Improved Sulfonate Leaving Groups for the Displacement and Elimination of 3β-Hydroxy and 11α-Hydroxy Steroids

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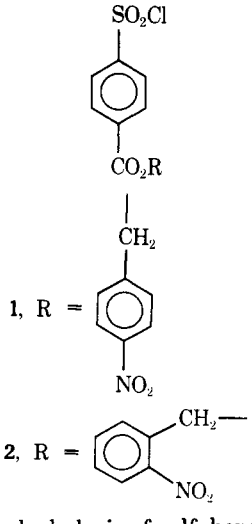
Received May 21, 1975

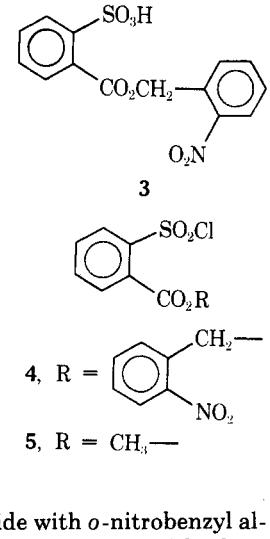
Steroidal 3β- or 11α-3-pyridinesulfonates and various *o*- and *p*-(alkyloxycarbonyl)benzenesulfonates undergo facile displacement. Elimination of these sulfonates, and particularly of *o*-nitrobenzenesulfonate, is very rapid and results in the corresponding olefins with very good yield under mild conditions.

In the course of chemical synthesis and structural modification one is occasionally faced with cases of extremely difficult displacements of sulfonates, typically, methanesulfonates or the better leaving *p*-toluenesulfonates.[1] The displacement of methanesulfonate esters of 11α-hydroxy steroids is particularly difficult and, in the past, the conversion of 11α-hydroxy functions into 11β-fluoro and with lesser efficacy into other substituents was carried out employing *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine with the corresponding lithium salt in great excess.[2] In the above case one starts from the alcohol and proceeds to the final product without isolating an intermediate. Other similar approaches are known (examples can be found in ref 3). It is not apparent, however, how applicable they might be to certain polyfunctional molecules of interest to us. An alternative approach, presented here, would be the utilization of sulfonates with better leaving group properties.[4] These might be advantageous also in providing us with facile eliminations. Our study included 11α-sulfonates and also the less hindered 3β-sulfonates.

Results and Discussion

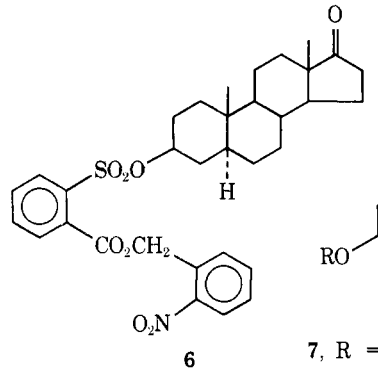
Compounds **1** and **2** were prepared by treating the corresponding nitrobenzyl alcohol with *p*-(chlorosulfonyl)benzoyl chloride.[5] Compounds **4** and **5** were prepared through





alcoholysis of sulfobenzoic anhydride with *o*-nitrobenzyl alcohol or with methanol[6] followed by treatment with phosphoric pentachloride. All the sulfonates described (compounds **6**, **7**, **8**, **9**, **13**, **14**, and **15**) were prepared by allowing the parent alcohol and the corresponding sulfonyl chloride to react in pyridine at room temperature.

p-Toluenesulfonates, and in particular steroidal 3β-*p*-toluenesulfonyloxy compounds, are known[7] to undergo both displacement and elimination in dimethylformamide. When sulfonates **7**, **8**, **9**, and the corresponding *p*-toluenesulfonate were heated in dimethylformamide, they gave



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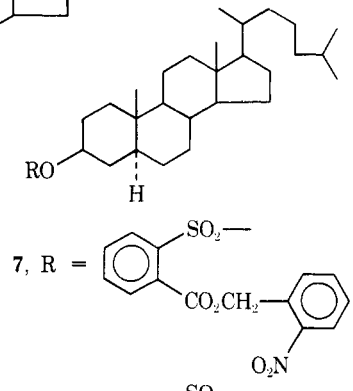

