progesterone (X) (5.0 g.) in 95% ethanol (250 cc.) and heated under reflux for 2 hr. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene (200 cc.) onto alumina (200 g.) (chromatogram A). Elution with benzene (1.2 l.) and benzene-ether (90:10; 600 cc.) gave a product (3.06 g.) which was dissolved in hexane-benzene (80:20; 150 cc.) and rechromatographed over alumina (120 g.) (chromatogram B). Elution with hexane-benzene (80:20; 300 cc.) and (70:30; 300 cc.) gave progesterone (X) (1.32 g.) m.p. 112–117°, raised by crystallization from hexane to 118–120° undepressed on admixture with an authentic sample. Further elution of chromatogram B with hexane-benzene (1:1, 300 cc.) and benzene (300 cc.) furnished 5α-cyanopregnane-3,20-dione (XI) (960 mg.) m.p. 212–234°, raised by crystallizations from acetone-hexane to 239–241°, $[\alpha]_D$ +113°; λ_{max} 286–288 mμ, ε 60. λ_{max}^{KBr} 2250, 1725, and 1708 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}O_2N$: C, 77.37; H, 9.15; O, 9.37; N, 4.10. Found: C, 77.19; H, 9.05; O, 9.76; N, 4.17.

Continued elution of chromatogram A with ether (600 cc.) and ether-acetone (90:10; 600 cc.) afforded pregnane-3,20-dione-5α-carboxamide (XIII) (500 mg.) m.p. 225–230°, raised by crystallizations from acetone to 243–245°, $[\alpha]_D$ +73°. λ_{max} 280–288 mμ, ε 63. λ_{max}^{KBr} 3330, 1705, and 1680 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; O, 13.35; N, 3.90. Found: C, 73.72; H, 9.10; O, 13.52; N, 4.13.

Further elution (chromatogram A) with ether-acetone (80:20, 1500 cc.) gave pregnane-3,20-dione-5β-carboxamide (XII) (900 mg.) m.p. 190–210°, raised by one crystallization from acetone to 230–237°. The analytical sample from acetone had m.p. 243–245°, depressed to 215–230° on admixture with the 5α-epimer (XIII); $[\alpha]_D$ +83°; λ_{max} 280–290 mμ ε 51. λ_{max}^{KBr} 3300, 1710, and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.77; H, 9.04; N, 4.17.

(b) When the reflux time was extended to 5 hr., no progesterone (X) was recovered, nor could any 5α-cyanopregnane-3,20-dione (XI) be isolated. The 5α-carboxamide (XIII) was isolated in 40% yield and the 5β-carboxamide (XII) in 16% yield.

Alkaline hydrolysis of 5α-cyanopregnane-3,20-dione (XI) (with E. Denot). Potassium hydroxide (500 mg.) was added to a solution of 5α-cyanopregnane-3,20-dione (XI) (150 mg.) in ethanol (12.5 cc.). After heating under reflux for 1 hr. water (25 cc.) was added and the solution acidified with dilute sulfuric acid. Filtration afforded the pregnane-3,20-dione-5α-carboxamide (XIII) (130 mg.) m.p. 215–218°, raised by one crystallization from acetone-hexane to 240–241°, undepressed on admixture with the sample described above. The infrared spectra of the two samples were identical. The m.p. was depressed (187–194°) on admixture with the 5β-carboxamide (XII).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. CLXIV.[1] Preparation of 6α,16α-Dimethylprogestational and Cortical Hormone Analogs

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Synthetic routes for the preparation of 6α,16α-dimethylprogesterone, 6α,16α-dimethyl-17α-acetoxyprogesterone and 6α,16α-dimethylhydrocortisone are described.

During recent years considerable interest has been attached to the synthesis of steroidal hormone analogs and amongst the more interesting variations in the progestational and cortical hormone series have been the introduction of halogen, hydroxyl, or methyl groups at various positions throughout the steroid molecule. Syntheses involving the latter group have been effected at C-2,[2] C-4,[3] C-6,[4] C-7,[5] C-9,[6] C-17,[7] and C-16[8,9] and of these, the preparation of the 6α-methyl and 16α-methyl analogs have been of special interest. As specific examples, the enhanced progestational activity in the 6α-methyl-17α-acetoxyprogesterone

