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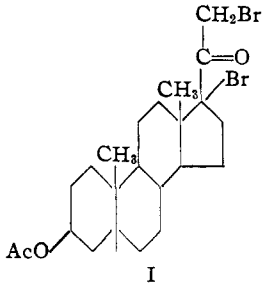
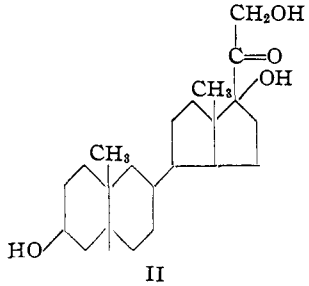
A New Synthetic Route to the Cortical Side Chain[1]

BY R. B. WAGNER AND JAMES A. MOORE

In the course of studies of steroidal bromoketones it has been found[2] that the 17-bromo- and 17,21-dibromopregnanolones, readily available from sapogenins, are subject to rearrangement reactions, even under mild hydrolytic conditions, and do not yield the highly desired compounds of the cortical series by direct metathesis. Thus 17,21-dibromopregnan-3β-ol-20-one acetate (I) when treated with alcoholic potassium hydroxide or aqueous methanolic potassium bicarbonate does not yield the 17,21-dihydroxy ketone (II) but rather the 17-pregnen-21-oic acid (III). This unsaturated acid and others obtained in a similar manner have now been further studied with the objective of utilizing them as starting materials in a practical synthetic route to compounds having a cortical side chain.



I



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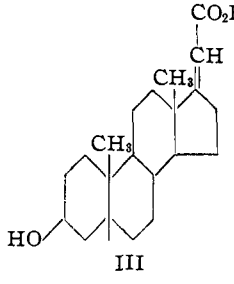
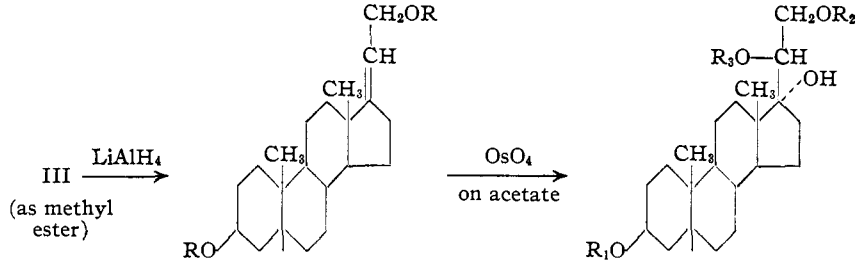


III

Numerous cortical steroids contain the 17,20,21-troil side chain (V), which has been introduced by osmium tetroxide hydroxylation of the corresponding 17-pregnen-21-ol compounds (IV). The latter have hitherto been obtained either by allylic rearrangement of 17-hydroxy-17-vinyl compounds[3] or by treatment of 20-tosylates with collidine.[4]

We have found that these pregnenol precursors can be readily prepared from the 17-pregnen-21-oic acids (III) by treatment of the acid esters with lithium aluminum hydride. The reduction leads to the desired carbinols in uniformly high yields. This reaction has been used to prepare three unsaturated carbinols, two of which were hydroxylated to furnish the previously unreported pregnan-3β,17α,20β,21-tetrol (Va) and allopregnan-17α,20β,21-triol.



IVa, R = H
b, R = Ac

Va, $R_1 = R_2 = R_3 = H$
b, R_1 = Ac, $R_2 = R_3 = H$
c, $R_1 = R_2 = R_3$ = Ac
d, $R_1 = R_2$ = Ac, $R_3 = H$