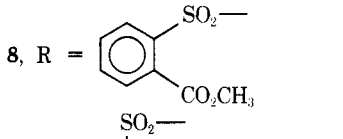

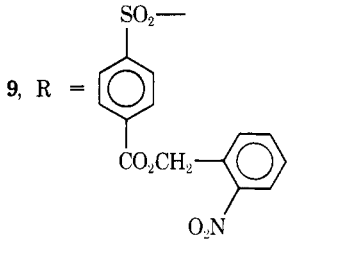

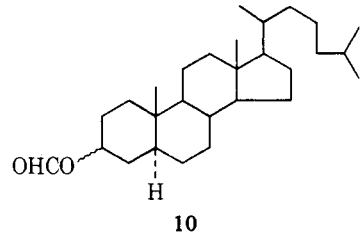

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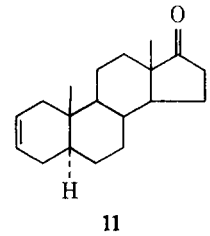

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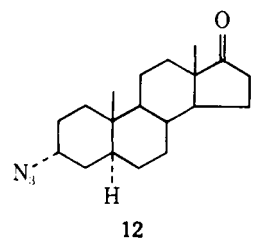
2,5α-cholestene and the 3-formate **10** in approximately 1:1 ratio. While a complete reaction for compound **7** required heating at 95° for 1 hr, the *p*-toluenesulfonate reaction proceeded under identical conditions to the extent of only 5%. The order of reactivity is **7** > **8**, **9** ≫ 3-*p*-toluenesulfonate. Elimination in hexamethylphosphoramide proceeded in a similar fashion. The reaction in dimethylformamide was further studied with compound **8**. The major products, 2,5α-cholestene and the formate **10** (apparently a result of inversion accompanied to a small extent by retention), were characterized.

Azide displacement of sulfonates in hexamethylphosphoramide occurs readily at the 3 position,[8] thus compound **6** was easily transformed to compound **12**. At the sterically hindered 11 position it is still a smooth reaction when the appropriate leaving groups are selected. Compounds **13** and



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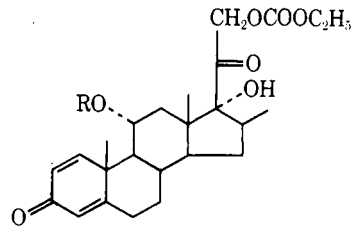
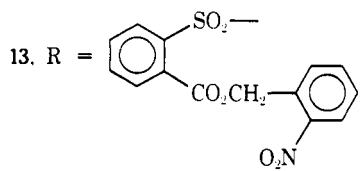
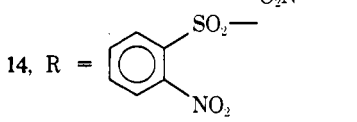
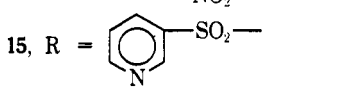




13, R =

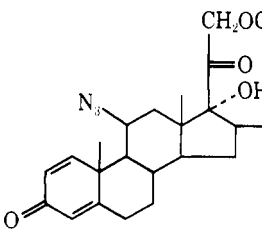


14, R =



15, R =

16, R = CH_3SO_2—



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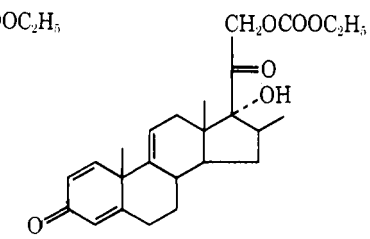

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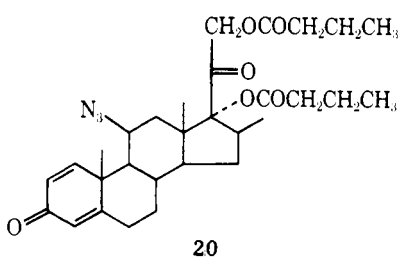

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15 were converted to compounds 17 (displacement and inversion) and 18 (elimination) in 30 min at 90°. Traces of the parent alcohol accompany these two major products. The configuration of compound 17 at C-11 was ascertained by NMR, employing a shift reagent. H-11 appears as a narrow multiplet, indicating that H-11 is equatorial. The reaction of the methanesulfonate 16 appears to be about 20 times slower. *o*-Nitrobenzenesulfonyloxy (compound 14) can be considered to be an excellent leaving group. It leads, however, to a complication of aromatic ring substitution: formation of the partially characterized compound 19 containing nitro, azide, sulfur, and aromatic ring protons.

