of ether. Evaporation of the ether yielded a glassy foam, 1.4 g., which was dissolved in benzene and chromatographed on Woelm neutral alumina, activity I. Benzene eluted an oil which was crystallized and recrystallized from *n*-hexane, 0.6 g., m.p. 119.5–120.0°.

N-Methyl-2,4,5-triphenylimidazole (XXVI). Procedure C (Table IV).—A mixture of 2,4,5-triphenylimidazole (0.5 g., 0.0017 mole) and diazomethane (0.006 mole) in 230 ml. of ether was irradiated 1 hr. with a G.E. sunlamp after standing 5 days at 5°. After evaporation of the ether and excess diazomethane, the yellow residue was chromatographed on Woelm neutral alumina, activity I. Elution with benzene afforded a white solid (0.1 g., m.p. 135–145°) which was recrystallized from *n*-hexane, m.p. 143.5–144.5°.

N-Methyl-2-(*p*-tolyl)-4,5-diphenylimidazole (XXVII) was prepared by procedure C. The product was recrystallized from *n*-hexane, m.p. 209–215°, lit.[18] m.p. 217°.

The 2*H*-isoimidazoles were prepared by the method of Weiss[23] from benzil (0.05 mole), the appropriate ketone (0.05 mole), and 40 g. of ammonium acetate in 100 ml. of acetic acid (procedure D). **2,2,4,5-Tetraphenyl-2*H*-isoimidazole** (XXXII) was recrystallized from pyridine, m.p. 195–198°, lit.[23] m.p. 199–201°. **2,2-Spirocyclohexane-4,5-diphenyl-2*H*-isoimidazole** (XXXIII) was recrystallized from aqueous pyridine, m.p. 105.5–106°, lit.[23] m.p. 107–108°.

2,4,4,5-Tetraphenyl-4*H*-isoimidazole (XXXVI).—A dried chloroform solution of benzamidine prepared from 14.0 g. of the hydrochloride salt was refluxed for 4 hr. with 9.0 g. of diphenylbenzoylbromomethane.[24] Water was removed as formed. The reaction mixture was freed of chloroform by evaporation and the brown residue was washed three times with warm dilute ammonium hydroxide. The orange residue was taken up in benzene and filtered. The evaporated benzene solution (9.2 g.) was chromatographed on alumina, and gave rise to 6.2 g. of crude material using petroleum ether (b.p. 30–60°) and benzene as eluents. Two recrystallizations from benzene–heptane gave 2.5 g. of impure isoimidazole, m.p. 170–177°. This sample was again chromatographed on alumina and a small amount of kyaphenine, m.p. 238–238.5°, lit.[15] m.p. 232°, was removed. Recrystallization from benzene–heptane gave 1.7 g. of the isoimidazole, m.p. 177–178°. A further recrystallization from aqueous pyridine did not affect the melting point.

The structural assignment for XXXVI was based on the method of synthesis, the elemental analysis (Table IV), infrared spectrum (no N–H stretching absorption), and direct comparison with the other two possible isomers, XXIV and XXXII.

Acknowledgment.—The authors are indebted to Dr. R. S. McDonald for helpful discussions and to Miss D. V. McClung for determining the infrared spectra.

(24) The bromo ketone [A. Werner, *Chem. Ber.*, **39**, 1286 (1906)] was prepared by refluxing diphenylbenzoylcarbinol with 32% hydrobromic acid and acetyl bromide in acetic acid for 2 hr.

Preparation of 9(11)-Unsaturated Steroids. A Novel Reagent System

GEORGE G. HAZEN AND DALE W. ROSENBURG

Merck Chemical Division, Merck and Company, Inc., Danville, Pennsylvania

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Sulfur dioxide in conjunction with various otherwise unreactive acid chlorides has been found to bring about the facile dehydration of 11β-hydroxy steroids. A rationale for this phenomenon is suggested.

Several instances are recorded in the literature[1] in which organic sulfonyl halides have been used to introduce the 9(11)-double bond into the steroid nucleus by the elimination of the elements of water from 11-hydroxylated starting materials. When the reaction involves an 11α-hydroxyl group, the intermediate sulfonic ester can be isolated and subjected to the action of a base such as pyridine or sodium acetate to complete the two-step reaction.[1a-d] Various sulfonyl halides may be used, the most common being *p*-toluenesulfonyl chloride[1a-d] and methanesulfonyl chloride.[1b] Alternatively, the reaction mixture (containing an excess of base such as pyridine) containing the sulfonic ester may be refluxed to complete the dehydration.