The third pregnenol, 5,17-prenadien-3β,21-diol was prepared in order to establish a basis for configurational assignment of the new triols. This diendiol has previously been obtained by a different method,[3] and found to yield, upon treatment with osmium tetroxide, the 17α,20β,21-triol side chain.[5] It has been shown by Fieser[6] that the 17α-hydroxyl configuration is a consequence of the rearward attack upon the 17,20-double bond, and that further, by virtue of the *cis* addition of osmium tetroxide, the configuration of the 20-hydroxyl group is determined by the relative positions of the 20-hydrogen atom and the 21-carbon atom in the olefin. In the series of reactions III→IV→V, then, the configuration of the triol side-chain of V is fixed by that of the unsaturated acid III. Thus the acid having the carboxyl group away from the ring system will furnish the 17α,20β-glycol, whereas the other geometrical isomer, with the carboxyl group toward the ring system, would yield the 17α,20α-glycol on hydroxylation. Since steric factors greatly favor the formation, during the rearrangement of the dibromo ketone, of the acid with the

(1) For a preliminary report, see Wagner and Moore, THIS JOURNAL, 71, 4160 (1949).

(2) Marker and Wagner, *ibid.*, 64, 216 (1942); Marker, Crooks and Wagner, *ibid.*, 64, 817 (1942).

(3) Ruzicka and Müller, *Helv. Chim. Acta*, 22, 416 (1939).

(4) Sarett, THIS JOURNAL, 70, 1690 (1948).

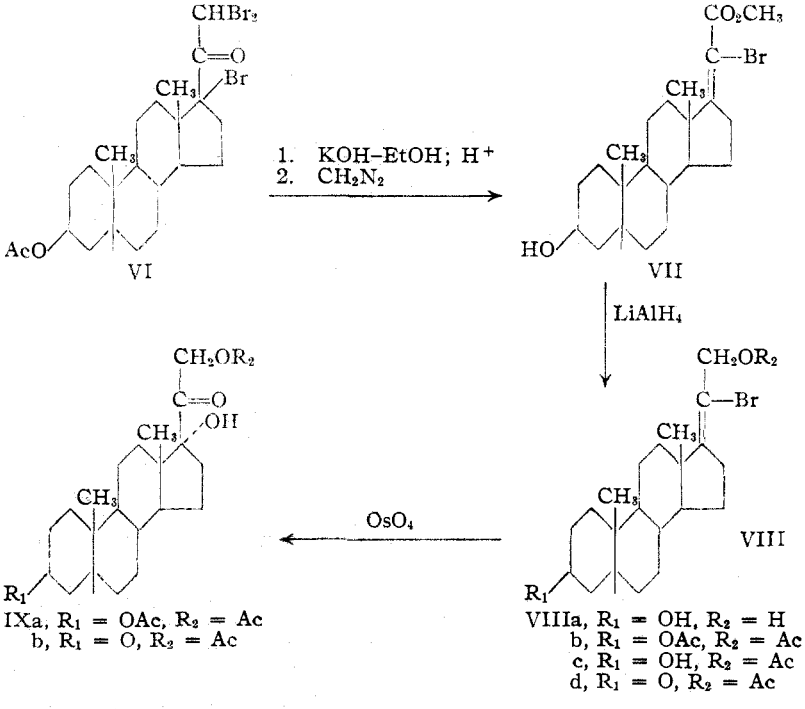
(5) Koechlin and Reichstein, *Helv. Chim. Acta*, 26, 1328 (1943).

(6) Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, pp. 410–452; see also Gallagher and Kritchevsky, THIS JOURNAL, 72, 882 (1950).

21-carboxyl group away from the nucleus, all of the triols obtained by this series of reactions may reasonably be assigned to the 17α,20β-series.

Many of the physiologically important cortical steroids are characterized by a 17,21-dihydroxy-20-keto side chain rather than the 17,20,21-triol type. A practical synthesis of this dihydroxy ketone system has now been devised, in which the starting materials are the 20-bromo-17-pregnen-21-oic acids obtained by rearrangement of 17,21,-21-tribromopregnanolones (VI).[7] This synthesis involves esterification of the 20-bromo acid, reduction of the ester (VII) with lithium aluminum hydride and hydroxylation of the 20-bromo-17-pregnen-21-ol acetate (VIIIb) with osmium tetroxide.