With respect to elimination (in hexamethylphosphoramide) the order is *o*-nitrobenzenesulfonyl > 3-pyridinesulfonyl > *o*-nitrobenzyl *o'*-(sulfonyl)benzoate ≫ *p*-toluenesulfonyl. The elimination of these improved leaving groups is not only fast; after 40 min at 85° compound 14 eliminates quantitatively. As the result, compound 11 was isolated in 93% yield and compound 18 in 87% yield.

It is pertinent to note that while in the sterically crowded 11α position elimination led always to compound 18, azide displacement could be complicated by undesired reactions. Thus, in analogy with the results of Wu, Anderson, Slife, and Jensen,[9] which appeared while this work was in progress, the *o*-nitrobenzenesulfonate (14) gave elimination, aromatic ring substitution,[10] and cleavage to the 11α-alcohol. We overcame this difficulty by selecting the somewhat less reactive 3-pyridine sulfonate (15) and the *o*-nitrobenzyl *o'*-(sulfonyl)benzoate derivative (13) that were considered less likely to undergo aromatic ring substitution. As expected, these lead smoothly to the required 11β-azido derivative (17).

The reactions discussed may be carried out on various intermediates of steroidal hormones and could lead to a host of biologically interesting products. The reaction conditions used are mild and compatible with the usually very sensitive side chain of corticosteroids, protected as a 21-ester, and with the dienone system. These rapid reactions lead to displacements at reasonable yields and eliminations in very good yields.

Experimental Section

Melting points were determined on a Reichart instrument and are not corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer in methylene chloride solutions. NMR spectra were obtained at 60 or 100 MHz on a Varian Model A-60A or on a XL-100-15 spectrophotometer, respectively. Mass spectra were recorded on a Varian MAT CH-5 spectrometer.

TLC was run on silica gel GF (Analtech, 250 μm) and materials were detected by uv, sulfuric acid, or phosphomolybdate sprays. Column chromatography was performed on silica gel (J. T. Baker, 60–200 mesh) presaturated with the indicated solvent.

***p*-(Chlorosulfonyl)benzoyl Chloride.** This compound was prepared according to ref 5, starting from *p*-(chlorosulfonyl)benzoic acid or starting from *p*-sulfobenzoic acid monopotassium salt and using a mixture of phosphoric oxychloride and phosphoric pentachloride. The product was crystallized from hexane, mp 58° (lit. 58°).

***p*-Nitrobenzyl *p'*-(Chlorosulfonyl)benzoate (1).** *p*-(Chlorosulfonyl)benzoyl chloride (2.2 g) and *p*-nitrobenzyl alcohol (1.28 g) were dissolved at room temperature in benzene (60 ml). Triethylamine (1.28 ml) was then added while the solution was stirred under a calcium sulfate seal. Immediate formation of a precipitate was observed. After a few minutes, the reaction mixture was diluted with benzene, washed with dilute hydrochloric acid and water, dried over magnesium sulfate, and concentrated. The product (2.04 g) crystallized as prisms following the addition of some hexane, mp 123–130°. For analysis it was recrystallized from benzene, mp 134°.

Anal. Calcd for $C_{14}H_{10}ClNO_6S \cdot \frac{1}{6}C_6H_6$ ($C_{15}H_{11}ClNO_6S$): C, 48.85; H, 3.00; Cl, 9.61; N, 3.80; S, 8.70. Found: C, 48.31; H, 2.84; Cl, 9.32; N, 3.90; S, 8.41.

***o*-Nitrobenzyl *p'*-(Chlorosulfonyl)benzoate (2).** This compound was prepared in the same manner as compound 1 but using *o*-nitrobenzyl alcohol. After recrystallization from benzene 2.0 g of prisms, mp 122°, was obtained.

Anal. Calcd for $C_{14}H_{10}ClNO_6S \cdot \frac{1}{6}C_6H_6$ ($C_{15}H_{11}ClNO_6S$): C, 48.85; H, 3.00; Cl, 9.61; N, 3.80. Found: C, 48.31; H, 3.42; Cl, 9.54; N, 3.82.

