A Novel Dehydration Reaction of Steroidal Alcohols

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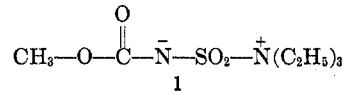
Various steroidal secondary and tertiary alcohols were treated with methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (**1**), to afford olefins. In most cases, the nature of the alcohol group (secondary, tertiary, homoallylic), its configuration, and the environment are the primary factors governing the course of the reaction. While tertiary alcohols seem to react under milder conditions, they are also subject to rearrangements. The compatibility of a saturated ketone, α,β-unsaturated ketone, aromatic ring, triple bond, acetate, and bismethylenedioxy function with the reagent and the mild reaction conditions (low temperature, neutral medium), the satisfactory yields which were often obtained, as well as the unexpected nature of some products, make it an attractive technique for introduction of double bonds into the steroid molecule.

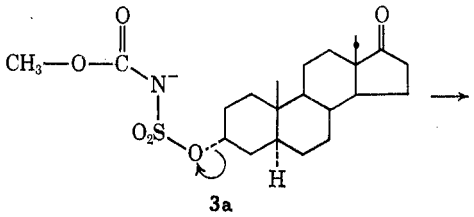
Recently, Burgess, *et al.*,[2] reported the preparation of methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (**1**) and showed[3] **1** to be a useful reagent for the dehydration of simple alcohols. The authors have also shown that the reaction is at least for secondary alcohols a stereospecific *cis* elimination of first order, which proceeds *via* an ion-pair mechanism and follows Saytzeff's rule.[3]

We wish to report the application of this elimination reaction to secondary and tertiary steroidal alcohols. It is shown that the inner salt **1** is a useful dehydration agent which gives rise to a variety of olefins whose yield and structure depend essentially on the nature of the starting steroidal alcohols.

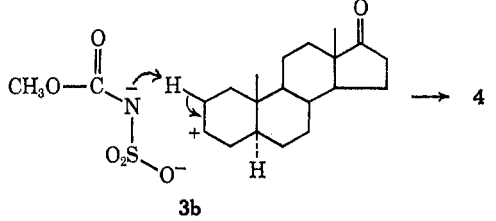


1

The course of the reaction of 3α-hydroxy-5α-androstan-17-one (**2**) with the N-sulfonylamine inner salt **1**, in anhydrous benzene solution at room temperature, was followed by thin layer chromatography (tlc). When there was no alcohol **2** left but only a more polar product, the solution was neutralized and extracted, yielding a compound presumed to be the ester **3a** which decomposed on heating at 90° *in vacuo* by a



3a



3b

cyclic intramolecular hydrogen transfer (see **3b**). Besides sulfur trioxide and methyl carbamate (NH_2COOCH_3), 75% 5α-androst-2-en-17-one (**4**) was obtained (see Table I).

Similarly, 3β-hydroxy-5α-androstan-17-one (**5**) and cholestanol **6** afforded the Δ^2 steroids **4** and **7** in 52 and 63% yield, respectively. The reasonable yield obtained in these dehydrations indicates that the 17-keto group is compatible with the elimination reaction of **2** and **5**. Moreover, no Δ^3 steroid could be isolated at the end of the reaction.

The alcohol group in cholesterol **8** proved to be less amenable to dehydration under the above conditions, since 40% of starting material **8** was recovered along with a 27% yield of cholesta-3,5-diene (**9**) (Table I). The $\Delta^{2,5}$-diene, which may have been formed, could conceivably have rearranged to the isomeric $\Delta^{3,5}$-diene (**9**) during the isolation procedure.

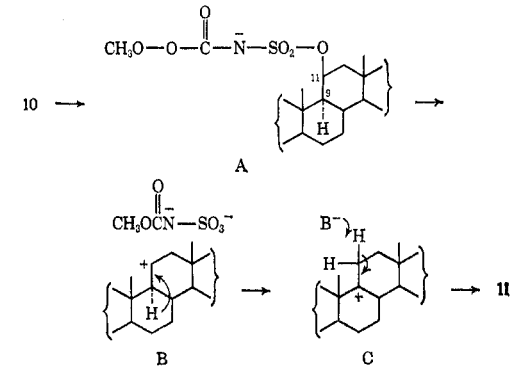
When the elimination reaction was performed with 11β,17α,21-trihydroxy-17:20,20:21-bismethylenedioxypregn-4-ene-3,20-dione (**10**), the $\Delta^{9(11)}$-pregnene (**11**) was formed in 96% yield. This is remarkable because it shows that there is no competing reaction between the inner salt **1** and either the conjugated Δ^4-3 ketone or the bismethylenedioxy grouping.