The 20-bromopregnendiol (VIIIa) obtained in the reduction could be converted to either the 3,21-diacetate (VIIIb) or the 21-monoacetate (VIIIc) in excellent yields by the pyridine method. The 21-monoacetate was smoothly converted to the 3-keto derivative (VIIId) by treatment with chromium trioxide in acetic acid at room temperature, the unsaturated side chain being unaffected.

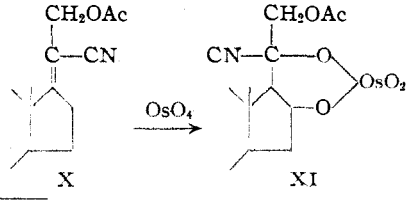


Hydroxylation of the vinyl bromide system presented some unusual features. The reaction was carried out by allowing an ethereal solution of the 20-bromopregnandiol diacetate (VIIIb) and an excess of osmium tetroxide to stand for at least one week, during which a heavy black deposit of osmium-containing material formed. When the ethereal solution was decanted from this precipitate and concentrated *the ketol diacetate (IXa) crystallized in essentially pure form.* The course of this reaction is somewhat obscure. The presence of a free hydroxyl group in the product obviously indicates that some compound capable of contributing at least a hydrogen atom enters into the process. This reactant has been assumed to be water, probably present in traces in the solvent, which, although of reagent grade, had not been rigorously dried.

In one experiment, a sample of the black residue was vigorously digested with aqueous alcoholic sodium sulfite, but only a trace of organic material was obtained. However, when the residue was cautiously treated with concentrated nitric acid and immediately extracted with benzene, the nitric acid was reduced and the benzene solution was found to contain an additional quantity of the ketol diacetate. The ketol product was somewhat less pure than the material obtained directly from the original ethereal solution; undoubtedly the drastic treatment which was employed to free the compound resulted in some degradation.

This hydroxylation has a counterpart in the cyanohydrin process which was employed by Sarett in the synthesis of Kendall's substance E.[8] In this synthesis, the 20-cyano-17-pregnen-21-ol acetate side chain (X) is treated with osmium tetroxide in the presence of pyridine and the product obtained is the relatively stable cyclic osmate ester (XI). Sarett has attributed the stability of this ester to the presence of the negative cyano group.[9] There is no evidence that such an ester is the primary product in the case of the 20-bromopregnenol diacetate. The fact that the ketol diacetate is present in the reaction mixture prior to any hydrolytic treatment indicates that this intermediate, if formed, is highly sensitive to hydrolysis despite the negative bromine atom.

This method of transformation of the 20-bromo-17-pregnene side chain to a dihydroxy acetone compound is highly sensitive to alterations



(7) Wagner and Moore, THIS JOURNAL, 72, 3655 (1950); 71, 4160 (1949).

(8) Sarett, *ibid.*, 70, 1454 (1948).

(9) Sarett, *ibid.*, 71, 2443 (1949).

in the steroid nucleus. Thus, the yield of ketol was significantly lower when the *allo* series was used, and when a 3-keto compound (VIIId) was subjected to these hydroxylation conditions, only a very small quantity of the pregnan-17α,21-diol-3,20-dione (IXb)[10] was obtained. The preparation of this key substance was desirable since it would represent a conversion of the new compounds prepared in the present work to a compound of known configuration. Unfortunately, this substance could not be isolated in analytically pure form.

The configuration of the ketol side chain formed by this method has been found to be the 17β (normal) series (17α-hydroxyl group). This was indicated in the case of pregnan-3β,17α,21-triol-20-one diacetate (IXa) by conversion to the 3β,-17α,20β,21-tetrol triacetate (Vc). Catalytic hydrogenation of the triolone diacetate furnished a mixture of the 20-epimeric tetrol 3,21-diacetates (Vd), from which the 20β compound was isolated as the triacetate, identical with the product (Vc) from the pregnenoic acid (III). Confirmatory proof of the configuration was obtained by application of the reaction to the preparation of allopregnan-3β,17α,21-triol-20-one diacetate (Reichsteins Substance P diacetate).