11β-Hydroxy steroids also respond to the action of methanesulfonyl chloride and base to furnish 9(11)-unsaturated products.[1e-g] There are two interesting points concerning this reaction. Among sulfonyl halides none except lower alkanesulfonyl halides have been made to work in the dehydration of 11β-hydroxy steroids. Furthermore, in limited cases only[2] has the isolation of the presumed intermediate 11β-mesylate been reported. The construction of a molecular model of this intermediate is at best difficult, creating some doubt that such an ester is truly a step in the mechanistic path from 11β-hydroxy steroids to 9(11)-unsaturated steroids. In addition, vigorous conditions or prolonged reaction times have been found necessary to bring about the desired reaction.[1g]

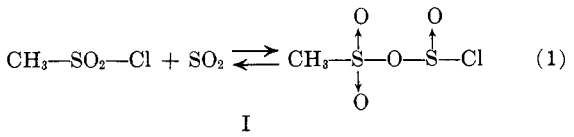
However, when mesyl chloride is distilled at atmospheric pressure prior to use, decomposition takes place in the still pot and the colorless distillate becomes a far more active agent in the dehydration reaction. Upon addition of this reagent to a cold solution of steroid, collidine, and dimethylformamide, a vigorous reaction ensues, the temperature rises, and, after a few minutes at 25–30°, the reaction is complete. Vapor phase chromatography revealed a volatile impurity in distilled mesyl chloride which was not present prior to distillation. Vacuum-distilled reagent likewise lacks the impurity and fails to bring about dehydration under the mild conditions employed. The volatile component was shown by experiment to be sulfur dioxide. Samples of mesyl chloride which failed to accomplish the desired reaction were rendered effective by the addition of small quantities of sulfur dioxide.

It may be interjected at this point that methyl chlorosulfite is also an effective agent for the elimination of the elements of water from 11β-hydroxy steroids.[1g]

(1) (a) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); (b) **79**, 1130 (1957); (c) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaur, W. Gebert, C. T. Conigilio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *ibid.*, **80**, 4431 (1958); (d) G. Rosenkranz, O. Mancera, and F. Sondheimer, *ibid.*, **76**, 2227 (1954); (e) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *ibid.*, **77**, 4181 (1955); (f) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *ibid.*, **80**, 3161 (1958); (g) E. M. Chamberlin, E. W. Tristram, T. Utne, and J. M. Chemerda, *J. Org. Chem.*, **25**, 295 (1960).

(2) E. J. Agnello and G. D. Laubach, U. S. Patent 2,877,157 (March 10, 1959); U. S. Patent 2,877,222 (March 10, 1959); U. S. Patent 2,877,233 (March 10, 1959). These authors report the isolation of the 11β-mesylates of $\Delta^{8(14)}$-androstene and $\Delta^{8(14)}$-19-norandrostene derivatives. Molecular models reveal that steric interference by the 18- and/or 19-methyl groups with the 11β-position is distinctly less than when the 8,14-bond is saturated.

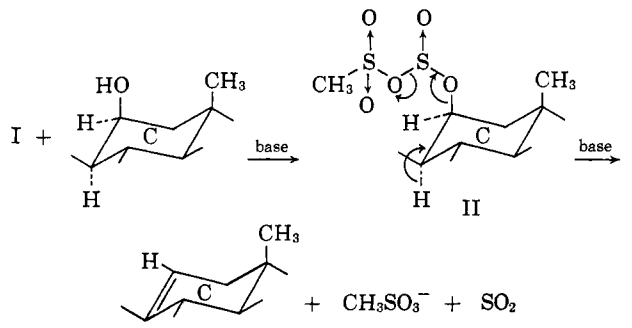
The intermediate methyl sulfite ester can be isolated and a model can be constructed.[3] This reagent resembles methanesulfonyl chloride in its over-all geometry except for the presence of only one branch (oxygen) on sulfur, whereas mesyl chloride possesses two branches. This knowledge, coupled with the fact that less than molar quantities of sulfur dioxide are ample, allow the formulation of a mechanism for the action of sulfur dioxide. It is first proposed that mesyl chloride and sulfur dioxide interact reversibly to form an unstable, reactive, mixed anhydride of methanesulfonic acid and the hypothetical chlorosulfinic acid (eq. 1).



