ES_1H to A but suffice to establish the point that pK_{app} can be greatly influenced by the bond making and breaking processes within the Michaelis complex (the intracacies of which are, to date, unknown for any enzyme).

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[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

Norsteroids. II. Application of the Favorskii Rearrangement to the Preparation of A-Norpregnanes

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Treatment of 2α-bromoallopregnane-3,20-dione with sodium methoxide in methanol gave, in 35–40% yield, a mixture of 2- and 3-carbomethoxy-A-norallopregnane-20-one. The 20-carbonyl group was converted to the ethylenethioketal group, and then these 2- and 3-carbomethoxy compounds were reduced to the 2- and the 3-methylol A-norallopregnane derivatives. The 2-isomer then was transformed to the 2-methylal compound, which on treatment with phenylmagnesium bromide gave the 2-phenylcarbinol derivative. After removal of the 20-ethylenethioketal blocking group, the carbinol was dehydrated and oxidized to give the known A-norallopregnane-2,20-dione.

In a previous publication[2] the preparation of A-norcholestane derivatives *via* the Favorskii rearrangement of 2α-bromocholestan-3-one was described. Similar results were obtained by Winternitz and de Paulet,[3] and Evans, de Paulet, Shoppee and Winternitz,[4] who also applied the reaction to the coprostane series.

Since the ring contraction step proceeded in high yield (72%), the reaction appeared to be attractive for the preparation of A-norpregnane derivatives. The results with 2α-bromoallopregnane-3,20-dione are reported here.

The most practical route to allopregnane-3,20-dione proved to be hydrogenation of pregnenolone in ethyl acetate with palladium-on-carbon, to give allopregnane-3β-ol-20-one in 87% yield. This compound then was oxidized with chromium trioxide in pyridine[5] to give an 88% yield of allopregnane-3,20-dione.

The dione next was brominated to 2α-bromoallopregnane-3,20-dione (I), as described by Rubin, Wishinsky and Bompard.[6] Although these authors made no assignment of conformation for the bromine, it is now possible to do so on the basis of the position of the infrared absorption band of the adjacent carbonyl group, as predicated by Corey.[7]

As predicted[7] for an A–B *trans*-3-ketone, bromination caused a shift of 19 $cm.^{-1}$ in the 3-keto absorption band (1712 → 1731 $cm.^{-1}$), and accordingly the 2-bromine must be equatorial and therefore α.

The Favorskii rearrangement was carried out by treating the 2α-bromoallopregnane-3,20-dione with sodium methoxide in methanol. By analogy with the same reaction in the cholestane series a mixture of A-noresters and non-rearranged by-products was expected. Accordingly the reaction mixture was saponified, thus making possible the separation of the sodium salts of the A-noracids from the non-acidic products. The nature of the products in the neutral fraction, which was mainly a mixture of hydroxy ketones, will be reported in a separate article.

For ease of handling, and for characterization, the A-noracid mixture was esterified with methanolic hydrogen chloride. The yield of A-noresters IIa and b, based on bromoketone, was 35–40% after purification by chromatography. The overall yield, based on allopregnane-3,20-dione, was increased from 22 to 34–36% if crude bromoketone was used directly in the Favorskii reaction without recrystallization. Repeated chromatography of the mixture, followed by fractional crystallization of the various fractions, did not yield a pure isomer, and the separation was therefore deferred to a later stage.

The most direct method of proving that ring contraction had occurred appeared to be the degradation of the A-noresters *via* the Barbier–Wieland method[8] to the known A-norallopregnane-2,20-dione[9a] (VIa) and A-norpregnane-3,20-dione[9b] (VIb).

Ethane dithiol was superior to ethylene glycol as a blocking group for the 20-ketone function and the mixed ethylenethioketals of the 2- and 3-carbomethoxy-A-norallopregnane-20-ones were obtained in 85% yield.

Treatment of this mixture with phenylmagnesium bromide gave the diphenylcarbinol derivatives IVa,b, which were treated with mercuric chloride, cadmium carbonate and acetone[10] to regenerate the 20-ketone function. Dehydration to the di-

(1) Abstracted from the Ph.D. Thesis of Nicholas Pappas, Brown University, 1957. Du Pont Research Fellow, 1954–1955; Brown University Fellow, 1955–1956.

(2) B. B. Smith and H. R. Nace, THIS JOURNAL, **76**, 6119 (1954).

(3) F. Winternitz and A. C. de Paulet, *Bull. soc. chim.*, 288 (1954).

(4) (a) D. E. Evans, A. C. de Paulet, C. W. Shoppee and F. Winternitz, *Chemistry & Industry*, 355 (1955); (b) *J. Chem. Soc.*, 1451 (1957).