Experimental[11]

Preparation of the 17,20,21-Triol Side Chain

Unsaturated Acid and Esters.—The unsaturated acids were obtained by treatment of the corresponding 17,21-dibromo-20-keto or the 16,17-dibromo-20-keto compounds with alcoholic potassium hydroxide according to the procedures of Marker and co-workers.[12] The methyl esters were obtained by treatment of the acids with diazomethane in ether.

Reductions with Lithium Aluminum Hydride

17-Pregnen-3β,21-diol (IVa).—To a solution of 250 mg. of pulverized lithium aluminum hydride in freshly-distilled anhydrous ether was added with stirring a solution of 1.0 g. of methyl 3β-hydroxy-17-pregnen-21-oate in ether. The ether refluxed slowly during the addition, which was carried out over a 30-minute period. After stirring for 15 minutes, water was added to decompose the excess hydride and the reaction mixture was then hydrolyzed with dilute sulfuric acid. The ethereal solution was washed with water and dried with sodium sulfate. This solution was concentrated until white needles separated. This material was recrystallized from methanol to give 600 mg. of needles, m. p. 202–203°, $[\alpha]^{25}D$ +27° (*c* 1.66 in dioxane).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.2; H, 10.2.

In a second reaction, 2.0 g. of the unsaturated ester was reduced and processed in the same manner, and the entire product was converted to the diacetate (IVb) by the acetic anhydride–pyridine method. The product was crystallized from ether, yield 1.70 g. The material was recrystallized from ether–pentane to give large white prisms, m. p. 118–119°, $[\alpha]^{25}D$ +29.5° (*c* 1.69 in chloroform).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.4; H, 9.5. Found: C, 74.6; H, 9.4.

5,17-Pregnadien-3β,21-diol.—A solution of 303 mg. of the methyl ester of 3β-hydroxy-5,17-pregnadien-21-oic acid, m. p. 184–185°, in 50 cc. dry ether was added to an ethereal solution of 180 mg. of lithium aluminum hydride. After processing as described above, the product was crystallized from ether; yield 239 mg. This material was recrystallized from methanol to give small prisms, m. p. 197–198°, $[\alpha]^{25}D$ −53.5° (*c* 1.29 in ethanol). This compound furnished an acetate which crystallized from pentane as silky needles, m. p. 135–136°.[13]

17-Allopregnen-21-ol.—In the manner described above, 754 mg. of methyl 17-allopregnen-21-oate, m. p. 86–87°, was treated with lithium aluminum hydride, and the resulting alcohol was converted directly to the acetate. This product was crystallized from ether–pentane, yield 654 mg. The acetate was recrystallized from ether–pentane, m. p. 101–102°.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.2; H, 10.5. Found: C, 79.9; H, 10.4.

Hydroxylation of Pregnenols with Osmium Tetroxide

Pregnan-3β,17α,20β,21-tetrol-3-acetate (Vb).—A solution of 725 mg. of 17-pregnen-3β,21-diol diacetate (IVb) and 504 mg. of osmium tetroxide in 60 cc. of anhydrous ether was allowed to stand for 116 hours. The black osmate ester began to precipitate after 24 hours. The ether was evaporated and the residue was refluxed for four hours with a solution of 1.5 g. of sodium sulfite in 50 cc. of water and 25 cc. of ethanol. After decanting the liquid from the cooled mixture, the residue was digested with three portions of ethanol. The combined solutions were then diluted with two liters of ether and the solution washed with water. The ether solution was dried and evaporated. The residue crystallized after standing 36 hours at 0°. This material was recrystallized from a mixture of acetone and ether to give white plates, m. p. 178–180°, yield 450 mg.

Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.0; H, 9.7. Found: C, 69.6; H, 9.6.

