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Bismethylenedioxy Steroids. VI. Synthesis of 9α-Methylhydrocortisone and 9α-Methylprednisolone[1,2]

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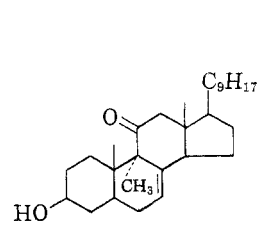
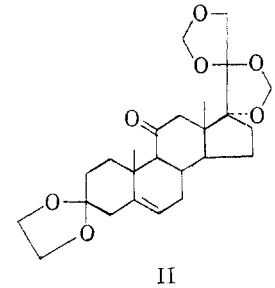
The synthesis of 9α-methylhydrocortisone acetate (XVIb) and 9α-methylprednisolone acetate (XVII) is described. The key step in the synthesis is the reaction of a bismethylenedioxy protected 9α-bromo-11-ketone (XII) with methyl Grignard reagent to give a 9α-methyl-11-ketone (XIII). Alternate methods used to synthesize 9α-methylsteroids are also discussed.

Substituents at the C_9-position of adrenocortical steroids have a profound effect on biological activity. Liver glycogen activities of C_9-substituted hydrocortisones are known to decrease in the following order: F > Cl > H > Br > OH > I > OCH_3 ≃ OC_2H_5. This order correlates (hydrogen and hydroxyl are exceptions) with the inductive effect of the substituents as measured by the acidity constants of the corresponding α-substituted acetic acids.[4] Fried has favored the view that the electronic effect at C_9 has a greater influence on biological activity than the steric effect. As the acidity constant of propionic acid (CH_3) is slightly less than acetic acid (H) and the methyl group approximates a chlorine atom in size[5] we felt that information on the bioactivity of 9α-methyl hydrocortisone would advance the theory of how these effects are mediated. The present study outlines methods for introduction of a methyl group at C_9 and reports on the synthesis of two 9α-methyl corticoids.

Jones, Meakins, and Stephenson[6] have synthesized 9α-methyl-7,22-ergostadiene-3β-ol-11-one (I) by alkylation of the Δ_7-11-ketone with methyl iodide–potassium *t*-butoxide. In a similar fashion we tried to introduce the 9α-methyl group by alkylation of bismethylenedioxy cortisone-3-dioxolane (II). Paper strip data on the alkylation product showed that a trace amount of bismethylenedioxy-9α-methylcortisone (after dioxolane removal) had formed when triphenylmethylsodium–methyl iodide was used. However the major products of the reaction were starting material and polar by-products so that this method did not prove practical for our purpose.[7]

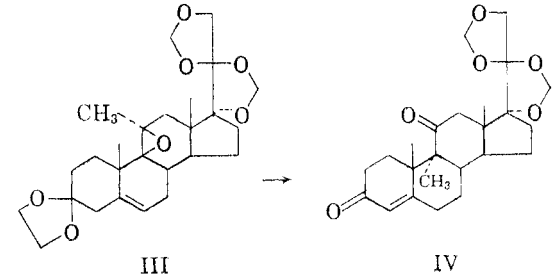


I



II

Another attractive method for synthesis of a 9α-methylsteroid involved an attempted Wagner-Meerwein rearrangement of 11α-methyl-9,11β-oxido - 17,20;20,21 - bismethylenedioxy - 3 - ethylenedioxy - 5 - pregnene (III)[8] to the 9α-methyl-11-ketone (IV). The Lewis acid catalyzed rearrangement of oxides to ketones is well known.[9] In most of our attempts we used boron trifluoride etherate in solvents of varying polarities (ether, tetrahydrofuran, benzene, methylene chloride, chloroform). In general the desired electrophilic attack on the



III IV

(1) Paper V in this series: R. E. Beyler, Frances Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

(2) A preliminary communication of part of this work has been published. Frances Hoffman, R. E. Beyler, and M. Tishler, *J. Am. Chem. Soc.*, **80**, 5322 (1958).

(3) Present address: Department of Chemistry, Southern Illinois University, Carbondale, Ill.

(4) J. Fried and A. Borman in *Vitamins and Hormones*, Academic Press, New York, Vol. 16, p. 322.

(5) A. Burger and R. D. Foggio, *J. Am. Chem. Soc.*, **78**, 4419 (1956).

(6) E. R. H. Jones, G. D. Meakins, and J. S. Stephenson, *J. Chem. Soc.*, 2156 (1958).

(7) More recently in another study, Dr. John Fried has treated bismethylenedioxycortisone-3-dioxolane (II) with sodium hydride–methyl iodide. From a chromatographic fraction which was less polar than starting material, we again obtained paper strip evidence for the presence of a trace of bismethylenedioxy-9α-methylcortisone after dioxolane removal.

(8) Paper IV in this series: R. E. Beyler, Frances Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960).