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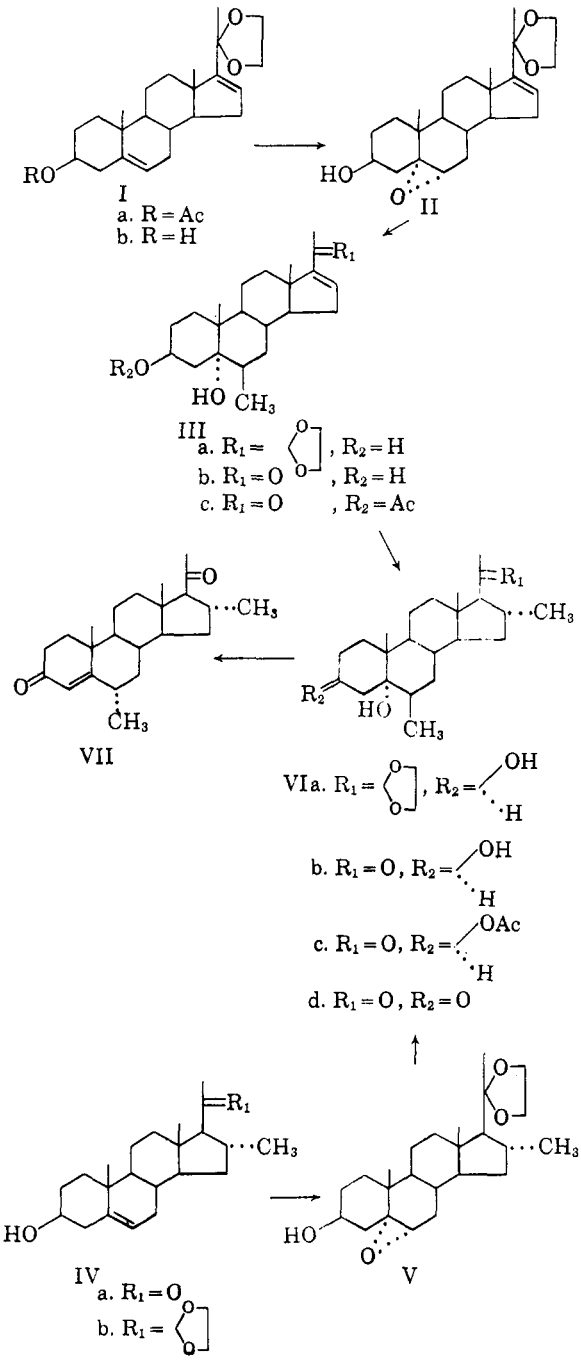

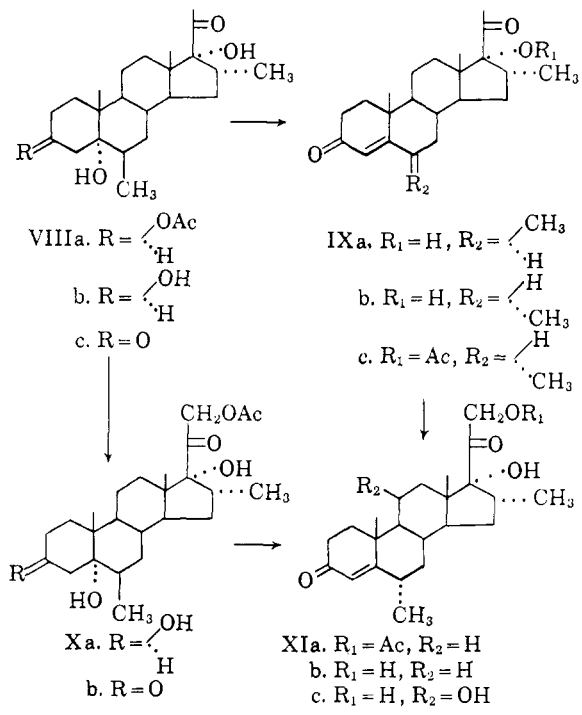

series[4c,4d] as well as the potentiated activities of 6α-methylprednisolone,[4a] 16α-methyl-9α-fluoroprednisolone[3b] or 16β-methyl-9α-fluoroprednisolone[8e] may be noted.

In view of these observations it appeared that the preparation of hormone analogs simultaneously bearing the 6α- and 16α-methyl groups would be of considerable interest if the potentiating properties of each group proved to be additive. Towards this end, the syntheses of 6α,16α-dimethylprogesterone (VII), 6α,16α-dimethyl-17α-acetoxyprogesterone (IXc) and 6α,16α-dimethylhydrocortisone (XIc) were undertaken.