(5) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

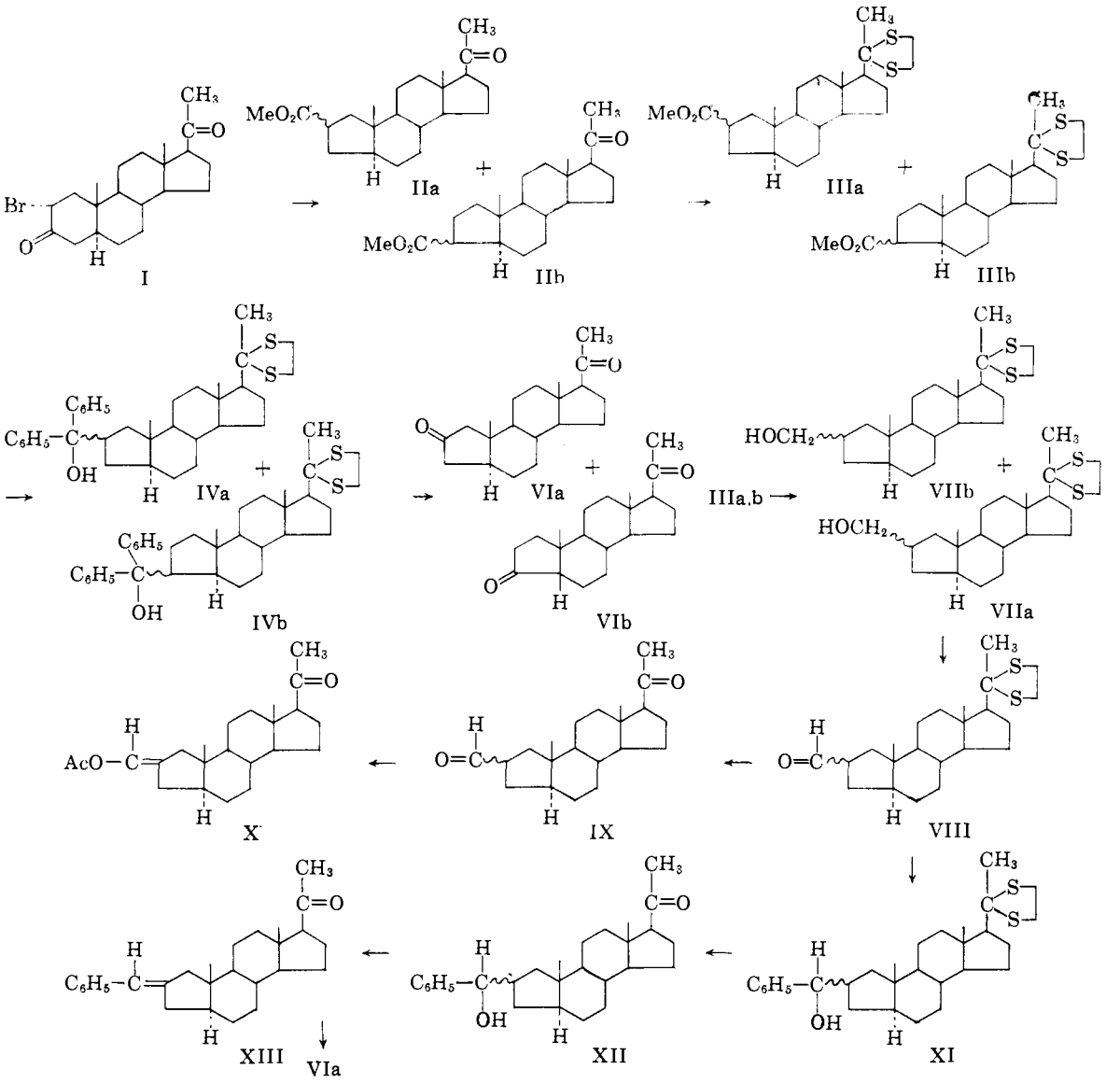
(6) M. Rubin, H. Wishinsky and F. Bompard, *ibid.*, **73**, 2338 (1951).

(7) E. J. Corey, *ibid.*, **76**, 175 (1954).

(8) P. Barbier and R. Locquin, *Compt. rend.*, **156**, 1443 (1913); H. Wieland, O. Schlichting and R. Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926).

(9) (a) R. E. Marker, O. Kamm and D. M. Jones, THIS JOURNAL, **59**, 1595 (1937); (b) A. Butenandt, F. Hildebrandt and H. Bruchet, *Ber.*, **64**, 2529 (1931).

(10) D. J. Cram and M. Cordon, THIS JOURNAL, **77**, 1810 (1955); M. L. Wolfrom, *ibid.*, **51**, 2188 (1929).



phenylethylene derivatives Va and b was effected with hydrogen chloride, and ozonization then yielded what appeared to be a mixture of A-norallopregnane-2,20-dione (VIa) and A-norpregnane-3,20-dione (VIb). This mixture resisted all attempts at separation as did all of the intermediate compounds. The diphenylethylene derivatives also proved to be as resistant to oxidation with potassium permanganate or chromic oxide as were the corresponding derivatives in the cholestane series.[2]

A different approach to the proof of structure involved the reduction of the mixture of the ethylene thioketals of 2- and 3-carbomethoxy-A-norallopregnane-20-one (IIIa,b) with lithium aluminum hydride to give a mixture of 2- and 3-methylol-A-norallopregnane-20-one ethylenethioketals (VIIa,b) in quantitative yield. Chromatography and subsequent recrystallization afforded the 2-methylol isomer VIIa in 51% yield. Careful fractionation of this material by chromatography and crystallization indicated that it was a single pure isomer, and the conversion, as described below, to the known A-norallopregnane-2,20-dione established the structure.

It was not possible to obtain the 3-isomer free from the 2-isomer, and therefore no data on the ratio of isomers present could be obtained. Although some 17-iso-compound probably was formed during the Favorskii reaction, it should have been isomerized back to the 17-normal epimer during the acid-catalyzed esterification,[11] and no iso-compounds could be isolated.

Although no effort was made to determine the configuration of the 2-methylol group, it should have the α-configuration if the hypothesis of Shoppee, *et al.*,[4b] is correct.