***o*-Nitrobenzyl *o'*-(Sulfonyl)benzoate (3).** Sulfobenzoic anhydride (18.4 g) and *o*-nitrobenzyl alcohol (15.3 g) in benzene (1000 ml) were refluxed for 4 hr and then allowed to crystallize at room temperature, yield 25.6 g of hygroscopic material, mp 102°, after recrystallization from benzene, mp 105–106°.

Anal. Calcd for $C_{14}H_{11}NO_7S \cdot \frac{1}{2}H_2O$: C, 48.55; H, 3.49; N, 4.04; S, 9.26; H_2O, 2.59. Found: C, 48.42; H, 3.73; N, 3.95; S, 9.27; H_2O (Karl Fischer), 2.2.

***o*-Nitrobenzyl *o'*-(Chlorosulfonyl)benzoate (4).** Compound 3 (18 g) was mixed with phosphoric pentachloride (42 g), fitted with a condenser and a calcium chloride seal (Teflon sleeves), and was immersed into a 170° bath for 10 min. The reaction mixture was then poured into ice–water (600 ml), extracted with chloroform (600 ml), and washed with water. The chloroform solution was dried over magnesium sulfate and evaporated, yielding 20.4 g of an oil that was crystallized from a mixture of benzene and hexane, mp 104–105° (12.8 g).

Anal. Calcd for $C_{14}H_{10}ClNO_6S$: C, 47.26; H, 2.83; Cl, 9.97; N, 3.94; S, 9.01. Found: C, 47.79; H, 2.93; Cl, 10.37; N, 3.85; S, 8.79.

Methyl *o*-(sulfonyl)benzoate was prepared according to ref 6.

Methyl *o*-(Chlorosulfonyl)benzoate (5). Methyl *o*-(sulfonyl)benzoate (10 g) and phosphoric pentachloride (25 g) were treated as described for the preparation of compound 4, yield 14.4 g of oil that failed to crystallize and contained a slow-moving impurity (TLC, benzene or chloroform).

3-Pyridinesulfonyl chloride was prepared according to ref 11.

3α-Sulfonate Derivatives of 5α-Androstan-3β-ol-17-one (Epiandrosterone) and of 5α-Cholestan-3β-ol (β-Cholestanol). The steroid (2.0 mmol) and the respective sulfonyl chloride (2.25 mmol) were dissolved in pyridine (6.0 ml) at room temperature; the reaction mixture was then left at room temperature overnight. A few crystals of ice were added and after 1 hr the reaction mixture was extracted with chloroform (350 ml) and washed with dilute hydrochloric acid, water, dilute sodium hydroxide, and water. The chloroform solution was dried over magnesium sulfate and evaporated.

A. 5α-Androstan-3β-ol-17-one 3-[(Benzoic acid *o*-nitrobenzyl ester)-2-sulfonate] (6). This material was further purified on a column of silica gel (45 g, 1.5 cm in diameter) and eluted with chloroform–ethyl acetate (1:20), yield 0.95 g (77%), recrystallized from ethyl acetate, mp 146° (microcrystalline, light yellow), $[\alpha]^{26}D$ +37.0° (*c* 0.4, chloroform), λ_{max} ($CHCl_3$) 246 nm (ϵ 7.29 × 10^3).

Anal. Calcd for $C_{33}H_{39}NO_8S$: C, 65.01; H, 6.45; N, 2.30. Found: C, 65.06; H, 6.51; N, 2.09.

B. 5α-Cholestan-3β-ol 3-[(Benzoic acid *o*-nitrobenzyl ester)-2-sulfonate] (7). The residue crystallized as elongated yellow needles, mp 129–131°. It was recrystallized from ethyl acetate, mp 133–134°, $[\alpha]^{26}D$ +8.6° (*c* 0.32, chloroform), yield 580 mg (42%), λ_{max} ($CHCl_3$) 265 nm (ϵ 6.96 × 10^3).

Anal. Calcd for $C_{41}H_{57}NO_7S$: C, 69.55; H, 8.11; N, 1.98. Found: C, 69.54; H, 8.50; N, 2.25.

C. 5α-Cholestan-3β-ol 3-[(Benzoic acid methyl ester)-2-sulfonate] (8). The oily residue was purified on a silica gel column (20 g, 1.5 cm in diameter) using chloroform as the eluent. The product emerged as a broad peak starting after the initial 15 ml, yield 0.257 g (23%) of yellowish oil, homogeneous by TLC.