For the preparation of VII, two routes were explored. One of these was based on 16α-methyl-5-pregnene-3β-ol-20-one (IVa) whose preparation from 5,16-pregnadiene-3β-ol-20-one by 1,4-methyl Grignard addition was first described by Marker and Crooks[10] in 1942. Transformation of IVa to its 20-ketal (IVb) was easily effected and the resultant product was epoxidized with monoperphthalic acid. By these means the *alpha* epoxide (V) was obtained in 47% yield; studies were then made of its fission with methylmagnesium bromide.[11]

In contrast to most 5α,6α-epoxides which undergo relatively facile opening,[12] V proved to be extremely sluggish and reaction periods of 235 hours were necessary to provide the 6β-methyl-5α-ol (VIa) in 66% yield. This material was then subjected to acid hydrolysis of the ketal moiety and following 8*N* chromic acid oxidation in acetone,[13] it provided the 6β-methyl-5α-ol-3,20-dione VId. Treatment of VId with boiling methanolic potassium hydroxide led to dehydration of the 5α-hydroxyl group as well as inversion of the axial 6β-methyl group to give 6α,16α-dimethylprogesterone (VII), which possesses the thermodynami-

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(11) (a) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939) [*Chem. Abstr.*, **33**, 9309 (1939)]; (b) L. F. Fieser and J. Rigaudy, *J. Am. Chem. Soc.*, **73**, 4660 (1951); (c) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 5362 (1952). See also Ref. 4.

(12) See ref. 4 as well as J. A. Zderic and D. Chávez L., *J. Am. Chem. Soc.*, **81**, 4570 (1959); J. A. Zderic and D. Chávez L., *J. Am. Chem. Soc.*, **82**, 2304 (1960), who have employed phenyl and ethynyl Grignard reagents.

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

cally more stable[14] equatorial methyl configuration at C-6. An alternate synthesis of VII was achieved by reversing the order in which the methyl groups were introduced into the molecule. Thus 5,16-pregnadiene-3β-ol-20-one acetate was first converted to its 20-ketal (Ia) and hydrolyzed with alkali to provide 5,16-pregnadiene-3β-ol-20-one 20-ketal (Ib). Selective epoxidation of Ib was then effected by the use of exactly one mole of monoperphthalic acid at 5° for two hours. In this manner the 5α,6α-epoxide (II) was obtained in 76% yield. That the position of epoxidation was correctly assigned followed from the observation that II upon being allowed to reflux in acetone containing *p*-toluensulfonic acid yielded a substance which possessed an ultraviolet maximum characteristic of the Δ^{16}-20-ketone system. With this point established, II was treated with methylmagnesium bromide: In contrast to the extremely slow epoxide fission previously noted for the conversion of V to VIa, II was found to react normally and provided the 6β-methyl-diol IIIa in 60% yield after eighteen hours at reflux temperature.

Acid hydrolysis of the 20-ketal moiety in IIIa led to IIIb, further characterized as its 3β-acetate (IIIc). Treatment of this latter compound with methylmagnesium bromide in the presence of cuprous chloride[15] then provided an intermediate 16α-methyl bromomagnesium enolate. When this substance was decomposed with dilute aqueous acid and the resultant semicrystalline product was acetylated, it provided 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-acetate (VIc), which proved to be identical in all respects with the material initially prepared from IVa.

With the completion of this alternate route for the preparation of 6α,16α-dimethylprogesterone (VII), attention was next turned to the preparation of the 17α-acetoxy and cortical hormone analogs. While normally 20-ketopregnanes may be converted via the Gallagher procedure[16] to 17α-hydroxypregnanes, the 16α-methyl group in VIc has a retarding effect on the formation of the corresponding 20-enolacetate.[17] For this reason[18] the preferred method employed was the procedure developed in the Ciba laboratories[15] which involves direct acetylation of the intermediate 16α-methyl bromomagnesium enolate mentioned above. The product thus obtained was not purified but was epoxidized and then hydrolized with potassium carbonate in refluxing methanol. By these means a semicrystalline product was obtained and, by subsequent acetylation and chromatography, it provided a 30% yield of 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-acetate (VIc). Presumably this substance arose from failure, in this case, to achieve complete acetylation of the bromomagnesium enolate or by incomplete epoxidation of the intermediate enol acetate. In addition to VIc, a 28% yield of the desired 17α-hydroxyderivative (VIIIa) was also obtained. Alkaline hydrolysis of this substance, followed by 8*N* chromium trioxide oxidation[13] then yielded the dione VIIIc. When dehydration of this substance was effected with dilute methanolic alkali, there resulted a mixture of the 6β- and 6α-methyl-Δ^4-3-ketones (IXa and IXb), which could be separated chromatographically. Concentrated hydrochloric acid in acetic acid was also employed for the dehydration step and in this case good yields of homogeneous 6α,16α-dimethyl-17α-hydroxyprogesterone (IXb) were obtained directly. Treatment of IXb with acetic anhydride and *p*-toluenesulfonic acid led to the corresponding 17α-acetoxy-3-enolacetate which was characterized only by its physical constants and converted by acid hydrolysis into 6α,16α-dimethyl-17α-acetoxyprogesterone IXc which was isolated and fully characterized.