In attempts to convert the methylol compound VIIa to the 2-methylene derivative, the cathylate and N-phenylcarbamate derivatives were prepared and pyrolyzed. Only starting material was recovered and the same result was obtained when the methylol compound was heated with boric

(11) L. F. Fieser and Huang-Minlon, THIS JOURNAL, **71**, 1840 (1949); G. I. Fujimoto and J. Prager, *ibid.*, **75**, 3259 (1953).

acid.[12] Similar results were obtained with the 2-methylol derivative in the A-norcholestane series, and the behavior of these compounds must be considered as abnormal, since several esters of hydroxymethylcyclopentane appear to behave normally on pyrolysis.[13]

Examination of Barton models of these compounds showed that the carbonyl oxygen of the ester readily can approach the C-2 hydrogen, and formation of the cyclic intermediate necessary for elimination should involve no difficulty. A model of the 2-methylene compound showed, however, that considerable strain and rigidity is introduced in the A-nor- and the B-ring when an *exo*-double bond is present at the 2-position in the A–B *trans* compound. Although no estimate of the strain involved can be made, enough could be present in the transition state to prevent the elimination reaction from taking place readily. No such strain is apparent when the cyclopentane ring is not fused to a cyclohexane ring.

Conversion of the 2-methylol compound VIIa to 2-methylal-A-norallopregnane-20-ethylenethioketal (VIII) was accomplished in 68% yield by using a modification of the pyridine–chromic oxide method,[5] and the ethylenethioketal blocking group was removed with the mercuric chloride–cadmium carbonate–acetone reagent.[10] The 2-methylal-A-norallopregnane-20-one (IX) was somewhat unstable, could not be obtained crystalline and was characterized by its infrared spectrum. It had been shown previously[14] that other carbonyl functions in a steroid molecule could be converted to the enol acetate, without affecting the 20-keto moiety, by using isopropenyl acetate in benzene solution. Application of this procedure to the keto-aldehyde resulted in the formation of the oily, highly unstable enol acetate, whose infrared spectrum indicated that the 20-ketone function was intact, and that the 2-methylal group had disappeared.

The enol acetate was ozonized and A-norallopregnane-2,20-dione (VIa) was obtained in 28% yield, thus establishing that ring contraction had taken place in the Favorskii reaction, and that the isomer in hand was derived from the 2-carbomethoxy compound IIa.

A more satisfactory route to the A-norallopregnane-2,20-dione (VIa) was the application of the Barbier–Wieland method to the ethylenethioketal of 2-methylal-A-norallopregnane-20-one (VIII). The aldehyde was treated with phenylmagnesium bromide to produce the monophenylcarbinol derivative XI. The ethylenethioketal group was removed as above, and the hydroxy ketone XII was dehydrated with *p*-toluenesulfonic acid in benzene[15] to produce the monophenylethylene derivative XIII. The potassium permanganate–periodic acid reagent[16] cleaved the double bond and A-norallopregnane-2,20-dione (VIa) was obtained in 14% over-all yield based on 2-methylal-A-norallopregnane-20-ethylenethioketal.

Although the Favorskii reaction does not proceed as well (lower yield, isomers more difficult to separate) in the allopregnane series as in the cholestane series, it still offers an attractive route to A-norallopregnane derivatives, since the carbomethoxy group can be transformed to a wide variety of functional groups. Some of these derivatives may be of physiological interest.

Experimental[17]

Allopregnane-3β-ol-20-one.—A solution of 2.23 g. (7.08 millimoles) of pregnenolone[19] in 200 ml. of ethanol was added to a suspension of 0.5 g. of palladium-on-carbon in 25 ml. of ethanol, and the mixture was stirred with hydrogen until 7.45 millimoles was taken up. After removal of the catalyst and evaporation of the solvent the residue was recrystallized from acetone to yield 1.95 g. (87%) of allopregnane-3β-ol-20-one, m.p. 192–194°, $[\alpha]_D$ +82°; reported[20] m.p. 194°, $[\alpha]_D$ +91° (EtOH).

Allopregnane-3,20-dione.—A solution of 1.95 g. (6.14 millimoles) of allopregnane-3β-ol-20-one in 150 ml. of pyridine was added to a solution of 2.0 g. of chromic oxide in 50 ml. of pyridine and the resulting solution was stirred overnight. Then 100 ml. of ether was added, the resulting slurry was filtered, the solid was washed with ether, and the washings were added to the filtrate. The ether–pyridine solution then was washed successively with 1 *N* hydrochloric acid, water, and saturated brine, and filtered through anhydrous sodium sulfate. After evaporation of the ether the residue was recrystallized from acetone–methanol–water to give 1.56 g. of allopregnane-3,20-dione, m.p. 200–201°, $[\alpha]_D$ +121°, λ_{max} 1712 cm.$^{-1}$; reported[21] m.p. 199–200.5°, $[\alpha]_D$ +127° (EtOH). Chromatography of the mother liquor gave an additional 0.15 g., m.p. 196–199°, total yield 88%. Essentially the same yield was obtained if the crude allopregnane-3β-ol-20-one was oxidized directly without recrystallization.

2α-Bromoallopregnane-3,20-dione (I) was prepared according to the procedure of Rubin, Wishinsky and Bompard,[6] and had m.p. 199–202°, λ_{max} 1705, 1731 cm.$^{-1}$; reported[6] m.p. 198–200°.

Favorskii Rearrangement of 2α-Bromoallopregnane-3,20-dione.—To a solution of sodium methoxide prepared by adding 7.0 g. (0.304 gram atom) of sodium to 250 ml. of absolute methanol was added 4.3 g. (10.9 millimoles) of 2α-bromoallopregnane-3,20-dione. This solution was boiled under reflux for 8 hours, allowed to stand overnight at room temperature, and then diluted with a solution of 3.0 g. of potassium hydroxide in 50 ml. of water. This solution was boiled under reflux for 4 hours, allowed to stand overnight at room temperature, and then concentrated under reduced pressure to a volume of 25 ml. Water (100 ml.) was added and the mixture was extracted with 400 ml. of ether. The ether layer was washed with five 50-ml. portions

(12) G. L. O'Connor and H. R. Nace, THIS JOURNAL, **77**, 1578 (1955).