D. 5α-Cholestan-3β-ol 3-[(Benzoic acid *o*-nitrobenzyl ester)-4-sulfonate] (9). The solid residue was recrystallized from ethyl acetate–hexane, yielding 0.70 g (57%) of yellowish product, mp 126–127°, $[\alpha]^{26}D$ +8.9° (*c* 0.34, chloroform).

Anal. Calcd for $C_{41}H_{57}NO_7S$: C, 69.55; H, 8.11; N, 1.98. Found: C, 69.61; H, 8.37; N, 2.07.

Comparative Dimethylformamide Reaction, Compounds 7, 8, 9, and 5α-Cholestan-3β-ol 3-*p*-Toluenesulfonate. Each compound (0.014 mmol/ml in dimethylformamide) was kept in a closed vial at 95°. Equal volumes (marked capillaries of ca. 3 μl) were drawn and (a) applied directly to TLC (chloroform–ethyl acetate, 20:1) and the residual starting material and the products (sometimes not well separated) could be observed; (b) an equal volume of 0.2 *N* NaOMe was added to each capillary and the content was spotted after 10 min. Following this treatment, the faster moving 2,5α-*cholestene remained unchanged, and compound* **10** disappeared to yield mostly 5α-cholestan-3α-ol. For compounds **7** and **9** it was also apparent (unexplained) that the amount of 2-nitrobenzyl alcohol released increased when the dimethylformamide reaction proceeded.

The proportion of products was similar for the different sulfonates. A complete reaction for compound **7** required approximately 1 hr. The order of reactivity was **7** > **8**, **9** ≫ *p*-toluenesulfonate (approximately 5% reaction in 1 hr).

Comparative Elimination, Compounds 7, 9, and 5α-Cholestan-3β-ol 3-(*p*-Toluenesulfonate). Solutions were made in hexamethylphosphoramide and handled as described for the dimethylformamide reaction, section a. 2,5α-Cholestene was formed in the three cases. Ninety minutes were required for complete reaction of compound **7**, compound **9** eliminated somewhat slower, and the *p*-toluenesulfonate reacted to the extent of not more than 5% during the same time.

Reaction of Compound 8 in Dimethylformamide. Compound **8** (100 mg) was dissolved in dimethylformamide (0.2 ml) and was kept in a closed vial under argon at 85° for 3 hr. The reaction mixture was evaporated in vacuo and applied to a silica gel column (6.0 g, 1.0 cm in diameter), eluted with chloroform, 1.0 ml per fraction, and monitored by TLC (chloroform-ethyl acetate, 20:1).

A. Fractions 1–7 contained 32 mg (48%) of **2,5α-cholestene,** mp 72°, giving no depression in mixture melting point with an authentic sample (mp 68–69°). The ir and mass spectrum (M 370) were also as required for this compound.

B. Fractions 8–14 contained a solid, mp 64–70°, identified as the **5α-cholestan-3α- (or 3β-) ol 3-formate (10)** in 14-mg (20%) yield. The material had ir absorbances at 1190 (O–R) and 1720 cm^{-1} (C=O). The mass spectrum indicated a molecular peak at *m/e* 416 ($C_{28}H_{48}O_2$) and fragmentation that supports the proposed structure. When treated with 0.2 *N* NaOMe, product **10** was converted to **5α-cholestan-3α-ol** and to **5α-cholestan-3β-ol** in a ratio of 9:1 (TLC). The reaction mixture was extracted with ethyl acetate and washed with water and the ethyl acetate solution was dried with magnesium sulfate and evaporated. The residue was crystallized from ethyl acetate to yield almost pure (TLC) 5α-cholestan-3α-ol, mp 179°, giving no depression in mixture melting point with an authentic sample (mp 183–184°). Ir and the mass spectrum were as required.