For the preparation of 6α,16α-dimethyl-"S" acetate, XIa, two routes were employed. Thus when 6α,16α-dimethyl-17α-hydroxyprogesterone, IXb, was treated under the Ringold-Stork[19] conditions an intermediate 21-iodo compound was obtained which after acetate displacement yielded XIa. The alternate method was based on the dimethyl-triol-one VIIIb which was first brominated at C-21 and next treated with sodium iodide and potassium acetate. By this sequence Xa was obtained and after oxidation at C-3 and acid catalized dehydration it provided the same compound "S" analog (XIa) described above. Hydrolysis of the 21-acetate function was then effected and the resulting free compound was incubated with freshly ground bovine adrenals.[20] From the incubation process a 22% yield of pure 6α,16α-dimethylhydrocortisone, XIc was obtained.

Biological data. In the granuloma pouch assay, XIc was found to be considerably more active than hydrocortisone. Of more interest, however is the fact that in sodium retention assays, employing adrenalectomized rats, XIc showed definite sodium excretion at 1, 25, and 100 μg dose levels.

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(18) And also because the 5α-OH group in VIc is very readily eliminated under the Gallagher procedure conditions.

(19) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, **80**, 250 (1958).

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EXPERIMENTAL[21]

5,16-Pregnadiene-3β-ol-20-one acetate cycloethylene ketal (Ia). A solution of 5,16-pregnadiene-3β-ol-20-one acetate (45 g.) in thiophene-free benzene (3 l.) containing ethylene glycol (150 cc.) and *p*-toluenesulfonic acid (1 g.) was heated under reflux for 72-hr. using a water separator. The reaction mixture was poured into sodium bicarbonate solution and extracted with benzene. Evaporation of the benzene under vacuum and crystallization of the residue from ether-methanol gave the crude ketal, m.p. 153–155°, in 60% yield (30.5 g.). Recrystallization from the same solvents furnished the analytical specimen as plates with m.p. 166–167°, $[\alpha]_D$ −62.5°, ν_{max}. 1740, 1245 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06; O, 15.98%. Found: C, 74.75; H, 8.84; O, 16.57%.

5,16-Pregnadiene-3β-ol-20-one cycloethyleneketal (Ib). Potassium hydroxide (15 g.) in aqueous methanol (800 cc. methanol-50 cc. water) was added to 5,16-pregnadiene-3β-ol-20-one acetate cycloethyleneketal (Ia) (21 g.) in methanol (1 l.) and the solution was heated under reflux for 2 hr. Addition of water, filtration of the precipitate, and drying on the steam bath provided the crude free ketal (19.3 g.) as plates with m.p. 167–170° in 90% yield. One crystallization from ether-methanol gave material with m.p. 176–177°, $[\alpha]_D$ −85.5°. Further purification by chromatography on alumina and elution with hexane-benzene 1:2 gave the analytical sample which was crystallized from ether-methanol: m.p. 180–181°, $[\alpha]_D$ −84.3°, no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39%. Found: C, 76.74; H, 9.39; O, 13.92%.

5α,6α-Oxido-16-pregnene-3β-ol-20-one cycloethyleneketal (II). Epoxidation of 5,16-pregnadiene-3β-ol-20-one cycloethyleneketal Ib (132 g. 0.368 m.) was carried out by dissolving the compound in methylene chloride (3.5 l.) and adding exactly 1 mole of monoperphthalic acid (736 cc. of a 1*N* solution) in ether at 5°. The oxidation was followed by periodical titration of aliquots and the peracid was found to be consumed completely during 2 hr. The reaction mixture was then poured into sodium bicarbonate solution and the methylene chloride layer was separated, washed with water, dried, and evaporated. Chromatography of the residue on alumina (5 kg.) afforded 22% of unchanged ketal (29.6 g., m.p. 176–177°) and 76% of 5α, 6α-oxide ketal II (100.5 g. m.p. 150–152°) eluted with benzene-ether (95:5). Crystallization from ether provided the analytical sample, m.p. 155–156° (hexagonal plates), $[\alpha]_D$ −76.5°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09%. Found: C, 73.56; H, 8.93; O, 17.26%.