(9) A recent example is the conversion of methyl acetyl-12,13α-oxido-18-isooleanolate to methyl acetyl-12 keto-dihydro-11-isooleanolate with boron trifluoride etherate in methylene chloride: E. J. Corey and J. J. Ursprung, *J. Am Chem. Soc.*, **78**, 183 (1956). Also see C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Sumners, *J. Chem. Soc.*, 630 (1959) for conversion of 4,5α-oxidocholestane to 5α-cholestan-4-one.

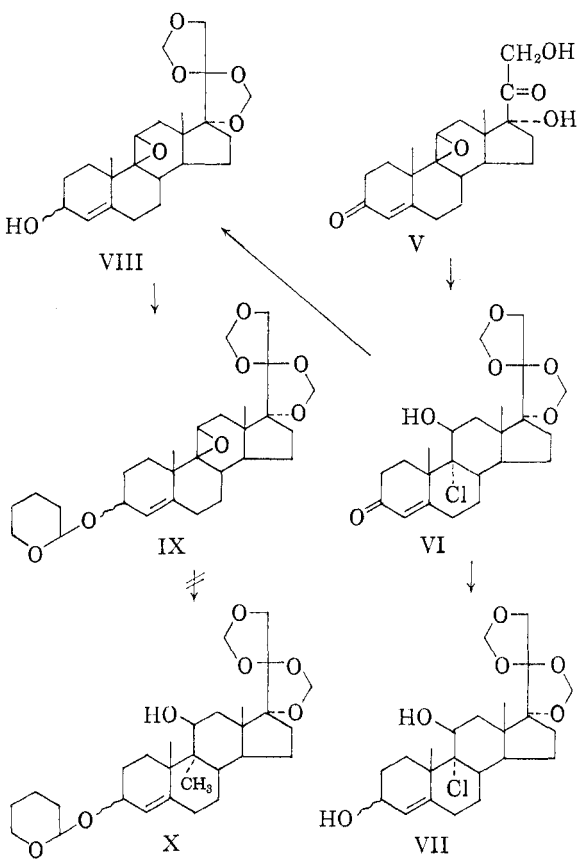
9,11-oxide was superseded by reaction at the dioxolane and to a lesser extent the bismethylenedioxy group; vigorous conditions (excess boron trifluoride in polar solvents) gave polar non-crystalline products and mild conditions (limited amounts of boron trifluoride in ether or tetrahydrofuran) gave starting material or the corresponding 3-keto-Δ^4 analog. Some of the crude material showed saturated ketone by infrared but no pure 9α-methyl-11-ketone was obtained in these experiments. Other catalysts tried on III or its 3-keto-Δ^4 analog include ferric chloride, perchloric acid, *p*-toluenesulfonic acid and hydrogen fluoride.

The cleavage of oxides with methyl Grignard reagent or methyllithium, which has been used to make 6- and 12-methylsteroids,[10,11] seemed to be a possible approach to the 9α-methyl-11β-ol. We are aware of one reported cleavage of a steroid oxide with Grignard reagents to give a bridgehead methyl substituent. That is the cleavage of 5,6β-oxidocholestan-3β-ol with methylmagnesium iodide to give 5α-methylcholestane-3β,6β-diol.[12] It was felt that this method for making a 9α-methylsteroid was deserving of our attention.

Therefore, the desired oxide (IX) for Grignard cleavage attempts was synthesized as follows: bismethylenedioxy - 9α - chlorohydrocortisone (VI) was prepared from either 9,11β-oxidocortexolone[13] (V) or from 9α-chlorohydrocortisone using hydrochloric acid–formalin in the standard way. Treatment of VI with sodium methoxide or potassium *t*-butoxide yielded bismethylenedioxy-9,11β-oxidocortexolone. The latter would have been useful for oxide cleavage if it could have been protected further with a 3-dioxolane. However attempts to make bismethylenedioxy-9,11β-oxidocortexolone-3-dioxolane met with failure due to acid catalyzed rearrangement in the C-ring.[14]

As an alternative, the chlorohydrin (VI) was reduced with sodium borohydride to the chlorohydrin -3 ξ-ol (VII). The latter could be transformed to the 9,11-oxide-3 ξ-ol (VIII) by means of potassium *t*-butoxide or refluxing sodium borohydride. With this information it was then found possible to go directly from bismethylenedioxy-9α-chlorohydrocortisone (VI) to 9,11β-oxido - 17α,20;20,21-bismethylenedioxy - 4 - pregnene-3 ξ-ol (VIII) in one step by means of sodium borohydride in refluxing ethanol. The required tetrahydropyranyl ether group was then added to give the fully protected oxide (IX) as an oil.