(1)

I

This compound, being an acid chloride also, reacts readily in the presence of base to form a labile ester (II), which decomposes to furnish 9(11) steroid, methanesulfonate ion, and sulfur dioxide. The latter then can participate again in the reaction sequence.



In support of the proposed mechanism, *p*-toluenesulfonyl chloride, benzenesulfonyl chloride, benzoyl chloride, and *p*-nitrobenzoyl chloride are all transformed from ineffective dehydrating agents to useful reagents by small amounts of sulfur dioxide.[4] The quantities of sulfur dioxide were in the range of 5–50 mole %, or greater (based on the steroid); values below 5 mole % were insufficient. The larger amounts were unnecessary. Consistently good results were obtained with about 10–20 mole %.

Experimental

For maximum yields, all solvents and reactants must be anhydrous. All melting points were taken in open-end glass capillary tubes and are uncorrected.

16α-Methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-Acetate. A. Methanesulfonyl Chloride and Sulfur Dioxide.—A solution of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate in 33 ml. of natural collidine and 100 ml. of dimethylformamide was cooled to 10°. The cooling bath was removed and during the course of 1–2 min., 10.0 ml. (14.7 g., 0.128 mole) of methanesulfonyl chloride (Eastman White Label) containing 3.5% (0.5 g., 0.008 mole) by weight of anhydrous sulfur dioxide was added to the clear solution. Efficient stirring was maintained throughout the reaction period. The temperature rose quickly and cooling was employed to maintain the mixture at 25–35°. The reaction was allowed to proceed between these temperatures for a period of 5 min., during which a light-colored precipitate separated and the solution assumed a reddish hue. At the end of the reaction period, the cooling bath was replaced and the excess mesyl chloride was decomposed by the slow addition of 17 ml. of water. The proper amount of water caused the precipitate to dissolve without causing precipitation of the product. The clear, orange to red solution was then added dropwise with efficient stirring to 1 l. of water during a period of 20 min. A small amount of methanol and then water were used to complete transfer of solution. After stirring the resulting slurry for 1 hr. at 20–25°, the product was collected, washed with water, and air-dried at 60° to constant weight. The yield of product which melted at 203–211° was 15.3 g. (96%). Recrystallization from ethanol raised the melting point to 216.5–218°; lit.[1c] m.p. 210–213°. Paper-strip chromatography showed that the crude product contained no unchanged starting material. An experiment similar in all respects except that sulfur dioxide was omitted gave only unchanged starting material.

B. *p*-Toluenesulfonyl Chloride and Sulfur Dioxide.—A solution of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 24.5 g. (0.128 mole) of *p*-toluenesulfonyl chloride, and 100 ml. of dimethylformamide was cooled to 10° and 33 ml. of collidine was added. After 5 min. at room temperature, a portion of the deep red solution was removed and quenched with water. Paper-strip analysis of this portion revealed that no dehydration had occurred.

The main batch was cooled to 10° immediately after removal of the aliquot, and was treated with 5.0 ml. of a solution of sulfur dioxide in dimethylformamide (4.7% by weight, *ca.* 3.5 mmoles). The temperature again rose sharply to a maximum of 33°. Five minutes after the temperature had reached 25°, the reaction was halted and the product was precipitated as in method A. The yield of bright yellow product was 14.9 g. (93%), m.p. 198–208°. Paper-strip analysis showed that complete dehydration had occurred.

Additional experiments showed that toluenesulfonyl chloride and sulfur dioxide together in dimethylformamide solution may be added as one reagent, or the collidine and sulfur dioxide may be mixed and added to the remaining reactants in solution.

C. Benzenesulfonyl Chloride and Sulfur Dioxide.—A mixture of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 90 ml. of dimethylformamide, and 33 ml. of collidine was cooled to 15° and treated with 16.4 ml. (22.6 g., 0.128 mole) of benzenesulfonyl chloride. The temperature rose sharply and the color of the mixture deepened to a red-orange. When the temperature reached 30°, the mixture was cooled to 10° by means of an ice bath and treated with 10 ml. of a solution of sulfur dioxide in dimethylformamide (3.6% by weight). The temperature again rose and was maintained at 25–28° by external cooling. Precipitation of the quenched solution into water gave 14.5 g. (91%) of yellow powder which melted at 184–204°. Recrystallization from ethanol raised the melting point to 211–215° (62% recovery).