For conversion to the free pregnantetrol (Va), 135 mg. of the above monoacetate was refluxed for 30 minutes with 50 cc. of 1% methanolic potassium hydroxide. The solution was then concentrated in vacuum, the excess base was neutralized by a stream of carbon dioxide, and water was added. The solution was extracted with ether, and the ether solution was dried and evaporated. The residue, which amounted to 116 mg., was recrystallized from ether containing a few drops of methanol to give white needles, m. p. 208–209°.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.6; H, 10.3. Found: C, 71.1; H, 10.3.

The monoacetate was also totally acetylated with acetic anhydride–pyridine to the triacetate (Vc), which crystallized from acetone–pentane as needles, m. p. 184–185°, $[\alpha]^{25}D$ +54.0° (*c* 1.91 in chloroform).

Anal. Calcd. for $C_{27}H_{42}O_7$: C, 67.8; H, 8.9. Found: C, 67.4; H, 8.9.

Allopregnan-17α,20β,21-triol.—An ether solution of 537 mg. of 17-allopregnen-21-ol acetate and 450 mg. of osmium tetroxide was allowed to stand for 100 hours. The reaction was processed as described above, and the product crystallized from ether on addition of a few drops of pentane. The ethereal solution was strongly fluorescent. The material was recrystallized from methanol to give beautiful rosettes of needles, m. p. 173–175°, yield 421 mg., $[\alpha]^{29}D$ −8.5° (*c* 3.31 in dioxane).

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.9; H, 10.8. Found: C, 74.6; H, 10.9.

(10) Koechlin, Garmaise, Kritchevsky and Gallagher, THIS JOURNAL, **71**, 3262 (1949).

(11) All melting points are uncorrected. Rotations were observed in a 1-dm. tube of 2-cc. volume.

(12) Marker, Wagner and Wittbecker, THIS JOURNAL., **64**, 2093 (1942); Marker, Crooks, Wagner, Shabica, Jones and Wittbecker, *ibid.*, **64**, 822 (1942); Marker, Crooks, Jones and Shabica, *ibid.*, **64**, 1276 (1942).

(13) Reported[2] for 5,17-pregnadien-3β,21-diol: m. p. 198–199° (cor.); $[\alpha]D$ −59.5 ± 1.5°; m. p. acetate 135–136°.

Preparation of the 17,21-Dihydroxy-20-one Side Chain

20-Bromo-17-pregnen-3β,21-diol (VIIIa).—To a solution of 1100 mg. of lithium aluminum hydride in 600 cc. of freshly distilled absolute ether was added a solution of 2.4 g. of the methyl ester of 20-bromo-3β-hydroxy-17-pregnen-21-oic acid (VII) in ether. The ester solution was added dropwise with stirring over a 30-minute period, during which the solvent refluxed slowly. Water was then added to the reaction mixture to destroy the excess lithium aluminum hydride, and the complex salt was hydrolyzed with dilute hydrochloric acid. The product was very sparingly soluble in ether, and most of the material was filtered directly from the hydrolysis mixture. The layers of the filtrate were then separated, and the ether layer was washed with dilute potassium hydroxide solution and water, and the ether evaporated. The residue was combined with the original precipitate, and the material was crystallized from methanol to yield 1.83 g. of tiny glistening prisms, m. p. 244–246° (dec.). The compound was recrystallized from methanol, m. p. 251–253° (dec.), $[\alpha]^{25}D$ +53° (*c* 1.50 in dioxane).

Anal. Calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.8; H, 8.5.

20-Bromo-17-pregnen-3β,21-diol Diacetate (VIIIb).—A sample of the bromopregnendiol, 400 mg., was allowed to stand for 10 hours in a solution of 8 cc. of acetic anhydride and 8 cc. of pyridine. After processing the reaction in the usual manner, the diacetate was crystallized from methanol as prisms, m. p. 149–150°, yield 453 mg., $[\alpha]^{28}D$ +47° (*c* 2.77 in chloroform).