All attempts to cleave IX with methyllithium, methylmagnesium iodide and methylmagnesium chloride were unsuccessful. Only starting material and polar oils resulted from these reactions. Similar reactions with the unprotected 3-hydroxy Δ^4-compound (VIII) also met with failure.



A usable yield of 9α-methylsteroid was finally obtained by reaction of a 9α-bromo-11-ketone with methyl Grignard reagent. It is well known[15] that α-halo ketones can react with Grignard reagents in at least four different ways: (1) normal addition to the C=O to give a tertiary alcohol, (2) replacement of the α-halogen by the organic radical of the Grignard reagent, (3) reductive enolization

(10) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hange, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956); J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, **81**, 1235 (1959).

(11) B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschmann, and J. M. Chemerda, *J. Am. Chem. Soc.*, **82**, 3995 (1960).

(12) M. Chuman, *J. Chem. Soc., Japan*, **70**, 253 (1949).

(13) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957); Cortexolone has been proposed as a trivial name for Reichstein's Substance S: L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, p. 602.

(14) The crude product from the dioxolanation always exhibited a sizeable ultraviolet absorption at *ca.* 240 mμ and a saturated carbonyl in the infrared spectrum. In another connection we have observed the conversion of 9,11β-oxidocortexolone acetate to cortisone acetate using *p*-toluenesulfonic acid in refluxing benzene in at least 40% yield.

Dioxolanation of 9α-halo-11β-hydroxysteroids is also not feasible, so we could not reverse the order of steps to get a bismethylenedioxy-9,11-oxide dioxolane. For example dioxolanation attempts on bismethylenedioxy-9α-fluorohydrocortisone gave a bad mixture of products which we have not characterized other than infrared spectra on selected chromatographic fractions.

(15) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 181.

with loss of halogen and (4) enolization of the α-halo ketone. The reaction we desired (number 2 above) is exemplified in the simplest case by conversion of 2-chlorocyclohexanone to 2-methylcyclohexanone.[16] A more recent example is that of the conversion of 2-chlorotetralone to 2-phenyltetralone.[17]

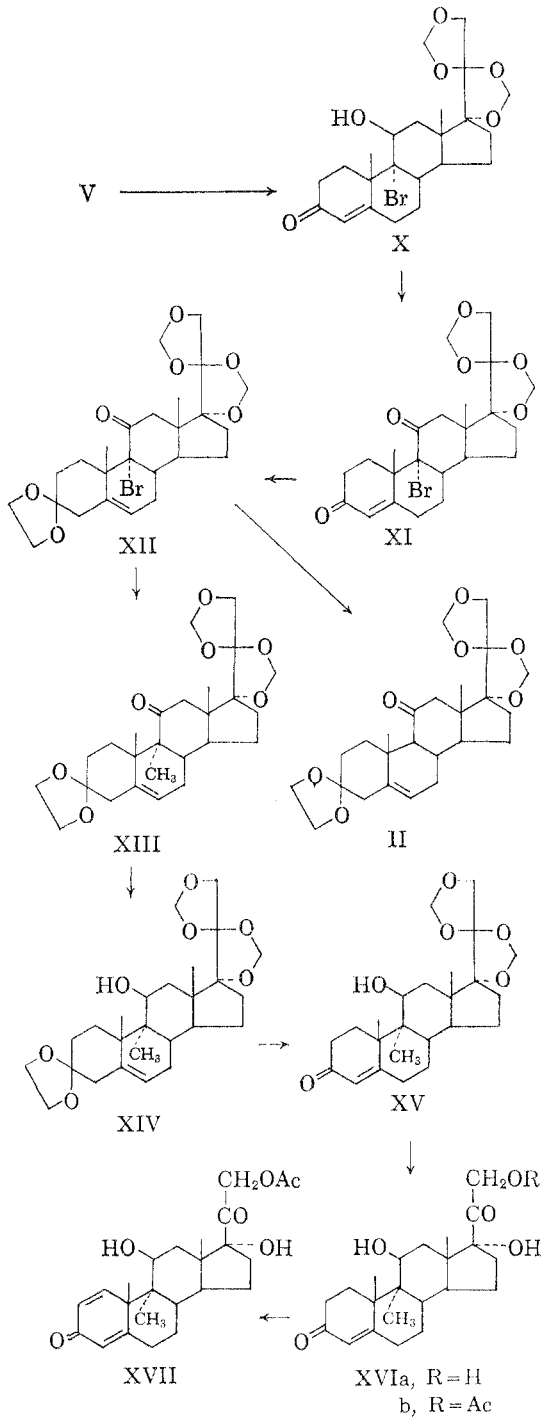
Synthesis of the requisite 9α-bromo-11-ketone (XII) was done as follows: 9,11β-Oxidocortexolone (V) reacted with formaldehyde–hydrobromic acid to give bismethylenedioxy-9α-bromohydrocortisone (X). Chromic acid oxidation of X gave bismethylenedioxy-9α-bromocortisone (XI). Conventional dioxolanation then yielded the fully protected 9α-bromo-11-ketone (XII).