(13) W. J. Bailey and W. F. Hale, *ibid.*, **81**, 647 (1959).

(14) C. Djerassi, O. Mancera, M. Velasco, G. Stork and G. Rosenkranz, *ibid.*, **74**, 3321 (1952).

(15) Attempts to dehydrate this compound with acetic anhydride and acetic acid (a smooth reaction with the diphenylcarbinol in the A-norcholestane series) yielded only the acetate, again illustrating the reluctance of this type of compound to undergo elimination.

(16) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710, 1714 (1955).

(17) All melting points are corrected. Analyses by Dr. S. M. Nagy and associates, Microchemical Laboratory, the Massachusetts Institute of Technology. The samples were recrystallized until the melting points were constant. The optical rotations were determined at room temperature in approximately 1% chloroform solutions. Merck and Co., Inc., alumina (suitable for chromatographic absorption) was used for chromatography. The infrared spectra were taken with a modified Perkin-Elmer model 1213 spectrometer, described elsewhere.[18] Unless otherwise stated, spectra were determined with 2% carbon tetrachloride solutions with a cell thickness of 1 mm., sodium chloride windows, and a sodium chloride prism.

(18) D. F. Hornig, G. E. Hyde and W. A. Adcock, *J. Opt. Soc. Amer.*, **40**, 497 (1950).

(19) The authors acknowledge with thanks generous gifts of pregnenolone from the Upjohn Co.

(20) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corporation, New York, N. Y., 1949, p. 498.

(21) A. Butenandt and G. Fleischer, *Ber.*, **68**, 2094 (1935).

of 5% potassium hydroxide solution and the washings and original basic aqueous layer were combined, acidified with concentrated hydrochloric acid, and extracted with ether. The ether extract was washed with water and saturated brine, and filtered through anhydrous sodium sulfate. Evaporation of the ether left 2.44 g. of mixed A-nor acids, $[\alpha]_D$ +57°, λ_{max} 2827–2020, 1708 cm.$^{-1}$.

The crude acids were esterified by dissolving them in 250 ml. of 2% methanolic hydrogen chloride and allowing the solution to stand at room temperature for 48 hours. The solution was then concentrated under reduced pressure to 30 ml., diluted with 100 ml. of water, and extracted twice with ether. The ether extract was washed with water and saturated brine, filtered through anhydrous sodium sulfate, and the ether was evaporated. The mixture of 2- and 3-carbomethoxy-A-norallopregnane-20-one (IIa, b) (2.35 g.) was taken up in 1:3 benzene–petroleum ether and chromatographed on 35 g. of alumina. The esters (1.45 g., 38% based on bromoketone[22]) were eluted with 1:1 benzene–petroleum ether. The specific rotations of successive fractions of the eluate varied from +39.5° for early fractions to +55° for middle fractions to +42° for the last fractions. The infrared spectra of these fractions were essentially the same, and had λ_{max} 1742, 1722 cm.$^{-1}$. Fractional crystallization of the various fractions did not result in the separation of a pure isomer. The combined fractions had m.p. 105–108° (with previous softening), $[\alpha]_D$ +95°, λ_{max} 1742, 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.28; H, 10.16.

Preparation of the 20-Ethylenethioketals of the 2- and the 3-Carbomethoxy-A-norallopregnane-20-ones (IIIa,b).—A solution of 1.45 g. (4.18 millimoles) of 2- and 3-carbomethoxy-A-norallopregnane-20-one in 1.5 ml. of ethanedithiol and 1.5 ml. of boron trifluoride etherate was allowed to stand at room temperature for 10 minutes. After the addition of 20 ml. of chloroform, the solution was allowed to stand overnight at room temperature. Then an additional 200 ml. of chloroform was added, the solution was washed with water and saturated brine, and filtered through anhydrous sodium sulfate and then alumina. After evaporation of the chloroform the residue was recrystallized from acetone–methanol–water to yield 1.50 g. (85%) of the 20-ethylenethioketals IIIa,b, m.p. 103–108° (with previous softening). An analytical sample had m.p. 105.5–107°, $[\alpha]_D$ +1°, λ_{max} 1742 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{38}O_2S_2$: C, 68.20; H, 9.06. Found: C, 67.88; H, 9.06.

2-Methylol-A-norallopregnane-20-ethylenethioketal (VIIa) and 3-Methylol-A-norallopregnane-20-ethylenethioketal (VIIb).—A mixture of the 2- and 3-carbomethoxy-A-norallopregnane-20-ethylenethioketals (1.84 g., 4.35 millimoles), 2.0 g. of lithium aluminum hydride, and 125 ml. of anhydrous ether was stirred overnight and then the excess lithium aluminum hydride was decomposed by the addition of water. The ether layer was saved, the water layer was extracted twice with ether, and the combined ether extract was washed successively with 1 *N* hydrochloric acid, water, and saturated brine, and filtered through anhydrous sodium sulfate. After evaporation of the ether the residue was dissolved in petroleum ether and chromatographed on 30 g. of alumina. Elution with 5:1 benzene–ether gave 1.8 g. of a mixture of 2- and 3-methylol-A-norallopregnane-20-ethylenethioketal (VIIa,b); λ_{max} 3620 cm.$^{-1}$, no absorption in the carbonyl region.