C. Fractions 22–30 contained ca. 10% of 5α-cholestan-3α-ol and 5α-cholestan-3β-ol.

2,5α-Androsten-17-one (11). Compound **6** (107 mg) was dissolved in hexamethylphosphoramide (0.5 ml) and kept in a closed vial under argon for 120 min at 85°. From TLC (chloroform–ethyl acetate, 20:1) it was apparent that the starting material was converted to product **11** at least to the extent of 95%. The reaction mixture was extracted with chloroform, washed with water, dried over magnesium sulfate, evaporated, and applied to a column of silica gel (10 g, 1.0 cm in diameter). Fractions of 1.6 ml were checked by TLC (as above) and fractions 8–14 contained the pure product, yield 44.7 mg (93%), mp 103–104°, $[\alpha]^{26}D$ +143.2° *c* 0.38, ethanol). The product gave no depression of mixture melting point with an authentic sample (mp 103–106°, $[\alpha]D$ +137° in ethanol). Ir spectra of the two were superimposable and the product gave the required mass spectrum with a molecular peak at *m/e* 272.

3α-Azido-5α-androstan-17-one (12). Compound **6** (105 mg) and sodium azide (700 mg) in hexamethylphosphoramide (5.0 ml) were stirred in a closed vial, under argon, at 80° and for 90 min. TLC (chloroform–ethyl acetate) indicated the formation of two major products: compound **11** and the 3α-azide **12** in a ratio of 1:1. The reaction mixture was extracted with ether and washed with water. The ether solution was dried and evaporated to yield 42.6 mg of crude mixture. Product **12** was crystallized from methanol as plates, yielding 23 mg (43%), mp 118–120°, $[\alpha]^{26}D$ +70.7° (*c* 0.2, chloroform) (lit.[8a] mp 116–117°, $[\alpha]D$ +79.8°). The product had a strong absorbance at 2100 cm^{-1} (N_3). In the NMR (100 MHz, $CDCl_3$) H-3 appears as a narrow (10 Hz) multiplet at τ 6.14.

11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 11-[(Benzoic acid *o*-nitrobenzyl ester)-2-sulfonate] 21-Cathylate (13). 11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-cathylate[12] (893 mg) and the sulfonyl chloride **4** (1.6 g) were dissolved in pyridine (6 ml) and left at room temperature for 72 hr. A crystal of ice was added to the reaction mixture and after 1 hr the pyridine was evaporated in vacuo. The residue was extracted into ethyl acetate and washed with saturated sodium hydrogen carbonate solution and with water. The solution was dried over magnesium sulfate, evaporated in vacuo, and applied to a column of silica gel (35 g, 1.6 cm in diameter). The column was eluted with chloroform–ethyl acetate (1:2) and 1.2-ml fractions were collected. Fractions 33–53 contained the product (0.4 g) that was obtained as an amorphous solid from a mixture of chloroform and hexane, mp 101–104°, $[\alpha]^{26}D$ +32.6° (*c* 0.17, chloroform).

Anal. Calcd for $C_{39}H_{43}NO_{13}S$: N, 1.83. Found: N, 1.87.

11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Cathylate 11-(*o*-Nitrobenzenesulfonate) (14). This compound was prepared with *o*-nitrobenzenesulfonyl chloride (0.5 g) by the procedure used for compound **13.** Similar fractionation was carried out by the use of 38 g of silica gel and collecting 1.5-ml fractions. Fractions 60–81 were pooled and evaporated to yield the pure product as needles (0.4 g), mp 101–104° dec. Recrystallization from ethyl acetate–hexane yielded the analytical sample, mp 104–106° dec, $[\alpha]^{26}D$ +80.4° (*c* 0.25, chloroform).

Anal. Calcd for $C_{31}H_{37}NO_{11}S$: C, 58.94; H, 5.90; N, 2.22; S, 5.08. Found: C, 59.38; H, 6.07; N, 2.16; S, 4.75.

11α,17α,21-Trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 11-(3-Pyridinesulfonate) 21-Cathylate (15). This compound was prepared like compound **13** but using 470 mg of 3-pyridinesulfonyl chloride. The product was slower on TLC (chloroform–ethyl acetate, 1:2) than the starting material. It was eluted from the silica gel column as a wide peak at least partially contaminated with the starting material, yield 0.75 g. For analysis, compound **15** was obtained from a center cut and recrystallized from chloroform–hexane, mp 103°, $[\alpha]^{26}D$ +110.3° (*c* 0.49, chloroform).

Anal. Calcd for $C_{30}H_{37}O_9NS$: N, 2.38. Found: N, 2.04.