Anal. Calcd. for $C_{25}H_{37}O_4Br$: C, 62.4; H, 7.8. Found: C, 62.6; H, 7.7.

Pregnan-3β,17α,21-triol-20-one 3,21-Diacetate (IXa).—To a solution of 1166 mg. of 20-bromo-17-pregnen-3β,21-diol diacetate in 50 cc. of ether was added 1500 mg. of osmium tetroxide. A black precipitate began to form after a few minutes. The solution was allowed to stand at room temperature with the flask loosely stoppered so that the solvent slowly evaporated. After 170 hours, well defined crystals had separated with the black precipitate. The crystalline material was redissolved in ether and the solution was filtered through Celite to remove the black precipitate of osmium compound. The brownish-purple solution was then washed with ten portions of sodium thiosulfate solution to remove excess osmium tetroxide. The ethereal solution was then washed with water, dried and evaporated to dryness. The crystalline residue, still slightly contaminated with black osmium compounds, was dissolved in methanol and treated with Darco G-60 and the product was then crystallized. Two crops of white needles were obtained; yield 670 mg., m. p. 149–151°. This material gave a negative Beilstein test, and depressed the melting point of the starting material 25°, $[\alpha]^{28}D$ +49° (*c* 3.02 in dioxane).

Anal. Calcd. for $C_{23}H_{38}O_6$: C, 69.1; H, 8.8. Found: C, 68.8; H, 8.8.

Hydrogenation of Pregnan-3β,17α,21-triol-20-one 3,21-Diacetate.—A solution of 300 mg. of the diacetate in 40 cc. of acetic acid was shaken with 350 mg. of platinum oxide in a hydrogen atmosphere for one hour at 25° and three atmospheres pressure. After removing the catalyst, the solvent was evaporated in vacuum and the residue was dissolved in ether. After treating this solution with Darco, it was divided into two equal portions.

One portion was acetylated with acetic anhydride and pyridine, the reaction mixture being processed in the usual way. Concentration of the ethereal extract followed by dilution with pentane caused a crop of small needles to crystallize. Upon further standing, the solution deposited some small droplets of oil. This oil was redissolved in ether and the crystals removed. Careful manipulation yielded several small additional crops of crystals. The total yield of crystalline material was 47 mg., recrystallized from ether–pentane, m. p. and mixed m. p. with pregnan-3β,17α,20β,21-tetrol 3,20-21-triacetate (Vc) prepared from another route (*vide supra*), 182–184°; $[\alpha]^{28}D$ +55° (*c* 3.93 in chloroform).

Two unsuccessful attempts were made to isolated the other C-20 epimer, since a comparison of the specific rotations of the two C-20 epimers would have furnished further evidence for the configuration of these compounds.

20-Bromo-17-pregnen-3β,21-diol 21-Acetate (VIIIc).—To a solution of 976 mg. of 20-bromo-17-pregnen-3β,21-diol in pyridine was added 264 mg. of acetic anhydride (1 mole plus 5% excess). After standing at 28° for ten hours, the reaction was processed in the usual manner to yield approximately 400 mg. of monoacetate. Several recrystallizations from methanol were necessary to bring the melting point to a constant value of 124–125°. This material formed a heavy precipitate when treated with an alcoholic solution of digitonin; $[\alpha]^{28}D$ +44.5° (*c* 2.95 in chloroform).

Anal. Calcd. for $C_{23}H_{35}O_3Br$: C, 62.8; H, 8.0. Found: C, 62.4; H, 8.1.

This experiment was repeated a number of times, and it was found that after removing a first crop corresponding to 40% of the total material, it was most practical to combine the mother liquor with that from the two or three recrystallizations which were usually necessary and convert all of the material to the diol by hydrolysis with methanolic potassium hydroxide. The recovery was nearly quantitative.