When this substance was heated for 1 hr. in aqueous acetone with *p*-toluenesulfonic acid it gave an α,β-unsaturated ketone as witnessed by its ultraviolet maximum: m.p. 225–230° (crystallization from ether), $[\alpha]_D$ −38° [chloroform, −43° (dioxane)], λ_{max} 240 mμ, log ε 3.92. This substance was not further characterized.

6β-Methyl-16-pregnene-3β-5α-diol-20-one cycloethyleneketal (IIIa). An ethereal methylmagnesium bromide solution (large excess) was added to 5α,6α-oxido-16-pregnene-3β-ol-20-one cycloethyleneketal (II) (50 g.) dissolved in anhydrous tetrahydrofuran (2 l.). The ether was distilled and the solution refluxed for 18 hr. Decomposition of the Grignard complex with ammonium chloride solution and extraction with ether gave an amorphous residue which was chromatographed on alumina. Unchanged α-oxidoketal II was recovered in 5% yield (2.5 g. m.p. 154–155°, $[\alpha]_D$ −74°) upon elution with benzene-ether 95:5. Elution with benzene-ether 4:1 and with pure ether then furnished 6β-methyl-16-pregnene-3β,5α-diol-20-one cycloethyleneketal, IIIa (31 g.), in 60% yield, m.p. 167–171°, $[\alpha]_D$ −34.4°. Recrystallization from ether gave the pure compound as needles with m.p. 170–171°, $[\alpha]_D$ −34.8°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81; O, 16.38%. Found: C, 73.68; H, 9.71; O, 16.59%.

6β-Methyl-16-pregnene-3β,5α-diol-20-one (IIIb). Cleavage of the ketal IIIa (30 g. m.p. 165–170°) by refluxing for 1 hr. in aqueous acetone (1.5 l.) with *p*-toluenesulfonic acid (3 g.) gave the free ketone, IIIb in 90% yield. This compound separated as plates from the refluxing solution and precipitation was completed by addition of water. The crude material was filtered, washed, and dried (24 g., m.p. 240–245°) whence crystallization from ethyl acetate gave the pure compound with m.p. 252–254°, $[\alpha]_D$ + 1.7° (dioxane), λ_{max} 240 mμ, log ε 3.96, ν_{max} 3420, 1640, 1575 cm^{-1}.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85%. Found: C, 75.91; H, 9.62; O, 14.64%.

Acetylation of the free hydroxy ketone IVa with acetic anhydride–pyridine by heating 1 hr. on the steam bath gave the 3-acetate IIIc: m.p. 200–201° (crystallized from acetone-ether), $[\alpha]_D$ −10, −14°, λ_{max} 240 mμ, log ε 3.96, ν_{max} 3560, 1735, 1640, 1580, 1260 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47%. Found: C, 74.53, 74.39; H, 9.25, 9.21; O, 16.44, 16.73%.

6β,16α-Dimethylpregnane-3β,5α-diol-20-one (VIb). *A. By 1,4-addition of methylmagnesium bromide to 6β-methyl-16-pregnene-3β,5α-diol-20-one acetate* (IIIc). The α,β-unsaturated ketone IIIc (1.5 g. 0.0039 m.) dissolved in anhydrous tetrahydrofuran (60 cc.) was slowly added with stirring to a solution of methylmagnesium bromide in tetrahydrofurane (30 cc. of 2.1 *N* methylmagnesium bromide in ether plus 30 cc. anhydrous tetrahydrofuran) to which 400 mg. of cuprous chloride had been previously added. The addition was carried out at room temperature and under a nitrogen atmosphere. After 1 hr. stirring the reaction mixture was poured into ice cold dilute hydrochloric acid and extracted with ethyl acetate. The semicrystalline residue obtained was acetylated with acetic anhydride (10 cc.) in pyridine (5 cc.) by heating on the steam bath for 1 hr. After the usual work up by addition of water, extraction with ethyl acetate, and crystallization from acetone, *6β,16α-dimethylpregnane-3β,5α-diol-20-one acetate* (VIc) was obtained in 50% over-all yield (0.77 g.), m.p. 235–238°, $[\alpha]_D$ +14.1°. Crystallization from ethyl acetate or from acetone gave the pure compound, m.p. 253–255°, $[\alpha]_D$ +22.2°, ν_{max} 3400, 1740, 1680, 1250 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97; O, 15.82% Found: C, 74.67; H, 9.72; O, 15.89%.