Two recrystallizations from ethanol–water gave 0.88 g. (51%) of the 2-methylol isomer VIIa, m.p. 148–150°, $[\alpha]_D$ +5.4°.

Anal. Calcd. for $C_{23}H_{38}OS_2$: C, 69.99; H, 9.70. Found: C, 69.87; H, 9.84.

A 35-mg. sample was further recrystallized from ethanol–water and ethanol to give 20 mg., m.p. 150–151°, $[\alpha]_D$ +5.3°, indicating that the sample was essentially free of other isomers.

The mother liquors gave 0.73 g. (42%) of an oil, $[\alpha]_D$ −8.3°, which could not be crystallized, and which presumably consisted of the 3-methylol isomer VIIb contaminated with the 2-methylol isomer VIIa.

Ethyl Carbonate Ester of 2-Methylol-A-norallopregnane-20-ethylenethioketal.—A solution of 0.070 g. (0.177 millimole) of 2-methylol-A-norallopregnane-20-ethylenethioketal (VIIa) and 0.10 ml. of ethylchlorocarbonate in 10 ml. of pyridine was allowed to stand at room temperature for two hours, and then was added to 10 ml. of glacial acetic acid and 50 ml. of water. The precipitate was collected, dried, and recrystallized from acetone–water to yield 0.060 g. (72%) of the ethyl carbonate ester, m.p. 40–41°, $[\alpha]_D$ +6°, λ_{max} 1747 cm.$^{-1}$. The analytical sample had m.p. 44–46°, $[\alpha]_D$ +6.3°.

Anal. Calcd. for $C_{26}H_{42}O_3S_2$: C, 66.90; H, 9.07. Found: C, 67.05; H, 9.26.

An 0.056-g. sample was heated at 270–280° (20 mm.) for 2.5 hours. The infrared spectrum of the product was identical with that of the starting material, indicating that no decomposition had occurred.

N-Phenylcarbamate of 2-Methylol-A-norallopregnane-20-ethylenethioketal.—A solution of 0.17 g. (0.43 millimole) of the 2-methylol-A-norallopregnane-20-ethylenethioketal (VIIa) and 0.5 ml. of phenyl isocyanate in carbon tetrachloride was boiled under reflux for 5 hours. The solvent then was evaporated and the residue recrystallized from ethanol to yield 0.17 g. (77%) of the N-phenylcarbamate derivative, m.p. 175–179°; λ_{max} 3386, 1735, 1597 and 1519 cm.$^{-1}$.

An 0.17-g. sample was heated at 250–260° (20 mm.) for 3 hours, and the residue chromatographed on 4 g. of alumina. An 0.158-g. fraction was eluted with 1:3 benzene–petroleum ether, and appeared to be a mixture of the carbamate and the 2-methylol compound, presumably formed by hydrolysis on the alumina. No olefinic material could be detected.

Attempted Boric Acid Dehydration of 2-Methylol-A-norallopregnane-20-ethylenethioketal (VIIa).—A mixture of 0.20 g. of the 2-methylol compound VIIa and 0.03 g. of boric acid was heated at 280–300° for 3 hours. The residue was extracted with ether, the ether extract was washed successively with 5% sodium bicarbonate solution, water, and saturated brine, filtered through anhydrous sodium sulfate, and then the ether was evaporated. The residue was recrystallized from ethanol–water to give 0.17 g. of unreacted methylol VIIa, m.p. 146–148°. λ_{max} 3620 cm.$^{-1}$.

2-Methylal-A-norallopregnane-20-ethylenethioketal (VIII).—A solution of 0.880 g. (2.23 millimoles) of 2-methylol-A-norallopregnane-20-ethylenethioketal (VIIa) in 45 ml. of pyridine was added to a slurry of 1.1 g. of chromic oxide in 25 ml. of pyridine, and the resulting mixture was stirred for 3.5 hours. Then 50 ml. of ether was added, the mixture was filtered, the solid was washed well with ether, and the combined filtrate and washings was washed with water. The water layer was extracted twice with ether, and the extracts were combined with the ether–pyridine solution and washed successively with water, 1 *N* hydrochloric acid, water, 5% potassium hydroxide solution, water, and saturated brine, and finally filtered through anhydrous sodium sulfate. After evaporation of the ether, the residue was recrystallized from acetone–water to give 0.595 g. (68%) of 2-methylal-A-norallopregnane-20-ethylenethioketal (VIII), m.p. 142–144°, $[\alpha]_D$ +12.4°, λ_{max} 2788, 1731 cm.$^{-1}$. The analytical sample had m.p. 147.5–148.5°, $[\alpha]_D$ +12.4°.

Anal. Calcd. for $C_{23}H_{36}OS_2$: C, 70.35; H, 9.24. Found: C, 70.12; H, 9.28.

2-Methylal-A-norallopregnane-20-one (IX).—To a solution of 0.250 g. (0.636 millimole) of 2-methylal-A-norallopregnane-20-ethylenethioketal (VIII) in 20 ml. of acetone was added 1 ml. of water, 0.25 g. of mercuric chloride and 0.25 g. of cadmium carbonate. This mixture was stirred for 25 hours and then an additional 0.1 g. of mercuric chloride and 0.1 g. of cadmium carbonate was added, and the stirring was resumed. This procedure was continued for 72 hours, and then the mixture was filtered and the acetone was evaporated from the filtrate. The residue was taken up in ether and the ether solution was washed successively with water, two 50-ml. portions of 10% potassium iodide solution, water, and saturated brine, and then filtered through anhydrous sodium sulfate. On evaporation of the ether, 0.188 g. (93%) of non-crystalline 2-methylal-A-norallopregnane-20-one (IX) was obtained, λ_{max} 2788 and 1731 cm.$^{-1}$. This compound was not characterized but used directly as described below.