When this α-halo ketone was allowed to react with methylmagnesium iodide and excess methyl iodide in refluxing ether-tetrahydrofuran two products resulted. These were separated by careful alumina chromatography and proved to be bismethylenedioxy 9α-methylcortisone-3-dioxolane (XIII) and bismethylenedioxy cortisone-3-dioxolane (II). The former was obtained in a maximum 30% yield and the yield of II varied widely depending upon the solvents and temperatures used. The 9α-methyl substituent was proven to be present by means of nuclear magnetic resonance, which showed three tertiary C—CH_3 bands.

The rotatory dispersion curves of II and XIII[18] were also very similar, as would be predicted for two compounds differing by only a CH_3 and H adjacent to the carbonyl. This data confirmed the fact that no serious rearrangement had occurred during the reaction.

With regard to the mechanism of this reaction, it seems probable that the first step is the formation of an enolate anion[19] with loss of the bromine atom at C_9. The resultant C_9-carbanion can then be alkylated with excess methyl iodide to give methyl ketone XIII. Alternatively, a proton supplied during the work-up would give the unmethylated ketone (II).

The completion of the synthesis was done as follows: the 11-keto compound (XIII) was reduced with lithium aluminum hydride to the bismethylenedioxy-9α-methylhydrocortisone-3-dioxolane (XIV). The dioxolane was removed with acetone–*p*-toluenesulfonic acid and the bismethylenedioxy-group was reversed with 50% acetic acid to give 9α-methylhydrocortisone (XVIa). Acetylation afforded the 21-acetate (XVIb).



Dehydrogenation of XVIb with selenium dioxide in *t*-butyl alcohol acetic acid produced 9α-methylprednisolone-21-acetate (XVII). The infrared spectra of all intermediates and the final products were consistent with the assigned structures.

It is of interest to examine the influence of 9α-substituents on the ultraviolet absorbing 3-keto-Δ^4-chromophore (Table I). Since an electronegative substituent such as fluorine at C_9 has a hypsochromic effect (−3 mμ) and the methyl group, which is electron releasing, has a bathochromic effect (+1 to 2.5 mμ) it seems probable that the

(16) M. Tiffeneau and B. Tchoubar, *Compt. rend.*, 198, 941 (1934).

(17) A. S. Hussey and R. R. Herr, Abstracts of Papers Presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959, p. 18-o.

(18) We are indebted to Dr. D. E. Williams for these measurements.

(19) E. P. Kohler and M. Tishler, *J. Am. Chem Soc.*, 54, 594 (1932); E. P. Kohler and M. Tishler, *J. Am. Chem. Soc.*, 57, 217 (1935).

TABLE I

11-Ketone Series	λ_{max}	
Cortisone-BMD	238 mμ	Δλ for F = −3 mμ Δλ for CH_3 = +1 mμ
9α-Fluorocortisone-BMD	235	
9α-Methylcortisone-BMD	239	
11-Hydroxy Series		
Hydrocortisone-BMD	241.5 mμ	Δλ for F = −3 mμ Δλ for CH_3 = +2.5 mμ
9α-Fluorohydrocortisone-BMD	238.5	
9α-Methylhydrocortisone-BMD	244	

C_9-C_5 transannular inductive effect has an appreciable influence on the ultraviolet absorption maximum.

The biological test results[20] expressed in terms of hydrocortisone, were as follows: 9α-Methylhydrocortisone (XVIa) was *ca.* 0.1 (p.o.) and 9α-methylprednisolone acetate (XVII) was *ca.* 1.75 (p.o.) in the liver glycogen assay. XVIa was *ca.* 0.25 (s.c.) and XVII was *ca.* 1.6–1.8 (p.o.) in the cotton pellet granuloma assay. Both XVIa and XVII caused slight sodium retention in adrenalectomized rats.

EXPERIMENTAL[21]