Hydrolysis of the purified acetate was effected by heating for 1 hr. under reflux with 1% methanolic potassium hydroxide whereafter addition of water and extraction with ethyl acetate furnished the free 16α-methyl substituted saturated ketone VIb: m.p. 213–214° (crystallized from acetone-ether), $[\alpha]_D$ +29.2°, ν_{max} 3400, 1685 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{36}O_3$:C, 76.20; H, 10.56; O, 13.24%. Found: C, 76.74; H, 10.29; O, 13.54%.

B. By reaction of methylmagnesium bromide with 16α-methyl-5α,6α-oxido-pregnane-3β-ol-20-one cycloethyleneketal (V) *followed by acid cleavage of the ketal.* An excess of methylmagnesium bromide in ether was added to a solution of 16α-methyl-5α,6α-oxido-pregnane-3β-ol-20-one cycloethyleneketal (67 g. m.p. 150°, $[\alpha]_D$ −63.5°) in anhydrous tetrahydrofuran (3 l.); the ether was distilled and the mixture heated to reflux temperature. Aliquots were taken periodically, poured into ice cold ammonium chloride solution, extracted with ether, and the residues chromatographed on alumina. In this manner it was found that after 24 hr. the reaction had taken place only to the extent of 8% and 85–90% of the starting oxideketal (V) could be recovered. In experiments with longer refluxing periods the yields in this Grignard reaction were increased as follows: 15% in 50 hr., 42% in 100 hr., 66% in 235 hr.

(21) Melting points are uncorrected. Infrared spectra were determined in potassium bromide pellets. All rotations were determined in chloroform and ultraviolet spectra in ethanol unless otherwise noted. We are indebted to Dr. J. Matthews and his staff for the determination of these constants.

6β,16α-Dimethylpregnane-3β,5α-diol-20-one cycloethyleneketal (VIa)., more polar than the starting epoxide, was eluted with benzene-ether 4:1 and recrystallized from ether: m.p. 180–183°, $[\alpha]_D$ −21.1°, ν_{max} 3430 cm.$^{-1}$ no carbonyl absorption.

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 73.85; H, 10.46; O, 15.69%. Found: C, 73.98; H, 10.33; O, 15.91%.

Cleavage of this ketal (VIa) (5 g.) by refluxing for 1 hr. in aqueous acetone (250 cc.) with *p*-toluenesulfonic acid (0.5 g.) gave crude *6β,16α-dimethylpregnane-3β,5α-diol-20-one* (VIb) in 90% yield (4 g.), m.p. 208–210°, $[\alpha]_D$ +36.5°. Crystallization from acetone-ether led to the analytical sample with m.p. 212–213° (3-monoacetate, m.p. 251–252°).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56; O, 13.24%. Found: C, 76.52; H, 10.27; O, 13.52%.

This compound was found identical in all respects (mixed melting point and infrared comparisons) to that prepared by the alternate procedure A, as described above.

16-Methyl-5α,6α-Oxido-pregnane-3β,ol-20-one cycloethyleneketal (V). Oxidation of 16α-methyl-5-pregnene-3β-ol-20-one cycloethyleneketal (IVb) (137 g. 0.367 mole) in methylene chloride (3 l.) was carried out at 5° with 0.66 *N* monoperphtalic acid in ether (1.23 l, 10% molar excess) during 20 hr. Addition of the reaction mixture into sodium bicarbonate solution, extraction with ether and chromatography of the amorphous residue on alumina (5 kg.) gave the crude α-epoxide V (67 g.) in 47% yield with m.p. 149–152°, $[\alpha]_D$ −63.5°. This compound was eluted from the alumina column with benzene-ether and it was crystallized from ether in the cold or better from ether-hexane as needles with m.p. 154–156°, $[\alpha]_D$ −60.1°, ν_{max} 3600 cm.$^{-1}$ No carbonyl absorption.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81; O, 16.38%. Found: C, 73.69; H, 9.49; O, 16.51%.

16α-Methyl-5-pregnene-3β-ol-20-one cycloethyleneketal (IVb). Ketalization of 16α-methyl-5-pregnene-3β-ol-20-one (IVa) was effected by dissolving the compound (41 g., m.p. 185–190°, $[\alpha]_D$ +6.2°) in thiophene-free benzene (3 l.) and heating the solution to reflux for 72 hr. with ethylene glycol (150 cc.) and *p*-toluenesulfonic acid (1 g.) using a water separator. Pouring into sodium bicarbonate and extraction with benzene-ether gave a crude crystalline material which was chromatographed on alumina (1.5 kg.) to remove any unchanged ketone. Elution with hexane-benzene (1:2) furnished a 68.5% yield of a crude ketal IVb (31.5 g.) with m.p. 165–170° and $[\alpha]_D$ −50.7°. Crystallization from ether gave the pure compound with m.p. 171–172°, $[\alpha]_D$ −47.4°.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23; O, 12.81%. Found: C, 77.25; H, 10.02; O, 12.65%.

