was collected and dried to furnish 1.33 g (45% yield) of title compound, mp 200–207°. One recrystallization from methanol afforded the analytical sample, mp 207–210°, $[\alpha]D$ + 52.4°, λ_{max} 241 mμ (ε 16,300).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.83; H, 9.60.

12α,17β-Dihydroxy-17α-methyl-5β-androstan-3-one 12-Acetate (**11**).—A solution of 9.50 g (25.9 mmoles) of 17α-methyl-5β-androstan-3α,12α,17β-triol 12-acetate (**6**) in 150 ml of acetone was treated with 38 ml of water and 10.5 g of N-bromoacetamide. The resulting solution was kept in the dark at 5° for 2 hr and then poured into 300 ml of water containing 20 g of sodium sulfite. The mixture was extracted with four portions of ether and the combined extracts were washed with water and saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The oily residue was crystallized from acetone–hexane, affording 4.85 g of title compound, mp 127–128.5°. Concentration of the mother liquor afforded a second crop of 2.0 g of product, mp 121–129° (73% total yield). One recrystallization of the first crop from acetone–hexane afforded the analytical sample with the melting point unchanged, $[\alpha]D$ + 82.5°.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.66; H, 9.51.

12α,17β-Dihydroxy-17α-methylandrost-4-en-3-one 12-Acetate (**12**).—To a stirred solution of 4.46 g (12.3 mmoles) of 12α,17β-dihydroxy-17α-methyl-5β-androstan-3-one 12-acetate (**11**) in 45 ml of acetic acid containing 1 drop of 30% hydrogen bromide

in acetic acid was added dropwise a solution of 1.96 g (12.3 mmoles) of bromine and 0.95 g (11.6 mmoles) of fused sodium acetate in 85 ml of acetic acid. The reaction mixture was at once poured into water and the aqueous mixture extracted with two portions of ether. The ether extracts were combined, washed with 10% sodium carbonate and water, and dried over powdered magnesium sulfate, then concentrated to dryness to give 5.1 g of 4β-bromo derivative as a clear, colorless oil. Without further purification, this oil was dissolved in 55 ml of dimethylformamide, and 3.36 g of lithium carbonate and 3.82 g of lithium bromide were added. The resulting suspension was stirred and heated on a steam bath for 16 hr. To the cooled reaction mixture were added 1 l. of ether and 250 ml of 1 *N* hydrochloric acid and the layers were separated. The ether layer was washed with saturated sodium bicarbonate solution, water, and saturated salt solution and dried over powdered magnesium sulfate, then evaporated to dryness. Crystallization of the residue from acetone–hexane afforded 1.80 g (40% yield) of title compound, mp 179–183°. Two further recrystallizations from the same solvent mixture gave the analytical sample, mp 186.5–188.5°, $[\alpha]_D$ + 157.2°, λ_{max} 240 mμ (ε 15,700).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.24; H, 9.25.

12α,17β-Dihydroxy-17α-methylandrost-4-en-3-one (13).—A solution of 1.00 g (2.77 mmoles) of 12α,17β-dihydroxy-17α-methylandrost-4-en-3-one 12-acetate (**12**) and 2.38 g of potassium hydroxide in 35 ml of methanol was refluxed for 4.5 hr under nitrogen. The reaction mixture was acidified with acetic acid and the methanol was removed by concentration *in vacuo* at <45°. To the residue were added 300 ml of ether and the minimum amount of water (10–20 ml) necessary to dissolve the solid residue completely. The layers were separated and the ether layer was washed with saturated salt solution, dried over powdered magnesium sulfate, and decolorized with charcoal, then concentrated to give a pale yellow crystalline residue. Recrystallization from acetone–hexane afforded 0.67 g (76% yield) of title compound, mp 192–194°. One further recrystallization from the same solvent mixture furnished the analytical sample, mp 193–194.5°, $[\alpha]_D$ +109.2°; λ_{max} 242 mμ (ε 15,700).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.77; H, 9.28.