Comparative Azide Substitution. Compounds 13, 14, and 15. A. The reactivities of compound **13** and of the corresponding 11α-methanesulfonate **16** were compared. Each sample (0.013 mmol/ml in hexamethylphosphoramide) and sodium azide (100 mg/ml) were stirred in a closed vial at 90° and samples (5 μl) were drawn for TLC (chloroform–ethyl acetate, 1:2). After 30 min the conversion of compound **13** to the 11β-azido derivative **17** and to the triene **18** (ratio 6:4) was complete with only minute traces of slower moving

material. At the same time the conversion of the 11α-methanesulfonate **16** to the same products proceeded in ca. 5% yield. Even after 240 min approximately 30% of the latter compound remained unchanged and the reaction was accompanied by degradation.

B. In an analogous experiment, compound **14** was shown to convert completely to compound **19** and to compound **18** (ratio 6:4) in 30 min.

C. Compound **15**, under similar conditions, reacted very similarly (rate and products) to compound **13**. Since compound **15** is slower on chromatography than any of the other sulfonates described here, it provided improved separation of the starting material from compound **17** and the still faster compound **18**.

Comparative Elimination. Compounds 14, 15, and 13. A. Compounds **14** and **15** (0.015 mmol/ml in hexylmethylphosphoramide) were kept in closed vials at 85°. Samples (5 μl) were applied to TLC (chloroform–ethyl acetate, 2:1). After 40 min, compound **14** was almost completely converted into compound **18** while compound **15** was converted into compound **18** to the extent of approximately 70%.

B. Under similar conditions, compound **13** eliminated to compound **18** to the extent of approximately 20%.

17α,21-Dihydroxy-16β-methyl-1,4,9-pregnatriene-3,20-dione 21-Cathylate (18). Compound **14** (211 mg) was dissolved in hexamethylphosphoramide (1 ml) in a closed vial and heated in a 80° bath for 80 min. The total reaction mixture was applied to a silica gel column (35 g, 1.6 cm in diameter) and was eluted with chloroform–ethyl acetate (2:1). The product (needles), homogeneous according to TLC, mp 217–221° dec, emerged after 25 ml and was eluted with an additional 40 ml of solvent mixture, yield 125 mg (87%). The product was shown to be identical with an authentic sample (TLC, ir, mass spectrum).

11β-Azido-17α,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Cathylate (17). A. Compound **13** (164 mg) and sodium azide (200 mg) in hexamethylphosphoramide (1 ml) were stirred in a closed vial at 85° (bath temperature) for 3 hr. TLC (chloroform–ethyl acetate, 1:2) indicated that compounds **17** and **18** were formed in a ratio of 7:3 and a minute amount of the 11α-hydroxy compound was also formed. The reaction mixture was extracted with ether, washed with water, and dried over magnesium sulfate. Product **17** was then isolated after chromatography on two thick (2 mm, 20 × 20 mm) plates and using the same solvent system. The yield was 42 mg (41%) of needles, mp 203–205°, after recrystallization from methylene chloride–hexane: mp 209°; ir shows absorbances at 1745 and 1760 (C=O), 2120 cm^{-1} (N_3); mass spectrum *m/e* 471 (M), 443 (M − N_2), 428 (M − HN_3) followed by fragmentation similar to compound **18**; NMR (100 MHz, $CDCl_3$) τ 2.84 (1 H, d, $J_{1,2}$ = 10 Hz, H-1), 3.67 (1 H, q, $J_{2,4}$ = 2 Hz, H-2), 3.96 (1 H, d, H-4), 5.02 (2 H, d, J = 1 Hz, H-21), 5.73 (3 H, apparent q, J = 7 Hz, OCH_2CH_3 and H-11). $Eu(fod)_3$ was added to the sample and the following resonances were recorded: τ 1.45 (1 H, apparent d, broad lines, J = 10 Hz, H-2), 1.83 (1 H, apparent s, H-4), 2.28 (1 H, d, $J_{1,2}$ = 10 Hz, H-1), 4.92 (2 H, apparent s, H-21), 5.34 (1 H, 15 Hz wide m, H-11α), 5.69 (2 H, q, J = 7 Hz, OCH_2CH_3).

B. Compound **15** (78 mg) was treated as described in section A, yield 6.0 mg of the azido derivative (**17**), mp 208°. It gave no depression of mixture melting point with compound **17** (section A) and these materials had identical ir spectra.