(22) If allopregnane-3,20-dione is brominated, and the crude 2α-bromoallopregnane-3,20-dione used directly, without recrystallization, for the Favorskii rearrangement, the over-all yield of mixed 2- and 3-carbomethoxy-A-norallopregnane-20-ones, after chromatography, is increased from 22 to 34–36%, based on allopregnane-3,20-dione.

Enol Acetate X of 2-Methylal-A-norallopregnane-20-one.—An 0.188-g. sample of keto-aldehyde IX obtained as described above was dissolved in 25 ml. of benzene and 0.02 g. of *p*-toluenesulfonic acid and 1 ml. of isopropenyl acetate were added. The resulting solution then was concentrated over a period of 8 hours by slow distillation of the benzene through a short Vigreux column. Every two hours an additional 0.5 ml. of isopropenyl acetate was added. Finally the remaining solvent was removed under reduced pressure, the residue was taken up in ether containing 1 ml. of pyridine, and the ether solution was washed successively with water, 5% sodium bicarbonate solution, water, and saturated brine, and then filtered through anhydrous sodium sulfate. Evaporation of the ether gave 0.20 g. of an oil which appeared to be the enol acetate X, λ_{max} 1757 and 1712 cm.$^{-1}$. Due to its instability it was used directly as described below.

Ozonolysis of the Enol Acetate X of 2-Methylal-A-norallopregnane-20-one.—A solution of 0.20 g. (0.56 millimole) of the enol acetate X in 75 ml. of chloroform was cooled in an ice-bath and a stream of ozone[23] was passed through at a rate such that 2.5 molar equivalents were added in 15 minutes. Then 5 g. of powdered zinc and 30 ml. of acetic acid were added and the mixture was allowed to stand overnight. The solution then was washed successively with water, 5% sodium carbonate solution, water, and saturated brine, filtered through anhydrous sodium sulfate, and the solvent evaporated. The residue (0.12 g.) was taken up in petroleum ether and chromatographed on 4 g. of alumina. Elution with 1:1 benzene–petroleum ether gave 0.047 g. (28%) of crystalline A-norallopregnane-2,20-dione (VIa), λ_{max} 1741 and 1710 cm.$^{-1}$. Recrystallization from ethanol–water gave 6 mg., m.p. 171–175°, reported[9a] m.p. 180°.

Monophenylethylene Derivative XIII of 2-Methylal-A-norallopregnane-20-one.—To a solution of phenylmagnesium bromide, prepared from 0.369 g. of magnesium, 1.59 ml. of bromobenzene, a trace of calcium hydride and 105 ml. of anhydrous ether, was added 0.60 g. (1.53 millimoles) of 2-methylal-A-norallopregnane-20-ethylenethioketal (VIII) in 50 ml. of anhydrous ether. The resulting solution was heated under reflux for 3 hours, allowed to stand overnight at room temperature, and then poured into an iced dilute hydrochloric acid solution. The ether layer was removed, the aqueous layer was extracted once with benzene, and the combined ether–benzene extract was subjected to steam distillation to remove bromobenzene and biphenyl. The residue was taken up in ether, washed with saturated brine, filtered through anhydrous sodium sulfate, and the ether evaporated to give 0.8 g. of oily monophenylcarbinol derivative XI of 2-methylal-A-norallopregnane-20-ethylenethioketal; λ_{max} 3620, 1603, and 1487 cm.$^{-1}$.

This sample was dissolved in 50 ml. of acetone, 1 ml. of water, 0.8 g. of mercuric chloride and 0.8 g. of cadmium carbonate were added, and the mixture was stirred for 4 days, with the addition of 0.2 g. of mercuric chloride and 0.2 g. of cadmium carbonate after each day. Then the mixture was filtered, the filtrate was evaporated, the residue was taken up in ether, and the extract washed successively with water, two 50-ml. portions of 10% potassium iodide solution, water, and saturated brine, and then filtered through anhydrous sodium sulfate. After evaporation of the ether, 0.6 g. of the oily monophenylcarbinol derivative XII of A-norallopregnane-20-one, contaminated with some unreacted ethylenethioketal XI, was obtained; λ_{max} 3620, 1712, 1605 and 1485 cm.$^{-1}$.

A solution of 0.6 g. of the crude monophenylcarbinol derivative XII and 0.15 g. of *p*-toluenesulfonic acid in 50 ml. of benzene was heated under reflux with a constant water separator for 1 hour. The solution then was washed successively with water, 5% sodium bicarbonate solution, water, and saturated brine, filtered through anhydrous sodium sulfate, and finally the benzene was evaporated. The residue (0.55 g.) was taken up in petroleum ether and chromatographed on 10 g. of alumina. With 2:1 petroleum ether–benzene, 0.4 g. of crude 2-monophenylethylene derivative XIII of A-norallopregnane-20-one was eluted; λ_{max} 1713, 1659, 1596, and 1492 cm.$^{-1}$. This material could not be crystallized and was used directly for the oxidation described below.