The $\Delta^{9(11)}$ steroid **11** results presumably from intramolecular hydrogen transfer of the hydrogen atom at C-9 to a cation formed at C-11, followed by proton extraction.[4]

The formation of the $\Delta^{9(11)}$ steroid **11** in high yield is particularly important because of the potential use of this reaction for further introduction of substituents at C-9 and C-11, known to increase the biological activity, *e.g.*, in the corticoid series.

In contrast to the 11β-hydroxy compound **10**, reaction of 11α-hydroxypregn-4-ene-3,20-dione (**12**) with **1** only afforded 9% $\Delta^{9(11)}$-pregnene (**13**). It may be that steric factors make the course of the elimination

(4) The suggested mechanism **10** → A → B → C → **11** also explains why no $\Delta^{11,12}$-elimination compound could be detected.



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(2) G. M. Atkins, Jr., and A. M. Burgess, *J. Amer. Chem. Soc.*, **90**, 4744 (1968).

(3) E. M. Burgess, E. A. Taylor, and H. P. Penton, Jr., 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, Abstracts, No. ORGN-105.

TABLE I

PRODUCTS AND YIELDS OF COMPOUNDS FORMED BY DEHYDRATION OF STEROIDAL ALCOHOLS

Steroidal alcohols	Steroidal olefins formed	Yields, %
3α-Hydroxy-5α-androstan-17-one (2)	5α-Androst-2-en-17-one (4)	75
3β-Hydroxy-5α-androstan-17-one (5)	5α-Androst-2-en-17-one (4)	52
3β-Hydroxy-5α-cholestane (6)	5α-Cholest-2-ene (7)	63
3β-Hydroxy-cholest-5-ene (8)	Cholesta-3,5-diene (9)	27
11β,17α,21-Trihydroxy-17:20,20:21-bismethylenedioxypregn-4-ene-3,20-dione (10)	17α,21-Dihydroxy-17:20,20:21-bismethylenedioxy-pregna-4,9(11)-diene-3,20-dione (11)	96
11α-Hydroxypregn-4-ene-3,20-dione (12)	Pregna-4,9(11)-diene-3,20-dione (13)	9
	17α-Pregna-4,9(11)-diene-3,20-dione (14)	2
3β,17β-Dihydroxy-3α-ethynyl-5α-androstane 17-acetate (15)	3-Ethynyl-17β-hydroxy-5α-androst-2-ene acetate (16)	25
3,17β-Dihydroxy-17α-ethynylestra-1,3,5(10)-triene 3-methyl ether (17)	3-Hydroxy-17-ethynylestra-1,3,5(10),16-tetraene 3-methyl ether (18)	61
	3-Hydroxy-17α-ethynyl-17β-methyl-18-norestra-1,3,5(10),13-tetraene 3-methyl ether (19)	11
2α,17α-Dimethyl-17β-hydroxy-5α-androstan-3-one (20)	2-Methyl-7-methylene-5α-androstan-3-one (21)	74
	2α,17,17-Trimethyl-18-nor-5α-androst-13-en-3-one (22)	10

reaction different in the case of 11α and 11β alcohols **10** and **12**. In any event, the dramatic difference in yields of **11** and **13** is surprising, since the formation of an intermediary 11β ester[4] of **10** should be subjected to more steric hindrance by the 18- and 19-methyl groups, as well as the bismethylenedioxy grouping than in the case of the 11α-hydroxypregnene (**12**).

Worth noting also is the formation of 2% 17α-pregna-4,9(11)-diene-3,20-dione (**14**) during this reaction. The 17α configuration of the methyl ketone is based on the chemical shift of the C-18 methyl resonance (Table II).[5,6]

Attempts to dehydrate some secondary 17β-hydroxy steroids led to a complex mixture of substances which could not be separated and in which no compound was observed in yields exceeding 10%.

Steroidal tertiary alcohols were also submitted to treatment with the N-sulfonylamine inner salt **1**. Reaction of the steroidal alcohols, **15**, **17**, and **20**, with **1** in anhydrous benzene at room temperature was followed by tlc. In these cases, only less polar products were formed. The organic solution was washed with water, dried, and concentrated under reduced pressure to afford *directly* the elimination compounds. No sulfonyl esters were detected which seems to indicate that they are decomposed *in situ* at room temperature.

Under these reaction conditions, 3β,17β-dihydroxy-3α-ethynyl-5α-androstane 17-acetate (**15**) provided 25% Δ^2-androstene **16**, besides 50% of recovered starting material **15**.