17β-Allyl-5β-androstane-3α,12α,17α-triol (14).—A solution of 6.5 ml of allyl bromide in 65 ml of absolute ether was added to 6.5 g of magnesium turnings and the mixture allowed to stand until considerable cloudiness had developed (about 5 min). The liquid was removed by decantation and 125 ml of anhydrous ether was added to the etched magnesium thus prepared. To the vigorously stirred mixture was added dropwise in 75 min a solution of 6.5 g (21 mmoles) of 3α,12α-dihydroxy-5β-androstan-17-one (**1**) and 15.5 ml (180 mmoles) of allyl bromide in 40 ml of tetrahydrofuran and 175 ml of anhydrous ether. Every 20 min during the dropwise addition, 2-g portions of magnesium were added. At the end of the addition, the reaction mixture was refluxed for 4 hr. More ether (150 ml) and 250 ml of methylene dichloride were added and the complex was decomposed by the addition of 300 ml of saturated ammonium chloride solution. The layers were separated and the organic layer was washed with salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. Recrystallization of the residue from acetone afforded 5.50 g of title compound, mp 217–219°. Concentration of the mother liquor gave 0.60 g of material, mp 207–214°, which upon recrystallization from acetone furnished an additional 0.50 g of **14**, mp 216–218° (total yield 81%). The analytical sample was prepared by recrystallization from acetone: mp 219–220°, $[\alpha]_D$ + 36.2°.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 76.03; H, 10.23.

Acetylation of **14** with acetic anhydride and pyridine furnished the **3,12-diacetate 15**, mp 97–98.5°, $[\alpha]_D$ + 107.2°.

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.90; H, 9.23.

Hydrolysis of 17β-Allyl-5β-androstane-3α,12α,17α-triol 3,12-Diacetate (15).—To 0.25 g (0.58 mmole) of the 3,12-diacetate (**15**) in 10 ml of methanol was added 0.5 ml of a solution of 2.0 g of potassium hydroxide in 5 ml of water and the reaction mixture refluxed for 30 min. The solution was cooled to room temperature and acidified with acetic acid (6 drops), then concentrated to about half the original volume by warming *in vacuo*. Methylene dichloride and water were added. The layers were separated and the organic layer was washed with saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. Recrystallization of the residue from acetone afforded 0.19 g (91% yield) of triol **14**, mp 222–223°, undepressed upon admixture with a sample prepared above. The infrared spectra of the two samples were identical.

17β-Propyl-5β-androstane-3α,12α,17α-triol (16).—To a solution of 1.00 g (2.87 mmoles) of 17β-allyl-5β-androstane-3α,12α,-17α-triol (**14**) in 25 ml of undenatured 95% ethanol was added 0.10 g of 10% palladium on carbon and the mixture was shaken at room temperature in 1 atm of hydrogen until 1 molar equiv was absorbed (90 sec). The catalyst was removed by filtration through Celite, and the filtrate was concentrated to dryness by warming *in vacuo*. Recrystallization of the residue from acetone gave 0.78 g of title compound, mp 215–217°, $[\alpha]_D$ + 18.3°.

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Found: C, 75.36; H, 11.04.

The **diacetate** of **16** (compound **17**) was prepared with acetic anhydride and pyridine and purified by recrystallization from methanol: mp 144–146°, $[\alpha]_D$ + 108.2°.

Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.91; H, 9.61.

Hydrolysis of 17β-Propyl-5β-androstane-3α,12α,17α-triol 3,12-Diacetate (17).—A 0.25-g sample of the 3,12-diacetate (**17**) was hydrolyzed by the method described for the hydrolysis of **15** (see above). The product was purified by recrystallization from acetone to give 0.18 g (89% yield) of 17β-propyl-5β-androstane-3α,12α,17α-triol (**16**), mp 216–218°, undepressed upon admixture with a sample prepared by hydrogenation of **14**. The infrared spectra of the two samples were identical.

17β-Allyl-12α,17α-isopropylidenedioxy-5β-androstan-3α-ol Acetate (19).—A suspension of 4.3 g (12 mmoles) of 17β-allyl-5β-androstane-3α,12α,17α-triol (**14**) in 430 ml of acetone was stirred as ten drops of 70% perchloric acid was added. After the mixture had been stirred for 10 min, all material was in solution and an amber color had developed. The solution was kept for 3 hr at room temperature and then 200 ml of water and 20 ml of saturated sodium bicarbonate solution were added. The acetone was removed by warming *in vacuo* and the aqueous residue was extracted with two portions of ether. The extracts were combined, washed with saturated salt solution, and dried over powdered magnesium sulfate, then concentrated to dryness. The pale yellow, oily residue was purified by chromatography on 175 g of Woelm neutral alumina. Elution with 10% methylene dichloride–50% ether–40% pentane afforded 3.70 g of **17β-allyl-12α,17α-isopropylidenedioxy-5β-androstan-3α-ol (18)** as an oil which resisted all attempts at crystallization: λ_{max} 3.00, 3.31, 6.14, 7.26, and 7.31 μ.