20-Bromo-17-pregnen-21-ol-3-one Acetate (VIIId).—To a solution of 1003 mg. of 20-bromo-17-pregnen-3β,21-diol 21-acetate in 35 cc. of acetic acid was added at 20° a solution of 440 mg. of chromium trioxide in 6 cc. of 80% acetic acid. After standing for 40 minutes, the excess oxide was destroyed with methanol and the solvent evaporated in vacuum. The residue was extracted with ether, and the ethereal solution was washed with base and water, dried and evaporated. The residue was crystallized and 740 mg. of material was obtained, m. p. 141–142°, $[\alpha]_D$ +62° (*c* 4.32 in chloroform).

Anal. Calcd. for $C_{23}H_{33}O_3Br$: C, 63.2; H, 7.6. Found: C, 63.5; H, 7.9.

Pregnan-17α,21-diol-3,20-dione Acetate (IXb).—To a solution of 581 mg. of 20-bromo-17-pregnen-21-ol-3-one acetate in 25 cc. of anhydrous ether was added 790 mg. of osmium tetroxide. A black precipitate began to form immediately. The solution was allowed to stand at 25° for 209 hours. (The presence of osmium tetroxide could not be detected after approximately 100 hours.) The mixture was filtered and the heavy black precipitate was digested with ether and then methanol, and the solutions were combined. After concentrating the dark-colored filtrate, a small additional amount of black material, apparently osmium compounds, settled out, and was removed by treatment with Darco. The product was then crystallized from aqueous methanol as fine white needles, yield first crop 42 mg., m. p. 188–190°. This material could not be obtained analytically pure.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.7; H, 8.8. Found: C, 69.8; H, 8.4.

20-Bromo-17-allopregnen-3β,21-diol Diacetate.—This compound was prepared by exactly the same procedures and techniques described in the normal series. **20-Bromo-17-allopregnen-3β-ol-21-oic acid** was obtained in 34% over-all yield from allopregnane-3β-ol-20-one without purification of the tribromoketone. The acid was crystallized from methanol; m. p. 253–255°, $[\alpha]^{26}D$ +31° (*c* 1.277 in dioxane). The methyl ester was not isolated, and the reduction product, 20-bromo-17-allopregnen-3β,21-diol, was converted directly to the diacetate; the over-all yield from the bromo acid was 65–70%. The diacetate crystallized from ether–pentane as needles; m. p. 125–127°, $[\alpha]^{26}D$ +39° (*c* 3.11 in chloroform).

Anal. Calcd. for $C_{25}H_{37}O_4Br$: C, 62.4; H, 7.8. Found: C, 62.5; H, 7.8.

Allopregnane-3β,17α,21-triol-20-one 3,21-Diacetate (Reichsteins Substance P Diacetate).—A solution of 2.0 g. of 20-bromo-17-allopregnen-3β,21-diol diacetate and

3.0 g. of osmium tetroxide in 30 cc. of ether was tightly stoppered and allowed to stand for 308 hours. After this time two types of solid were present in the reaction mixture, a fine, black adherent precipitate and a quantity of coarse granules, coated with the black material. Since the desired product is quite sparingly soluble in ether, the mixture was extracted and digested with benzene. The dark-colored benzene solution was washed free of osmium tetroxide with aqueous sodium thiosulfate; a very heavy emulsion which developed was separated by filtration through Darco. The benzene layer was then washed with water, dried with sodium sulfate and concentrated. Three crops of crystals were obtained from this solution, amounting to 550 mg. The first crop was recrystallized from ethyl acetate to give white needles, m. p. 208–210°; $[\alpha]^{26}D$ +31° (*c* 1.126 in chloroform).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.1; H, 8.8. Found: C, 69.3; H, 8.9.

The benzene-insoluble osmium residue from the reaction mixture was treated with 10 ml. of concd. nitric acid. The black solid became gummy, and copious red fumes were evolved. After 15 seconds, the mixture was treated with ice-water and extracted with benzene. The benzene solution was processed in the manner described above. The residue remaining after removal of the benzene was crystallized from ethyl acetate to give white crystals, wt. 80 mg., m. p. 189–191°; after several recrystallizations from this solvent, m. p. and mixed m. p. with first crop above 205–207°.