Dehydration of 3,17β-dihydroxy-17α-ethynylestra-1,3,5(10)-triene 3-methyl ether (**17**) under the same reaction conditions provided as major product the Δ^{16}-elimination compound **18** (61%), along with 3-hydroxy-17α-ethynyl-17β-methyl-18-norestra-1,3,5-(10),13-tetraene 3-methyl ether (**19**) (11%) which could be separated by tlc. Similarly, 2α,17α-dimethyl-17β-hydroxy-5α-androstan-3-one (**20**) afforded the $\Delta^{17(20)}$-elimination product **21** (74% yield) and the rearranged 17,17-dimethyl compound **22** (10%) (see Table I). The rearranged products, **19** and **22**, presumably result from methyl migration after formation of a carbonium ion at C-17.

It is of interest to note that in the case of dehydration of compounds **15** and **17** the inner salt **1** does not seem to have reacted either with the ethynyl group, or the acetate of **15**, or the aromatic ring of **17**. This emphasizes the applicability of the elimination reaction to numerous polyfunctional molecules. Worth noting also is the good yield in which the methylene compound **21** was formed. In the present case, Saytzeff's rule was not followed. In any event, this constitutes a new method of introducing an *exo*-methylene group at C-17 with potential use in the elaboration of the pregnane and corticoid side chains.

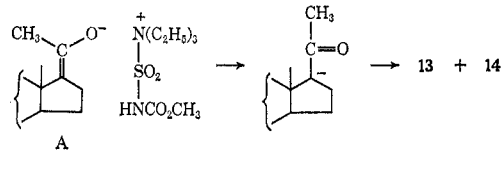
Experimental Section[7]

The physical properties and appropriate references of steroidal olefins are listed in Table II.

Typical Procedure. Reaction of the Secondary Alcohol 2 with the Inner Salt 1.—To a solution of 1 g of **2** in 50 ml of anhydrous benzene, 6.5 g of salt **1**[2] was slowly added. The mixture was stirred for 2 hr at room temperature, the reaction

(5) A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964); (b) J. Romo, L. Rodriguez-Hahn, P. Joseph-Nathan, M. Martínez, and P. Crabbé, *Bull. Soc. Chim. Fr.*, 1276 (1964); (c) X. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(6) The partial inversion of configuration at C-17 is attributed to the formation of an enolate of type A. During work-up, A leads to the anion B



A

which gets protonated at C-17 from both sides. A recent experiment has shown that dehydration of 11β-hydroxypregn-4-ene-3,20-dione with the same reagent gives an identical mixture of **13** (four parts) and **14** (one part).

(7) Microanalyses were done by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany. Melting points were determined in capillary tubes with a Mel-Temp apparatus; they are corrected. Optical rotations were taken between 16 and 22° with a 1-dm tube at sodium D light in chloroform solution. Infrared spectra were taken with a Perkin-Elmer Model 21, NaCl prism. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU, in ethanol solution. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer, for 5–8% (w/v) solutions in deuteriochloroform containing tetramethylsilane (TMS) as internal reference. Resonance frequencies are quoted as parts per million downfield from TMS. Coupling constants are accurate to ±0.5 Hz.

TABLE II

PHYSICAL PROPERTIES OF STEROIDAL OLEFINS

Steroidal olefins	Mp, °C	[α]D, deg	Uv λmax (nm)	Uv ε	Nmr, ppm	Ref
5α-Androst-2-en-17-one (**4**)	105–106	+136			0.77 (18 H), 0.87 (19 H), 5.6 (2 H, 3 H)	*a*
5α-Cholest-2-ene (**7**)	73–74	+68			5.6 (2 H, 3 H)	*b*
Cholesta-3,5-diene (**9**)	77–78	−110	236	7,940	5.65 (m, 3 H, 4 H, 6 H)	*c*
17α,21-Dihydroxy-17:20,20:21-bismethylenedioxypregna-4,9(11)-diene-3,20-dione (**11**)	222–223	−21	240	16,600	0.8 (18 H), 1.33 (19 H), 3.96 (21 H), 4.66, 5.06, 5.2, 5.56 (BMD), 5.5 (t, J = 3 Hz, 11 H), 5.73 (4 H)	*d*
Pregna-4,9(11)-diene-3,20-dione (**13**)	118–119	+143 (acetone)	240	15,900	0.67 (18 H), 1.4 (19 H), 2.17 (21 H), 5.56 (t, J = 3 Hz, 11 H), 5.75 (4 H)	*e*
17α-Pregna-4,9(11)-diene-3,20-dione (**14**)	175–176	±0	238	14,000	0.90 (18 H), 1.31 (19 H), 2.12 (21 H), 5.61 (t, J = 2 Hz, 11 H), 5.76 (4 H)	*f*
3-Ethynyl-17β-hydroxy-5α-androst-2-ene acetate (**16**)	93–94	+62	224	12,600	0.80 (18 H), 0.81 (19 H), 2.03 (OAc), 2.8 (acetylenic H), 6.0 (d, J = 12 Hz, 2 H)	*g*
3-Hydroxy-17-ethynylestra-1,3,5-(10),16-tetraene 3-methyl ether (**18**)	153–154	+66	226 278 287	17,400 1,820 1,700	0.82 (18 H), 2.98 (21-acetylenic H), 3.67 (O-CH_3), 6.05 (16 H), 6.8 (m, aromatic H)	*h*
3-Hydroxy-17α-ethynyl-17β-methyl 18-norestra-1,3,5(10),13-tetraene 3-methyl ether (**19**)	108–109	±0	278 287	2,040 1,860	1.29 (17 Me), 2.14 (21-acetylenic H), 3.72 (O-CH_3), 6.91 (m, aromatic H)	*i*
2α-Methyl-17-methylene-5α-androstan-3-one (**21**)	142–143	+45			0.8 (18 H), 1.03 (d, J = 4 Hz, 2 Me), 1.09 (19 H), 4.63 (d, J = 2 Hz, C = CH_2)	
2α,17,17-Trimethyl-18-nor-5α-androst-13-en-3-one (**22**)	129–130	±0			0.97 (17-*gem*-di-Me), 1.05 (d, J = 3 Hz, 2 Me), 1.09 (19 H)	