The 3.70 g of amorphous hydroxy compound was acetylated with acetic anhydride and pyridine and the product purified by chromatography on neutral alumina. Elution with 10% ether–90% pentane afforded crystalline material which was recrystallized from pentane to give 2.2 g of **acetate 19**, mp 134–137°. A second recrystallization from pentane furnished the analytical sample (1.3 g): mp 136.5–138°; $[\alpha]_D$ + 11.0°; λ_{max} 3.25, 5.74, 6.11, 7.23, 7.30, and 8.00 μ.

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.56; H, 10.03.

The mother liquors from the two recrystallizations above were combined and concentrated to give a second crop of 1.5 g, mp 132–134° (53% yield for the two steps).

17β-Propyl-12α,17α-isopropylidenedioxy-5β-androstan-3α-ol Acetate (20).—To a solution of 1.1 g (2.6 mmoles) of 17β-allyl derivative (**19**) in 300 ml of undenatured 95% ethanol was added 0.5 g of 10% palladium on carbon and the resulting mixture shaken in 1 atm of hydrogen until 1 molar equiv was absorbed (2.5 min). The catalyst was removed by filtration through Celite and the filtrate concentrated by warming *in vacuo*. The residue was dissolved in ether and dried over powdered magnesium sulfate and the solution was concentrated to dryness. The residue was recrystallized from methanol to give 0.84 g (76% yield) of title compound, mp 116–118°. One recrystallization from methanol afforded the analytical sample with the melting point unchanged, $[\alpha]_D$ + 26.1°.

Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.94; H, 10.06.

N-Bromoacetamide Oxidation of 17β-Propyl-5β-androstane-3α,12α,17α-triol (16).—A solution of 6.6 g (19 mmoles) of triol **16** in 130 ml of *t*-butyl alcohol was treated with 5 ml of pyridine, 5 ml of water, and 3.2 g (1.25 equiv) of N-bromoacetamide and the resulting solution kept for 7 hr at room temperature. The

reaction mixture was poured into 1.5 l. of cold water containing 6 g of sodium sulfite and the precipitate which formed was collected, dried, and recrystallized from methanol to give 3.0 g (46% yield) of the 3-keto derivative **21**, mp 211–212°. One further recrystallization from methanol furnished the analytical sample: mp 215–216°; $[\alpha]D$ +14.3°; λ_{max} 3.10, 5.85 μ.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.98, H, 10.48.

The 12α-Acetyl Derivative 22.—**22** was prepared with acetic anhydride and pyridine and purified by recrystallization from acetone–hexane: mp 126–128°; $[\alpha]D$ + 83.3°; λ_{max} 2.80, 5.81, and 7.94 μ.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 74.03; H, 9.94.

Chromium Trioxide–Pyridine Oxidation of 17β-Propyl-5β-androstane-3α,12α,17α-triol (16).—To the chromium trioxide–pyridine complex prepared by adding 5.8 g of chromium trioxide to 60 ml of pyridine was added a solution of 2.9 g (8.3 mmoles) of triol **16** in 20 ml of pyridine and the resulting mixture stirred for 20 hr at room temperature. The reaction mixture was diluted with hot benzene and filtered through Celite, and the filter cake was rinsed with two portions of hot benzene. The combined filtrates were diluted with ether, washed successively with water, 2 *N* hydrochloric acid, 2 *N* sodium hydroxide, water, and saturated salt solution, and dried over powdered magnesium sulfate, then concentrated to dryness. Recrystallization of the residue from acetone–hexane afforded 1.8 g (63% yield) of the 3,12-diketo derivative **23**, mp 159–160°. One further recrystallization from the same solvent mixture gave the analytical sample: mp 160–162°; $[\alpha]D$ + 46.1° (1% in acetone); λ_{max} 2.85, 5.77, and 5.93 μ; $\lambda_{max}^{CHCl_3}$ 5.83 and 5.91μ.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.21; H, 9.93.