11β-Azido-17α,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 17α,21-Dibutyrate (20). A. Compound **17** (40 mg) was dissolved in a mixture of methanol (2.5 ml) and chloroform (0.5 ml). Aqueous sodium hydroxide (1 *N*, 0.09 ml) was added and the reaction mixture was kept in an ice bath for 65 min. It was then acidified with dilute acetic acid, extracted with ethyl acetate, washed with saturated sodium hydrogen carbonate and water, dried over magnesium sulfate, and evaporated in vacuo. TLC (chloroform–ethyl acetate, 1:2) showed a major slow-moving product that was purified on a thick plate (same solvent system): ir 1660, 1720 (C=O), 2100 cm^{-1} (N_3). The 1760-cm^{-1} absorbance in the starting material had disappeared.

B. The dihydroxy derivative of stage A was esterified according to Shapiro et al.[13] *p*-Toluenesulfonic acid (10 mg) was added to the sample followed by butyric acid and trifluoroacetic anhydride (1.0 ml, 10:4). The reaction mixture was allowed to stand overnight at room temperature. It was then poured into water, extracted with methylene chloride, washed with water, saturated sodium hydrogen carbonate, and water, and dried over magnesium sulfate. The product, almost pure by TLC, chloroform–ethyl acetate (1:2), was purified by using the same system, yield 7.2 mg of oil. The ir spectrum contained absorbances at 2100 (N_3), 1750 cm^{-1} (C=O, broad). Mass spectrum includes *m/e* 567 (M), 539 (M − N_2), 511, 494, 487, but also *m/e* 609 (M + N_3), 581 (M + N) that might result from an ion–molecule reaction.

Reaction of Compound 14 with Sodium Azide. Compound **14** (0.39 g) and sodium azide (400 mg) in hexamethylphosphoramide (3 ml) were stirred in a closed vial at 85° (bath temperature) for 30 min. TLC (chloroform–ethyl acetate, 1:2) indicated the formation of the substitution product **19** and the faster moving elimination product **18** alongside some 11α-hydroxy compound (6:3:2). The reaction mixture was extracted with ether, washed with water, dried over magnesium sulfate, evaporated, applied to a column of silica gel (35 g, 1.6 cm in diameter), and eluted with chloroform–ethyl acetate, 1:1. Fractions of 2.5 ml were collected. Fractions 36–41 contained product **19** homogeneous according to TLC (oil, 57 mg, more in mixed fractions). It was crystallized from chloroform–hexane), amorphous, mp 97–101°. Ir includes 2100 cm^{-1} (N_3) but different from compound **17**. The mass spectrum includes *m/e* 519, 501, 471, 428; NMR (100 MHz, $CDCl_3$) includes τ 1.8–2.7 (4 H, m, aromatic).

Anal. Calcd for $C_{31}H_{36}N_4O_{11}S$: N, 8.33; S, 4.76. Found: N, 7.50; S, 3.30

Acknowledgment. The author thanks Mr. E. L. Shapiro and Dr. T. Popper for their continuous interest and encouragement.

Registry No.—**1**, 56650-26-1; **2**, 56650-27-2; **3**, 56650-28-3; **4**, 56650-29-4; **5**, 26638-43-7; **6**, 56650-30-7; **7**, 56650-31-8; **8**, 56650-32-9; **9**, 56650-33-0; **11**, 963-75-7; **12**, 7795-05-3; **13**, 56650-34-1; **14**, 56650-35-2; **15**, 56650-36-3; **17**, 56650-37-4; **18**, 56666-79-3; *p*-(chlorosulfonyl)benzoyl chloride, 7516-60-1; *p*-nitrobenzyl alcohol, 619-73-8; *o*-nitrobenzyl alcohol, 612-25-9; sulfobenzoic anhydride, 81-08-3; phosphonic pentachloride, 10026-13-8; 5α-androstan-3β-ol-17-one, 481-29-8; 5α-cholestan-3β-ol, 80-97-7; 5α-cholestan-3β-ol 3-*p*-toluenesulfonate, 3381-52-0; 11α,17α,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-cathylate, 56650-38-5; *o*-nitrobenzenesulfonyl chloride, 1694-92-4; 3-pyridinesulfonyl chloride, 16133-25-8.

References and Notes

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