[a] Reference 8. [b] A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **28**, 275 (1949). [c] J. C. Eck, R. L. van Peursem, and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, **61**, 171 (1939); F. S. Spring and G. Swain, *J. Chem. Soc.*, 83 (1941). [d] L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964). [e] G. Rosenkranz, O. Mancera, and P. Sondheimer, *J. Amer. Chem. Soc.*, **76**, 2227 (1954); H. Reimann, E. P. Oliveto, R. Neri, M. Eisler, and P. Perlman, *ibid.*, **82**, 2308 (1960). [f] *Anal.* Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.65; H, 8.90. Mass spectrum: *m/e* 312 (M^+), 297 ($M - CH_3$). [g] Unpublished result from L. H. Knox, R. Grezemkovsky, and P. Crabbé, (Syntex, S.A.): mp 93–94°; [α]D + 62°; λ_{max} 224 nm (ε 13,200); ν_{max} 1730 cm^{-1}. *Anal.* Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.74; H, 9.33. [h] P. Crabbé, P. Anderson, and E. Verlarde, *J. Amer. Chem. Soc.*, **90**, 2998 (1968). [i] Unpublished result from E. Velarde and P. Crabbé, (Syntex, S.A.): mp 108–109°; [α]D ±0°; λ_{max} 278, 287 nm (ε 2000, 1900). *Anal.* Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 85.63; H, 8.46.

being followed by tlc. The benzene solution was washed with 5% hydrogen chloride and then with water. After distillation of the solvent, the amorphous material obtained was heated under reduced pressure at 90° for 2 hr giving 1 g of product which was chromatographed over Florisil. Elution with hexane–ether (95:5) afforded 680 mg of crystalline **4** (mp 100–104°) (see Table II).[8]

Typical Procedure. Dehydration of the Tertiary Alcohol 20 with the Inner Salt 1.—To a solution of 1 g of **20** in 20 ml of anhydrous benzene, 2.7 g of salt **1**[2] was added. The reaction mixture was stirred at room temperature for 2 hr. The benzene solution was washed with water until neutral, then dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crystalline product was chromatographed over Florisil.

Elution with hexane–ether (96:4) provided 100 mg of the 18-nor steroid **22** (mp 127–128°), which was purified by recrystallization from methanol to afford the analytical sample: mp 129–130°; [α]D ±0°; ν_{max} 1710, 1445 cm^{-1} (see Table II).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.80; H, 10.65.

(8) (a) R. E, Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *J. Amer. Chem. Soc.*, **59**, 1363 (1937); (b) J. Iriarte, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, **20**, 542 (1955); (c) V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *Helv. Chim. Acta*, **28**, 618 (1945).

Further elution with hexane–ether (95:5) afforded 700 mg of crystalline **21** (mp 134–135°) of which the analytical sample was prepared by recrystallization from methanol: mp 142–143°; [α]D +45°; ν_{max} 1710, 1660, 885 cm^{-1} (see Table II); *m/e* 300 (M^+), 285 ($M^+ - CH_3$).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73; O, 5.32. Found: C, 84.12; H, 10.68; O, 5.30.

Registry No.—**4**, 963-75-7; **7**, 570-73-0; **9**, 747-90-0; **11**, 4777-89-3; **13**, 17652-16-3; **14**, 24742-95-8; **16**, 24799-53-9; **18**, 23640-47-3; **19**, 24742-97-0; **21**, 24742-98-1; **22**, 1971-61-5.

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