Methylation of bismethylenedioxycortisone-3-dioxolane. To 2.59 g. of dry bismethylenedioxycortisone-3-dioxolane suspended in 50 ml. of sodium dried ether was added 4.7 ml. (1 equivalent) of 0.128*M* triphenylmethyl sodium in ether. The mixture was stirred at room temperature for 20 min. Since a loss of red color indicated the base was being consumed, 15.3 ml. more triphenylmethyl sodium was added. Stirring was continued for another hour during which time a fine yellow solid formed. Then 5.0 ml. of methyl iodide was added and stirring was continued at room temperature for 96 hr. About 20 ml. of water was cautiously added and the ether layer separated. The aqueous layer was extracted with two portions of methylene chloride, the combined ether–methylene chloride extract dried and concentrated to give 3.36 g. of yellow gum. This was chromatographed on 100 g. of alumina. From the early petroleum ether–ether (3:7) fractions 506 mg. of crystalline product was selected for removal of the 3-dioxolane group. It was dissolved in 10 ml. of acetone and 100 mg. of *p*-toluenesulfonic acid added. After 24 hr. at room temperature it was concentrated to dryness under reduced pressure. The residue was dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate. After concentration of the extract the residual 447 mg. of gum was chromatographed on 20 g. of alumina. A crystalline product was obtained in the ether to ether–chloroform (1:4) effluents. Paper strips on the first three fractions, totalling 49 mg., showed a spot more mobile than bismethylenedioxycortisone. The relative Rf with respect to bismethylenedioxy cortisone was about 1.4 in a cyclohexane–formamide system and about 1.3 in a cyclohexane–propylene glycol system. The major spot from these fractions, however, was bismethylenedioxy cortisone; it was estimated to approximate 75% of the ultraviolet absorbing material.

(20) We are indebted to Dr. R. H. Silber and Dr. H. C. Stoerk of the Merck Institute for Therapeutic Research for these data. The designation p.o. and s.c. designates oral and subcutaneous administration, respectively.

(21) All melting points were determined on a Kofler micro hot stage. Ultraviolet spectra were determined in methanol.

Similar results were obtained with methyl iodide and bismethylenedioxycortisone-3-dioxolane using metallic potassium in refluxing benzene or toluene with vigorous stirring. With potassium *t*-butoxide no evidence for methylation was obtained in two experiments.

9α-Chloro-17α,20;20,21-Bismethylenedioxy-4-pregnene-11β-ol-3-one (VI) *A. From 9α-Chlorohydrocortisone acetate.* One gram of 9α-chloro-4-pregnene-11β,17α,21-triol-3,20-dione-21-acetate was dissolved in 100 ml. of methylene chloride and stirred at room temperature for 18 hr. with 25 ml. of 37% formaldehyde and 25 ml. of concd. hydrochloric acid. The methylene chloride layer was separated, washed with aqueous sodium bicarbonate and dried. Evaporation *in vacuo* yielded crystals which, upon recrystallization from methylene chloride–methanol gave 550 mg. of analytically pure 9α-chloro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one, m.p. 220–230° dec.

Anal. Calcd. for $C_{28}H_{31}O_6Cl$: C, 62.93; H, 6.95; Cl, 8.07; CH_2O, 13.6. Found: C, 62.46; H, 6.97; Cl, 8.59; CH_2O, 13.8. λ_{max}^{Nujol} 5.99, 6.10, 9.0 μ.

B. *From 9,11β-oxidocortexolone* (V). One gram of 9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione[18] was dissolved in 100 ml. of methylene chloride and stirred for 18 hr. at room temperature with 25 ml. of formalin and 25 ml. of concd. hydrochloric acid. After the usual work-up, the resultant crystals were recrystallized from methylene chloride–methanol to yield 350 mg. of 9α-chloro-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one, m.p. 220–230° dec. The infrared spectrum of this compound was identical with that of the sample prepared above.

9,11β-Oxido-17,20;21,21-bismethylenedioxy-4-pregnene-3-one. A. *Potassium t-butoxide method.* To a stirred solution of 1.0 g. of 9α-chloro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one in 50 ml. of *t*-butyl alcohol was added, in an atmosphere of nitrogen, 4.0 ml. of 0.84*M* potassium *t*-butoxide. After 48 hr., a few drops of acetic acid were added and the *t*-butyl alcohol was concentrated *in vacuo*. The residue was extracted with methylene chloride, washed with a saturated solution of sodium bicarbonate, dried and concentrated to yield 1.02 g. of amber gum. Trituration with methylene chloride–ether afforded 155 mg. of the desired product. The residue was chromatographed on acid-washed alumina and elution of the column with ether and ether-chloroform (4:1) gave, after recrystallization from methylene chloride–methanol, 540 mg. of analytically pure 9,11β-oxido-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one, m.p. 210–215°.

Anal. Calcd. for $C_{28}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.52; H, 7.54. λ_{max}^{Nujol} 6.0, 6.15, 9.0–9.1 μ.

B. *Sodium methoxide method.* Two hundred milligrams of 9α - chloro - 17α,20;20,21 - bismethylenedioxy - 4 - pregnene-11β-ol-3-one was combined under nitrogen with 20 ml. of methanol and 1.0 ml. of 2*N* sodium methoxide and heated under reflux for 18 hr. The reaction mixture was cooled, enough 2.5*N* hydrochloric acid added to effect neutrality, the methanol concentrated to a small volume *in vacuo* and the residue extracted with ethyl acetate. After washing the organic phase with water, drying over magnesium sulfate, and concentrating under reduced pressure, crystals were obtained. Recrystallization from methanol afforded 50 mg. of analytically pure 9,11β-oxido-17,20;20,21-bismethylenedioxy-4-pregnene-3-one, m.p. 205–215°, identical with the sample prepared above.