D. Benzoyl Chloride and Sulfur Dioxide.—A mixture of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 33 ml. of collidine, and 95 ml. of dimethylformamide was cooled to 10° and 14.8 ml. (18.0 g., 0.128 mole) of freshly distilled benzoyl chloride was added gradually. Heat was evolved, a precipitate appeared, and the color of the solution changed gradually to chocolate brown. After 5 min. at 25–30°, an aliquot was removed and analyzed by paper-strip chromatography. No dehydration had occurred.

The remaining mixture was cooled to 10° immediately after the aliquot was removed and was treated with 5.0 ml. of 4.7% sulfur dioxide in dimethylformamide (*ca.* 3.5 mmoles). The temperature was allowed to rise to 30°, and, after 5 min. at 25–30°, the excess reagent was destroyed by a small quantity of water. Only gum was obtained when the clear, red solution was added to water. The aqueous phase was decanted from the gum which was then washed with fresh water, dried by azeotropic distillation with benzene, and finally dissolved by warming in 100 ml. of ethanol. Cooling and seeding the solution caused white crystals of 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate to separate. The product was collected, washed with cold ethanol, and dried in air at 50°. The yield was 4.0 g. (*ca.* 25%), m.p. 210–213°. Paper-strip analysis showed that the product contained about 98% of the desired triene and about 2% of unchanged starting material.

(3) Unpublished communication from Dr. Erwin Schoenewaldt of the Merck, Sharp and Dohme Research Laboratories Division. The workers in ref. 1g report that they were unable to isolate the intermediate methyl sulfite ester.

(4) Small, highly reactive acid chlorides, such as acetyl chloride, lead only to the formation of the 11β esters. No dehydration products were detected.

The mother liquor solids consisted of about 60% product and 40% starting material.

In another experiment, the sulfur dioxide solution was added to the mixture of steroid, dimethylformamide, and collidine prior to the addition of benzoyl chloride. Only unchanged starting material was recovered. This observation has not been checked.

E. *p*-Nitrobenzoyl Chloride and Sulfur Dioxide.—A mixture of 16.7 g. (0.04 mole) of 16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, 33 ml. of collidine, and 90 ml. of dimethylformamide at 10° was treated with a solution of 23.7 g. (0.128 mole) of *p*-nitrobenzoyl chloride in 10 ml. of dimethylformamide which also contained about 3% sulfur dioxide by weight. After 5 min. at 25–45° (initial heat evolution quite pronounced), the reaction mixture was worked up in the manner described for the benzoyl chloride run. The gum, which separated when the batch was added to water, solidified upon standing over the weekend. It was collected, washed with water, and recrystallized still wet, from 75 ml. of ethanol (hot filtration). There was obtained 6.55 g. (*ca.* 41%) of 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate which melted at 212–215.5°. Paper-strip analysis of this product and its mother liquor revealed that essentially quantitative conversion had taken place.

4,9(11)-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate [11-(9)-Anhydrocortisol Acetate].—A change of 60.0 g. (0.148 mole) of 4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (cortisol acetate) was slurried with 122 ml. of natural collidine, and then 370 ml. of dimethylformamide was added. This sequence of addition allows the cortisol acetate to dissolve momentarily and then quickly separate as fine crystals of the dimethylformamide complex. Good stirring is essential to keep the resulting thick slurry mobile. The mixture was cooled to 10° and treated in about 2 min. with 37 ml. of methanesulfonyl chloride containing 3.2% sulfur dioxide. The batch was allowed to stir at 25–35° for 10 min. and then excess reagent was destroyed by the gradual addition (1 min.) of 60 ml. of water. Despite ice-bath cooling the temperature of the reaction mixture rose to 59°. The thin slurry was cooled to room temperature and added gradually to 3700 ml. of hot (80–90°) water with good agitation.[5] This mixture was stirred at 85–90° for 1 hr., cooled to room temperature, and filtered. The product was washed several times with water and dried in air at 60°. There was obtained 56.0 g. (97.7%) of cream-colored powder which melted at 226–228.5°, contained 0.6% water (by Karl Fischer titration), and possessed a specific rotation (*c* 0.5) in chloroform of +131.8°. Treatment of this product with ten parts of refluxing methanol gave a recovery of about 92% of 11(9)-anhydrocortisol acetate which melted at 234–237°; lit.[1a] m.p. 236–237°, [α]D (*c* 1, chloroform) +117°; lit.[6] m.p. 231.5–234.5°, [α]D (*c* 1.04, chloroform) +124°; lit.[1g] m.p. 232.5–236.5°.