6β,16α,-Dimethylpregnane-5α-ol-3,20-dione (VId). A solution of 6β,16α-dimethylpregnane-3β,5α-diol-20-one, VIb, (600 mg.) in acetone (100 cc.) was oxidized with 8*N* chromic acid[13] at 5° for 4 min. Water was then added and the compound was extracted with ethyl acetate. The crude material (500 mg.) obtained upon evaporation showed m.p. 260–265°. Recrystallized several times from ethyl acetate it gave the analytical sample with m.p. 270–273°, $[\alpha]_D$ +57 ±4°, ν_{max} 3330, 1695 cm.$^{-1}$

Anal: Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07; O, 13.31%. Found: C, 76.24; H, 10.34; O, 13.61%.

6α,16α-Dimethylprogesterone (VII). Dehydration of 6β, 16α-dimethylpregnane-5α-ol-3,20-dione (VId) was effected by dissolving it (1 g., m.p. 260–265°) in methanol (300 cc.), adding 15% aqueous potassium hydroxide solution (15 cc.) and heating to reflux temperature for 1 hr. under a nitrogen atmosphere. The solution was then acidified with acetic acid, water was added and the compound was extracted with ethyl acetate. After evaporation the amorphous residue was dissolved in benzene and passed through a column of alumina (30 g.). Elution with benzene gave crystalline 6α,16α-dimethylprogesterone (800 mg.) in 84% yield, m.p. 115–120°. The material was purified by crystallization from ether and from ether-hexane: Needles with m.p. 126–128°, $[\alpha]_D$ +147°, λ_{max} 242 mμ log ε 4.19, ν_{max} 1720, 1690, 1610 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 80.65; H, 10.01; O, 9.34% Found: C, 81.09; H, 9.95; O, 9.37%.

6β,16α-Dimethylpregnane-3β,5α,17α-triol-20-one 3-monoacetate (VIIIa). An ethereal solution of methylmagnesium iodide (118 cc. of 1.7*N* methylmagnesium iodide, 0.1 mole) was added with stirring and under nitrogen to anhydrous tetrahydrofuran (200 cc.). The ether was removed by gentle warming and 0.5 g. of cuprous chloride was added while stirring. A solution of 6β-methyl-16-pregnene-3β,5α-diol-20-one 3-acetate, IIIc, (11.6 g. 0.03 m.) in tetrahydrofuran (60 cc.) was then added at room temperature and the yellow solution formed was stirred for 1 hr. more and cooled to −5°. Freshly distilled acetyl chloride (5 cc. 0.095 mole) in tetrahydrofuran (50 cc.) was then added and the suspension was stirred for 15 min. more. After pouring into an ice cold ammonium chloride solution and extracting with methylene chloride, the extracts were washed with sodium thiosulfate and ammonium chloride solutions. Evaporation of the solvent at low temperature under vacuum gave an amorphous mixture of the 17,20-enol acetates which was dissolved in methylene chloride (300 cc.) and oxidized directly with 0.91 *N* ethereal monoperphthalic acid (132 cc. 0.06 mole, 2 : 1 molar ratio) for 20 hr. at 10°. The solution was worked up by pouring into sodium bicarbonate solution and extracting with methylene chloride. After evaporation, the residue was dissolved in methanol (300 cc.), potassium carbonate (4 g.), and water (10 cc.) were added and the solution was boiled under reflux for 1 hr. Addition of water and extraction with ethyl acetate gave a semicrystalline residue which was acetylated by heating for 1 hr. with acetic anhydride (100 cc.) and pyridine (50 cc.) on the steam bath. The acetylated mixture was diluted with water and worked up by extraction with ethyl acetate, washing with sodium bicarbonate drying and evaporation. The residue was chromatographed on washed alumina (500 g.): Elution with hexane-benzene and with pure benzene furnished the 17-desoxy compound, 6β,16α-dimethylpregnane-3β,5α-diol-20-one 3-monoacetate (VIc) m.p. 240–241° (4 g.) in 30% yield.