9α-Chloro-17α,20;20,21-bismethylenedioxy-4-pregnene-3ξ,11β-diol (VII). Two hundred milligrams of bismethylenedioxy-9α-chlorohydrocortisone (VI) was dissolved in 10 ml. of 95% ethanol and 10 ml. of methylene chloride. To this was added 200 mg. of sodium borohydride and the mixture stirred at room temperature for 16 hr. Water was added and the solution concentrated to an aqueous suspension of oil. This was extracted thrice with methylene chloride, dried and concentrated to give 208 mg. of crystalline residue, m.p. 180–195°. Recrystallization from ether–methylene chloride gave 102 mg., m.p. 193–202°. The analytical sample of VII

was prepared by recrystallization from acetone-ether and methylene chloride–ether, m.p. 205–208° dec.

Anal. Calcd. for $C_{23}H_{33}O_6Cl$: C, 62.64; H, 7.53; Cl, 8.04. Found: C, 62.91; H, 7.27; Cl, 8.78. λ_{max}^{Nujol} 2.75–3.0, 6.0 (weak), 9.0–9.2 μ.

9,11β-Oxido-17α,20;20,21-bismethylenedioxy-4-pregnen-3β-ol (VIII) A. *Potassium t-butoxide on* VII. To 30 mg. of the above chlorohydrin (VII) in 1.5 ml. of *t*-butyl alcohol was added 0.1 ml. of 1*M* potassium *t*-butoxide. This mixture, under nitrogen, was kept at room temperature for 2 hr. Then two drops of glacial acetic acid was added and it was concentrated to near-dryness. Saturated aqueous sodium bicarbonate was added and the resultant suspension extracted with methylene chloride. Drying and concentration of solvent gave 13 mg. of crystalline residue. It was recrystallized from ether to give 8 mg. of analytically pure oxide (VIII), m.p. 176–178°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29, H, 7.97. Found: C, 68.00; H, 8.32. λ_{max}^{Nujol} 3.0–3.3, 6.0 (weak), 8.9–9.4 μ.

B. *Sodium borohydride on* VII. To 25 mg. of chlorohydrin (VII) in 1.0 ml. of 95% ethanol was added 25 mg. of sodium borohydride. The mixture was heated under reflux for 1.5 hr. Work-up was the same as above except for the use of ethyl acetate in the extraction. The residual 29 mg. was recrystallized from ether and methanol to give VIII, m.p. 176–178°, undepressed when mixed with the sample above.

C. *Sodium borohydride on* VI. To 200 mg. of bismethylenedioxy-9α-chlorohydrocortisone (VI) in 10 ml. of 95% ethanol and 10 ml. of methylene chloride was added 200 mg. of sodium borohydride. The methylene chloride was distilled and the ethanol solution stirred under reflux for 20 hr. Using a work-up as in A above, 162 mg. of crude product was obtained. This was recrystallized to give 86 mg. of VIII, m.p. 165–175°. Further recrystallization from methanol and ether–methylene chloride gave a pure sample, m.p. and mixed m.p. with the analytical sample above, 175–178°.

9α-Bromo-17α,20;20,21-Bismethylenedioxy-4-pregnene-11β-ol-3-one (X). Seventy-six grams of 9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione (V)[13] was suspended in 3 l. of chloroform. A mixture of 600 ml. of 36% formaldehyde and and 600 ml. of 42% hydrobromic acid was then added. The reaction mixture was stirred at room temperature for 76 hr. After 4.5 hr. 300 ml. of methylene chloride was added to effect complete solution of the suspension. The layers were separated and the chloroform layer was washed with water and saturated sodium bicarbonate solution, dried over magnesium sulfate and evaporated *in vacuo*. Trituration of the resulting oil with methanol, filtration and methanol washing gave 22 g. of 9α-bromo-17α.20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one, m.p. 170–190°C.

Anal. Calcd. for $C_{23}H_{31}O_6Br$: C, 57.14; H, 6.46. Found: C, 57.35; H, 6.34. λ_{max} 243 mμ, ϵ 15,500.

9α-Bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (XI). Sixteen grams of 9α-bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (X) was dissolved in 160 ml. of glacial acetic acid. To this was added a solution of 16 g. of chromium trioxide in 5 ml. of water and 160 ml. of glacial acetic acid. The reaction mixture was stirred at room temperature for 1.25 hr. After the addition of 3 ml. of methanol, the reaction mixture was cooled and 700 ml. of cold 40% aqueous potassium hydroxide was added slowly with stirring. It was extracted with ethyl acetate three times, washed with a saturated solution of sodium bicarbonate, dried, and evaporated *in vacuo*. The resulting 9.5 g. of crystalline 9α-bromo-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (XI) was collected, m.p. 175–205° dec.