Summary

1. A new method for the preparation of 17-pregnen-21-ol compounds from the 17-pregnen-21-oic acids is reported. The 17-pregnen-21-ol compounds so obtained have been converted to the corresponding products containing the 17α,20β,-21-triol side chain.

2. A new synthesis of compounds containing the 17α,21-diol-20-one side chain from the corresponding 20-bromo-17-pregnen-21-oic acids has been described.

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[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Nucleophilic Displacement in the Naphthalene Series

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The greater reactivity of the α-position in naphthalene, predicted by modern theories, is well substantiated by substitution reactions, measurements of physical constants and quantum mechanical calculations.[2] The α-position should also be more reactive toward displacement reactions, but very little is known about nucleophilic displacements on the halonaphthalenes.[3] The present investigation was undertaken in order to see whether, under comparable conditions, the α-position is more reactive toward nucleophilic reagents than the β-position, as demanded by the theory and all available experimental evidence. While this work was in progress, Pullman, Rumpf and Kieffer[4] determined the rate of exchange of the bromonaphthalenes with radioactive lithium bromide. They found that in every case β-bromonaphthalene reacted faster than the α-isomer and attributed this to the greater amount of double bond character of the α-isomer.

In the present study the displacement reactions were carried out on α- and β-halonaphthalenes, 1-nitro-2-halo- and 2-nitro-1-halonaphthalenes with piperidine as the nucleophilic reagent and solvent. In Table I are recorded the results for the halonaphthalenes, which were studied at 165 and 200°; data on the halobenzenes are also included. In all cases the β rather than the α-isomer is the more reactive. The energies of activation and *PZ* factors indicate that the relative order of reactivity of the α- and β-isomers is not caused by a difference in activation energies, but by a difference in the *PZ* factors. This is particularly evident with the bromonaphthalenes. Although β-displacement proceeds with the greater energy of activation, the faster reaction occurs at the β-position because of a greater *PZ* factor. The halobenzenes, as expected, react invariably slower than the corresponding halonaphthalenes.

TABLE I

THE REACTIONS OF HALONAPHTHALENES WITH PIPERIDINE

Naphthalene	k_{165} × 10⁴, hours⁻¹	k_{200} × 10⁴, hours⁻¹	*E*, kcal.		log *PZ*	
1-Iodo-	17.0	121	23.1	±0.95	8.76	±0.45
2-Iodo-	21.1	171	24.6		9.60	
1-Bromo-	8.56	70.9	24.9	±0.7	9.36	±0.35
2-Bromo-	14.9	156	27.6		10.95	
1-Chloro-	1.48					
2-Chloro-	1.86					
Iodobenzene	9.4	70	23.6	±1.0	8.75	±0.5
Bromobenzene	5.2					
Chlorobenzene	0.64					

The reversal of the relative rates from those expected is perhaps somewhat misleading *because* of the high temperature at which the reactions had to be carried out. The *E* and *PZ* factors of the two reactions are such that relatively less β-substitution must occur as the temperature decreases and at some sufficiently low temperature the α-halonaphthalenes will be more reactive than the

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(2) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 267; Ketelaar and van Oosterhout, *J. Chem. Phys.*, **13**, 448 (1945); *Rec. trav. chim.*, **65**, 448 (1946); see also ref. 4; Wheland and Pauling, THIS JOURNAL, **57**, 2086 (1935); Wheland, *ibid.*, **64**, 900 (1942); Daudel, *J. Chem. Phys.*, **16**, 639 (1948); Pullman, *Ann. chim.*, **2**, 5(1947).

(3) Petrenko-Kritschenko, *Ber.*, **62**, 581 (1929).

(4) Pullman, Rumpf and Kieffer, *J. chim. phys.*, **45**, 150 (1948).