A-Norallopregnane-2,20-dione (VIa).—To a solution of 0.4 g. of crude 2-monophenylethylene XIII in 35 ml. of acetone were added solutions of 0.158 g. of potassium permanganate in 4 ml. of water, 0.3 g. of potassium carbonate in 2 ml. of water and 0.18 g. of periodic acid in 2 ml. of water. The resulting solution was stirred 24 hours, filtered to remove manganese dioxide, the acetone was evaporated, and the residue was taken up in petroleum ether and chromatographed on 6 g. of alumina. With 1:1 benzene–petroleum ether, 0.066 g. (14.3% yield based on 2-methylal-A-norallopregnane-20-ethylenethioketal) of crude A-norallopregnane-2,20-dione (VIa) was eluted, λ_{max} 1741, 1712 cm.$^{-1}$. Two recrystallizations from ethanol–water gave 0.025 g., m.p. 174–178°, $[\alpha]D$ + 134°, λ_{max} 1740, 1712 cm.$^{-1}$; reported[9a] m.p. 180°.

The bis-2,4-dinitrophenylhydrazone was prepared by the procedure of Reich, Crane and Sanfilippo[24] and had m.p. 261–263° dec.

Anal. Calcd. for $C_{32}H_{38}O_8N_8$: C, 57.99; H, 5.78; N, 16.91. Found: C, 57.16; H, 5.54; N, 17.17.

Preparation of the Mixture of the 2- and the 3-Diphenylcarbinol Derivatives (IVa,b) of A-Norallopregnane-20-ethylenethioketal.—To a solution of phenylmagnesium bromide prepared from 0.836 g. of magnesium and 3.59 ml. of bromobenzene in 105 ml. of ether was added 1.45 g. (3.43 millimoles) of a mixture of 2- and 3-carbomethoxy-A-norallopregnane-20-ethylenethioketal in 100 ml. of ether. The resulting solution was heated under reflux for 3 hours, allowed to stand overnight, and then poured into an iced dilute hydrochloric acid solution. The ether layer was removed, the water layer was extracted with benzene, and the ether and benzene extracts were combined and steam distilled to remove bromobenzene and biphenyl. An ether solution of the residue was washed with saturated brine, filtered through anhydrous sodium sulfate, and the ether then evaporated to give 1.9 g. of a mixture of the 2- and the 3-diphenylcarbinols of A-norallopregnane-20-ethylenethioketal; λ_{max} 3620, 1605 and 1488 cm.$^{-1}$.

Preparation of the Mixture of the 2- and the 3-Diphenylcarbinols of A-Norallopregnane-20-one.—The 1.9-g. sample described above was dissolved in 50 ml. of acetone and added to a mixture of 2.0 g. of mercuric chloride, 2.0 g. of cadmium carbonate, 50 ml. of acetone and 5 ml. of water. After the mixture had been stirred for 24 hours 0.5 g. of mercuric chloride and 0.5 g. of cadmium carbonate were added, and this stirring and addition was repeated two more times.

The mixture then was filtered, the acetone evaporated from the filtrate, and the residue taken up in ether. The ether solution next was washed successively with water, two 50-ml. portions of 10% potassium iodide solution, water, and saturated brine, then filtered through anhydrous sodium sulfate, and the ether removed to leave 1.53 g. of a mixture of the 2- and the 3-diphenylcarbinols of A-norallopregnane-20-one, λ_{max} 3620 and 1717 cm.$^{-1}$.

Preparation of the 2- and the 3-Diphenylethylene Derivatives (Va,b) of A-Norallopregnane-20-one.—The mixture described above was dissolved in 100 ml. of benzene, which had previously been saturated with hydrogen chloride. After the solution had stood at room temperature for two hours, it was washed with water and saturated brine, then filtered through anhydrous sodium sulfate, and the benzene removed to yield 1.4 g. of the crude mixed diphenylethylene derivatives.

The mixture was taken up in 30 ml. of 1:9 benzene–petroleum ether, and this solution was chromatographed on 40 g. of alumina. When the column was eluted with 3:1 petroleum ether–benzene, 0.841 g. (54.2%) of the amorphous mixed diphenylethylenes was obtained; λ_{max} 1714, 1606 and 1470 cm.$^{-1}$.

Ozonolysis of the Mixed 2- and 3-Diphenylethylenes of A-Norallopregnane-20-one.—A solution of 0.35 g. of the above mixture in 150 ml. of chloroform was cooled in an ice-bath and 2.5 molar equivalents of ozone was passed through in 20 minutes. Then 5 g. of zinc and 30 ml. of acetic acid were added, and the mixture was allowed to stand overnight. After filtration and successive washing with water, 5% sodium carbonate solution, water, and saturated brine, the solution was dried over anhydrous sodium sulfate, and then the solvent was removed. The 0.34-g. residue was taken up in petroleum ether and chromatographed on 7 g. of alumina. With 3:2 benzene–petroleum ether, 0.105 g. of material was eluted, which appeared to be a mixture of

(23) The authors are grateful to Arnold Hoffman and Co. and Dr. John Conbere for the use of their ozonization apparatus.

(24) A. Reich, K. F. Crane and S. J. Sanfilippo, *J. Org. Chem.*, **18**, 822 (1953).

A-norallopregnane-2,20-dione and A-norpregnane-3,20-dione, as evidenced by the infrared spectrum, λ_{max} 1742 and 1714 cm.$^{-1}$.