Anal. Calcd. for $C_{23}H_{29}O_6Br$: C, 57.38; H, 6.07. Found: C, 57.48; H, 5.97. λ_{max}^{Nujol} 5.65, 5.90, 6.1, 9.0 μ.

9α-Bromo-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11-one (XII). One gram of 9α-bromo-17α,20;20,-21-bismethylenedioxy-4-pregnene-3,11-dione (XI) was suspended in 150 ml. of benzene to which 10 ml. of ethylene glycol and 100 mg. of *p*-toluenesulfonic acid was added. The reaction mixture was refluxed with a water separator for 5 hr. It was cooled and a saturated solution of sodium bicarbonate was added. It was then separated and extracted further with ether, dried, and evaporated *in vacuo*. Chromatography of the resulting 950 mg. of oil on 20 g. of acid-washed alumina yielded 320 mg. of 9α-bromo-3-ethylenedioxy-17α, 20;20,21-bismethylenedioxy-5-pregnene-11-one (XII) upon elution with petroleum ether–ether (2:3), m.p. 190, 215–220° dec.

Anal. Calcd. for $C_{25}H_{33}O_7Br$: C, 57.14; H, 6.33. Found: C, 57.48; H, 6.04. λ_{max}^{Nujol} 5.85, 9.0 μ.

9α-Methyl-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-pregenene-11-one (XIII). One hundred milligrams of magnesium was suspended in 20 ml. of sodium dried ether. Methyl iodide was added to the stirred suspension until all the magnesium was consumed in the formation of the Grignard complex. An excess of 5 ml. of methyl iodide was then added. To this Grignard reagent was added 15 ml. of tetrahydrofuran (freshly distilled from lithium–aluminum hydride) containing 100 mg. of 9α-bromo-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11-one. The reaction was stirred for 15 min. at room temperature and was then heated under reflux for 1 hr. It was cooled, decomposed carefully with water, extracted well with ethyl acetate, dried over magnesium sulfate and evaporated *in vacuo*. The resulting 100 mg. of oil gave a negative Beilstein test. It was chromatographed on 4 g. of acid-washed alumina and elution with petroleum ether–ether (1:1) gave crystals which were combined and recrystallized from methylene chloride–ether to yield 30 mg. of analytically pure 9α-methyl-3-ethylenedioxy - 17α,20;20,21 - bismethylenedioxy - 5-pregnene-11-one, m.p. 222–228°.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67,85; H, 7.51, $[\alpha]_D^{23} = -85.9 \pm 2°$ (c = 1,$CHCl_3$). NMR analysis indicates three C-methyl groups. λ_{max}^{Nujol} 5.87, 9.0–9.2 μ.

Further elution of the column with petroleum ether–ether (1:4) gave crystals which melted at 195–200° and whose infrared spectrum was identical with 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (cortisone BMD-3-dioxolane).

9α-Methyl-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11β-ol (XIV). Sixty milligrams of 9α-methyl-3-ethylenedioxy - 17α,20;20,21 - bismethylenedioxy - 5-pregnene-11-one (XIII) was dissolved in 20 ml. of tetrahydrofuran. To this solution was added 25 mg. of lithium aluminum hydride. The reaction mixture was stirred for 1 hr. at room temperature and then heated under reflux for 2 hr. It was decomposed by adding ethyl acetate, then water to the reaction mixture and then concentrated to a small volume *in vacuo*. The remaining aqueous solution was extracted with ethyl acetate and the ethyl acetate dried and evaporated *in vacuo*. Chromatography of the residual, 50 mg. of oil, on 4.2 g. of acid-washed alumina gave 24 mg. of 9α-methyl-3-ethylenedioxy-17α,20;20,21-bismethylenedioxy-5-pregnene-11β-ol (XIV) m.p. 230–233°.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.61; H, 7.94. λ_{max}^{Nujol} 2.65, 9.0–9.1 μ.

9α-Methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one-11β-ol (XV). Forty-four milligrams of 9α-methyl-3-ethylenedioxy - 17α,20;20,21 - bismethylenedioxy - 5 - pregnene-11β-ol (XIV) was dissolved in 2 ml. of acetone and 10 mg. of *p*-toluenesulfonic acid added to the solution. It was allowed to stand at room temperature for 2 days. The acetone was then distilled and 3 ml. of a saturated solution of sodium bicarbonate was added. It was extracted with ethyl acetate, dried and evaporated *in vacuo*. Upon trituration of the resulting oil with methanol–methylene chloride, 38 mg. of 9α-methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one-11β-ol (XV) was obtained, m.p. 295–305°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.40; H, 8.15. $\lambda_{max}^{CH_3OH}$ 244 mμ, ϵ 14,800. λ_{max}^{Nujol} 2.7, 5.99, 6.15, 9.0 μ.