The above procedure in the absence of sulfur dioxide gave only unchanged starting material.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-Acetate.—A charge of 16.2 g. (0.04 mole) of 1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (prednisolone acetate) was dehydrated by the procedure described for 11(9)-anhydrocortisol acetate. The crude product was obtained in a yield of 15.85 g. (103%), m.p., 154–205°. Paper-strip analysis showed complete dehydration had occurred. Refluxing the product with five parts of acetone permitted a recovery of 46.8% of triene which melted at 220–222°, lit.[7] m.p. 223–226°.

Acknowledgment.—We wish to express our appreciation to Mr. Charles B. Muchmore for the preparation and help in the interpretation of the vapor phase chromatograms. We also wish to thank Dr. Erwin Schoenewaldt of the Merck Sharp and Dohme Research Laboratories for his valuable suggestions and information. It was he who proposed the mechanism which we have described here.

(5) Precipitation of the product by hot water allows the isolation of a partially hydrated material which is easily freed of water at moderate temperatures. Precipitation by cold water furnished the dimethylformamide complex of the product which requires vigorous drying conditions in order to be rid of the solvent or a slurry treatment with hot water, in which case the hydrate is obtained.

(6) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 4722 (1953).

(7) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. D. Schneider, P. F. Beal, and J. Korman, *ibid.*, **77**, 4438 (1955).

Steroids of Unnatural Configuration. The Absence of Long-Range Conformational Effects in Ring A Modified 20-Ketopregnanes[1a,b]

MORDECAI B. RUBIN AND ERICH C. BLOSSEY[2]

Department of Chemistry, Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

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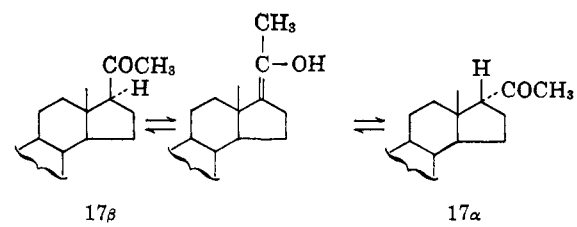
Syntheses of 5α,17α-pregnane-3,20-dione, 5β,17α-pregnane-3,20-dione, and 17α-1-dehydroprogesterone are described. No detectable long-range conformational effects were observed in the n.m.r. spectra or relative stabilities (*vs.* 17β-isomers) of these three compounds as well as 17α-pregnenolone and 17α-progesterone.

A large variety of 20-ketopregnanes, unsubstituted at C-17, have been described. Although the two C-17 isomers of these ketones are interconvertible through a common enol (or enolate ion), only the 17β-epimers are naturally occurrring.[3] We have undertaken a systematic study of the unnatural (17α) isomers of these ketones[4a] with the objectives of evaluating the role of C-17 configuration in biological activity and investigating the operation of a variety of steric effects in fused ring systems. This report describes the first stage of this investigation and is concerned with the



17β 17α

(1) (a) This research was supported in part by a Public Health Service Research Grant, A-3943, from the National Institute of Arthritis and Metabolic Diseases; (b) presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(2) National Institutes of Health Predoctoral Fellow, 1961–1962.

(3) Two exceptions to this generalization have been reported: (a) H. I. Calvin and S. Lieberman [*Biochemistry*, **1**, 639 (1962)] have isolated tritiated IIα from human urine after ingestion of tritiated 16-dehydroprogesterone. Earlier isolations of IIα from human urine were explicable on the basis of isomerization of 17β-isomer during vigorous acid hydrolysis involved in the isolation procedures [S. Lieberman, K. Dobriner, B. R. Hill, L. F. Fieser, and C. P. Rhoads, *J. Biol. Chem.*, **172**, 263 (1948); G. Birke, C. A. Gemzell, L. O. Plantin, and H. Robbe, *Acta Endocrinol.*, **27**, 389 (1958)]; (b) P. D. Meister, D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, and H. M. Leigh [*J. Am. Chem. Soc.*, **75**, 55 (1953)] isolated 25% of 11α-hydroxy-17α-progesterone from incubation of 16-dehydroprogesterone with *Rhizopus nigricans*.

(4) (a) A review of 17α-20-ketopregnanes has recently appeared [M. B. Rubin, *Steroids*, **2**, 561 (1963)]. (b) In this report 20-ketopregnanes (unsubstituted at C-17) are designated by a Roman numeral followed by α or β to indicate the stereochemistry at C-17.