When this material was chromatographed on 3 g. of alumina, 3 fractions were eluted with 1:1 benzene–petroleum ether, as follows: (1) 50 ml. eluted 0.0215 g. which gave 0.011 g., m.p. 152–159°, after crystallization from ethanol–water; (2) 200 ml. eluted 0.0148 g. which could not be obtained crystalline; and (3) 200 ml. eluted 0.0189 g. which gave 0.0060 g., m.p. 161–167°, after recrystallization from ethanol–water (reported for the 2,20-diketone,[9a] m.p. 180°, and for the 3,20-diketone,[9b] m.p. 144–146°).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY, AND THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

D-Homosteroids. I. 3β-Hydroxy-17a,17a-dimethyl-D-homoandrostane-17-one and Related Compounds[1]

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Treatment of 3β,17α-dihydroxypregn-5-en-20-one 3β-acetate with methylmagnesium iodide gave bisnorchol-5-ene-3β,17α,20-triol, the structure of which was ascertained by its oxidation with sodium bismuthate to dehydroepiandrosterone. Bisnorcholane-17α,20-diols rearrange under acidic conditions and give 17a,17a-dimethyl-D-homoandrostane-17-one derivatives; arguments in support of that structure are presented.

Many publications[2–7] dealing with the synthesis and the biological activities of 17a-monomethyl-D-homosteroids have appeared in previous years; we now wish to report our work on the synthesis of some 17a,17a-dimethyl-D-homoandrostanes, obtained by the rearrangement of bisnorcholane-17α,20-diol derivatives with acid.

These bisnorcholane-17α,20-diols were obtained by the Grignard reaction on the corresponding 17α-hydroxy-20-keto-pregnanes. Thus, 3β,17α-dihydroxypregn-5-en-20-one 3β-acetate (VIII) was treated with methylmagnesium bromide and the resulting bisnorchol-5-en-3β,17α-20-triol (IXa) was obtained in 75% yield. The structure of IXa was ascertained by its elemental analysis, by the absence of a ketonic band in its infrared spectrum, and finally by obtaining dehydroepiandrosterone (X) as the only reaction product from its oxidation with sodium bismuthate. The acetylation of the triol IXa with acetic anhydride and pyridine gave bisnorchol-5-ene-3β,17α,20-triol 3β-acetate (IXb) which was reduced catalytically to bisnorallocholane-3β,17α,20-triol 3β-acetate (Vb) in quantitative yield; Vb also was obtained from 3β,17α-dihydroxyallopregnane-20-one 3β-acetate (IV) by treating it first with methylmagnesium iodide followed by reactylation of the thus produced triol Va. The 17α,20-dihydroxybisnorchol-4-en-3-one (XI) was obtained from 17α-hydroxyprogesterone (XVIII). Partial etherification of XVIII was accomplished with one mole of triethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid. The usual procedure, using hydrochloric acid as catalyst, failed in this case for unknown reasons. The quantitatively produced 17α-hydroxyprogesterone 3-ethyl enol ether (XIX) showed the characteristic infrared absorption bands at 1650 and 1625 cm.$^{-1}$ for a conjugated diene and showed ether bands at 1230 and 1178 cm.$^{-1}$. The enol ether XIX was treated with a 10 molar excess of methylmagnesium iodide and the resulting mixture was separated chromatographically into 17α,20-dihydroxybisnorchola-3,5-diene 3-ethyl ether (XV) and XI. These products were characterized by elemental analysis, infrared absorption spectra and by a positive periodic acid test.

The Oppenauer oxidation of bisnorchol-5-ene-3β-17α,20-triol (IXa) did not give the expected XI. Although the product appeared to be pure judging from its sharp melting point and from its single ultraviolet maximum at 242 mμ, it was definitely different from XI as could be seen in the infrared absorption spectrum. Its periodic acid test was positive, but it did not undergo the rearrangement as did XI which will be discussed below. It seems probable that we deal here with a rearrangement of the glycolic side chain under Oppenauer conditions and attempts to elucidate the structure of this product are being continued.

The rearrangement of the glycols was studied under the following conditions: (1) either in refluxing glacial acetic acid containing catalytic amounts of elemental iodine or *p*-toluenesulfonic acid or (2) in 98% formic acid at 100°.

The main product was in every case the 17a,17a-dimethyl-17-keto-D-homosteroid, though the yields varied from 30% (elemental iodine) to 86% (formic acid). The rearrangement[8] proceeds very likely by the dissociation of the 20-hydroxyl group,[9]

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(2) W. A. Yarnall and E. S. Wallis, THIS JOURNAL, **59**, 951 (1937).

(3) K. Miescher and H. Kägi, *Chem. Ind.*, **57**, 276 (1938).

(4) K. Miescher and H. Kägi, *Helv. Chim. Acta*, **22**, 184 (1939).

(5) L. Ruzicka and H. F. Meldahl, *ibid.*, **23**, 364 (1940).

(6) F. Ramirez and S. Stafiej, THIS JOURNAL, **77**, 134 (1955).

(7) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

(8) Compare A. Serini, W. Logemann and W. Hildebrand, *Ber.*, **72B**, 391 (1939); H. L. Herzog, C. C. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg and D. H. R. Barton, *J. Org. Chem.*, **22**, 1413 (1957); D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, **226**, 725 (1957).

(9) Compare these results with the rearrangement of pregn-5-ene-3β,17α,20β-triol, pregn-5-ene-3β,17α,20β-triol 3β-acetate and 17α,20β-dihydroxypregn-4-en-3-one with acetic acid and a catalytic amount of elemental iodine (unpublished results), whereby in all three cases the 17β-acetyl product was obtained.[10] These results indicate that 17α,20β-dihydroxypregnane derivatives rearrange through initial formation of a 17-carbonium ion, while the 17α,20β-dihydroxybisnorcholane derivatives favor a 20-carbonium ion, due to its stabilization by the inductive effects of an additional methyl group.

(10) Compare D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, **226**, 725 (1957).