17β-Allyl-17α-hydroxy-5β-androstane-3,12-dione (24).—To the chromium trioxide–pyridine complex prepared by adding 9 g of chromium trioxide to 90 ml of pyridine was added a solution of 4.5 g (13 mmoles) of triol **14** in 30 ml of pyridine and the mixture stirred at room temperature for 24 hr. The reaction mixture was diluted with 350 ml of hot benzene and filtered through Celite, and the filter cake was washed with two portions of hot benzene. The filtrate was diluted with ether, washed successively with water, 2 *N* hydrochloric acid, water, and saturated salt solution, dried over powdered magnesium sulfate, decolorized with charcoal, and then concentrated to a white crystalline residue. Recrystallization from acetone–hexane afforded 2.4 g (54% yield) of title compound, mp 156–158°. A second recrystallization from acetone–hexane produced the analytical sample which had the melting point unchanged; $[\alpha]D$ +31.8°; λ_{max} 2.84, 3.28, 5.77, 5.93, and 6.09 μ.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.55; H, 9.23.

Sodium Borohydride Reduction of 17β-Allyl-17α-hydroxy-5β-androstane-3,12-dione (24).—To 0.20 g (0.58 mmole) of diketone **24** in 5 ml of methanol was added 50 mg of potassium hydroxide and 0.20 g of sodium borohydride in 1 ml of water and the solution was refluxed for 6 hr. The reaction mixture was poured into water and the product separated by extraction with methylene dichloride to give, after recrystallization from acetone–hexane, 0.07 g (35% yield) of 17β-allyl-5β-androstane-3α,12α,17α-triol (**14**), mp 213–218°, undepressed upon admixture with a sample prepared by the Grignard reaction described above; the infrared spectra of the two samples were identical.

Acknowledgment.—The author wishes to thank Dr. Robert L. Clarke for helpful discussions during the course of this work. Analyses were carried out by Mr. K. D. Fleischer and staff and spectral determinations by Dr. F. C. Nachod, Miss Catherine Martini, and Mr. M. Priznar.

Homoallylic Rearrangements of 19-Substituted Steroids[1]

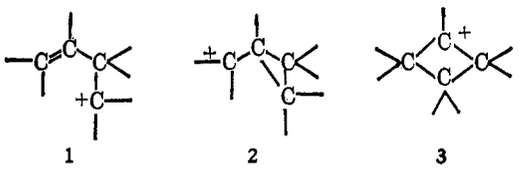
JACK TADANIER

Organic Chemistry Department, Research Divisio , Abbott Laboratories, North Chicago, Illinois 60064

Received February 8, 1966

Homoallylic rearrangements of 19-substituted steroids in elimination reactions and in nucleophilic substitution reactions lead to products the nature of which require the intervention of two discrete, interconvertible, homoallylic cations. Reactions of these cations under conditions of both kinetic and thermodynamic control are described.

The interconversions of homoallylic, cyclopropylcarbinyl and cyclobutyl derivatives in nucleophilic displacement reactions have been the subject of numerous investigations in a variety of systems.[2] Kinetic and stereochemical results have been interpreted to indicate that both the carbonium ion intermediates involved and the transition states leading to them are stabilized by considerable delocalization of positive charge. The charge delocalization in the intermediates has been described in terms of canonical structures such as **1**, **2**, and **3**, and the intermediates have been referred to as homoallylic cations[3] or bicyclobutonium ions,[4] depending on whether there is any significant 1,4 interaction, *i.e.*, whether there is appreciable con-



1 **2** **3**

tribution to the resonance hybrid by **3**.[5] The distinction is governed by the geometry of the system involved.

Perhaps the classic case of rearrangement involving a homoallylic cation is that of the interconversion of Δ^5-3β- and 3α,5α-cyclo-6-substituted steroids.[6] For this system the homoallylic and cyclopropylcarbinyl derivatives are related mechanistically by a homoallylic cation which may be described as a resonance hybrid of the canonical structures **4** and **5**. Formation of the kinetically favored 3α,5α-cyclo steroids occurs by stereospecific β attack of a nucleophile at C_6. A similar

(1) Preliminary communications have appeared in (a) J. Tadanier and W. Cole, *Tetrahedron Letters* 1345 (1964); (b) J. Tadanier, *Experientia*, **21**, 563 (1965). A portion of this material was presented at the Symposium on Steroids Made through Intramolecular Functionalization of the C_{18}- and C_{19}-Methyl Groups, at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) For a recent review, see R. Breslow in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 233.

(3) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954).

(4) R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

(5) For discussion of this distinction, see S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(6) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 314; (b) N. L. Wendler, in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1075; (c) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).