9α-Methylhydrocortisone (XVIa). Thirty-four milligrams of 9α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one was suspended in 2 ml. of 50% acetic acid and treated at 100° for 2.5 hr. It was then evaporated *in vacuo* and extracted with ethyl acetate and with methylene chloride, washed with a saturated sodium bicarbonate solution, dried and evaporated. Trituration of the resulting oil with methanol–methylene chloride gave 26 mg. of 9α-methylhydrocortisone (XVIa), m.p. 220–230°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.42; H, 8.73. λ_{max} 244 mμ ε 14,300. λ_{max}^{Nujol} 2.8, 5.80, 6.0, 6.15, 7.2 μ.

9α-Methyl-4-pregnene-3,20-dione-11β,17α,21-triol-21-acetate (XVIb). Two hundred twenty-four milligrams of 9α-methyl-4-pregnene-3,20-dione-11β,17α,21-triol was combined with 1 ml. of pyridine and 1 ml. of acetic anhydride and allowed to stand at room temperature for 18 hr. It was then diluted with water, extracted with methylene chloride and the organic phase washed with 2.5*N* hydrochloric acid, a saturated solution of sodium bicarbonate, dried and evaporated to dryness *in vacuo*. Trituration with acetone afforded crystals which upon recrystallization from acetone-ether yielded 136 mg. of analytically pure 9α-methyl-4-pregnene-3,20-dione-11β,17α,21-triol-21-acetate, m.p. 235–238.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.16; H, 8.15. λ_{max} 243 mμ, ε 16,500. $\lambda_{max}^{CHCl_3}$ 2.9, 5.75, shoulder 5.80, 6.04, 6.26, 8.2 μ.

9α-Methylprednisolone acetate (XVII). Fifty milligrams of 9α-methylhydrocortisone acetate (XVIb) was dissolved in 2.2 ml. of *t*-butyl alcohol. To this solution was added 0.04 ml. of glacial acetic acid, 30 mg. of selenium dioxide, 50 mg. of mercury and 50 mg. of mercuric oxide. This reaction mixture was refluxed with stirring for 3.5 hr. After cooling, the mixture was filtered through Supercel and washed with additional *t*-butyl alcohol. The *t*-butyl alcohol was then concentrated to dryness and the residue dissolved in ethyl acetate. The organic phase was washed with a saturated solution of sodium thiosulfate until no more color was removed and with a 10% sodium bicarbonate solution. After drying over magnesium sulfate and concentrating *in vacuo*, the resulting 40 mg. of oil was chromatographed on acid-washed alumina. Elution of the column with ether-chloroform (1:4) and chloroform yielded 9α-methylprednisolone acetate (XVII), m.p. 228–230°.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.02; H, 7.91. λ_{max}^{Nujol} 2.8, 5.70, 5.79, 6.01, 6.18, 6.25, 8.05 μ. λ_{max} 244 mμ, ε 14,000.

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Rearranged Steroid Systems. I. Studies in the Pregnane Series[1,2]

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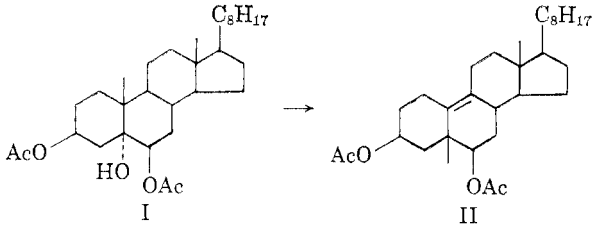
Pregnenolone and prenenolone methyl ether have been converted to 19-nor-5-methyl steroids by the Westphalen rearrangement. An attempt to carry pregnenolone ethylene ketal through a similar series of reactions was unsuccessful. An isomeric substance, obtained in the preparation of pregnenolone methyl ether, was identified as the 17α-epimer.

In 1915, Westphalen[5] obtained a dehydration product from cholestane-3β,5α,6β-triol diacetate (I) by treating this compound with acetic anhydride and sulfuric acid. The product was shown by later workers[6] to have structure II, the C-10 methyl group having migrated to the C-5 position. Spectrographic[7] and chemical[8] evidence are in accord with assigning the 9,10 position to the double bond, while the probable *beta* orientation of the C-5 methyl group is supported by optical rotatory dispersion measurements.[9]



I II

This C-10 to C-5 methyl shift, commonly referred to as the Westphalen rearrangement, has been investigated mainly in the cholestane series[10] and to a lesser extent with androgen derivatives.[11] The current interest in 19-nor steroids as progestational, antiestrogen and cancer agents led us to extend this rearrangement to some

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(4) Postdoctoral Research Associate, 1959–60.

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