Elution with ether gave 6β,16α-dimethylpregnane-3β, 5α,17α-triol-20-one 3-monoacetate (VIIIa) in 28% yield (3.5 g.). The crude compound, m.p. 183–185° was purified by further chromatography on washed alumina (100 g.), elution with hexane-benzene 1:1 and crystallization from ether: Fine needles m.p. 197–198°, $[\alpha]_D$ −34.4°, ν_{max} 3600, 1740, 1720, 1255 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59; O, 19.02%. Found: C 71.02; H, 9.41; O, 19.28%.

Experiments in which methylmagnesium bromide was used instead of the corresponding iodide led essentially to the same results.

6β,16α-Dimethylpregnane-3β,5α,17α-triol-20-one (VIIIb). Chromatographically pure 6β,16α-dimethylpregnane-3β,5α, 17α-triol-20-one 3-monoacetate (3 g., m.p. 197–198°) was hydrolized by heating under reflux for 1 hr. with 1% methanolic potassium hydroxide (200 cc.). The solution was then neutralized with acetic acid and extracted with ethyl acetate. The crude triol (VIIIb) thus obtained (2.4 g.) in 89% yield had m.p. 230–235,° $[\alpha]_D$ −17° (dioxane), ν_{max} 3500, 1710 cm.$^{-1}$. Four crystallizations from acetone raised the melting point to 246–247°. After drying under vacuum the analytical sample showed m.p. 260–270° dec.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12; O, 16.91%. Found: C, 72.68; H, 9.93; O, 16.84%.

6β,16α-Dimethylpregnane-5α,17α-diol-3,20-dione (VIIIc). The free triol VIIIb (0.86 g. m.p. 240–247°) dissolved in acetone (200 cc.) was oxidized by titration with 8*N* chromic acid[13] at 5°. Addition of water and extraction with ethyl acetate afforded a crystalline residue (0.65 g.) with m.p. 236–240°. The crude ketone was purified by crystallization from acetone-ether to provide pure 6β,16α-dimethylpregnane-5α,17α-diol-3,20-dione (VIIIc) m.p. 250–251°, $[\alpha]_D$ −26.7° ν_{max} 3680, 3500, 1710, 1690 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00%. Found: C, 73.51; H, 9.38; O, 17.10%.

6β,16α-Dimethyl-17α-hydroxyprogesterone (IXa). Dehydration of 6β,16α-dimethylpregnane-5α,17α-diol-3,20-dione (VIIIc) (0.6 g., m.p. 236–240°) by boiling for 2 hr. with 0.25% potassium hydroxide in methanol (200 cc.) under nitrogen, followed by addition of water and extraction with ethyl acetate gave a mixture m.p. 160–170°, $[\alpha]_D$ +34° which was separated by chromatography on washed alumina (40 g.). Elution with benzene and with benzene-ether 9:1 afforded *6α,16α-dimethyl-17α-hydroxyprogesterone* (IXb) in 61% yield (350 mg.), m.p. 198–200°. Crystallized from ethyl acetate–ether it gave a pure sample with m.p. 203–204°, $[\alpha]_D$ +51°, λ_{max} 240–242 mμ, log ε 4.22. Elution with benzene-ether 4:1 afforded an isomer with m.p. 217–218° in 31% yield (178 mg.). This isomer, probably *6β,16α-dimethyl-17α-hydroxyprogesterone* (IXa) was recrystallized from ethyl acetate–ether several times to give material with m.p. 219–221°, $[\alpha]_D$ + 4.7°, λ_{max} 240–242 mμ, log ε 4.18, ν_{max} 3600, 1710, 1660, 1600 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39%. Found: C, 77.25; H, 9.39; O, 13.45%.

6α,16α-Dimethyl-17α-hydroxyprogesterone (IXb). Dehydration of 6β,16α-dimethylpregnane-5α,17α-diol-3,20-dione, VIIIc (0.8 g. m.p. 220–225°) with concentrated hydrochloric acid (6 cc.) was effected in acetic acid (30 cc.) at room temperature for 20 hr. Following addition of water and extraction with ethyl acetate the extracts were washed with sodium bicarbonate and gave after evaporation a crude residue (0.64 g.) with m.p. 185–190° in 84% yield. This material proved to be homogeneous since chromatography on neutral alumina (40 g.) afforded exclusively 6α,16α-dimethyl-17α-hydroxyprogesterone (IXb), m.p. 200–202°, $[\alpha]_D$ + 51.4°, λ_{max} 240–242 mμ, log ε 4.22. ν_{max} 3660, 1725, 1675, 1625 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39%. Found: C, 76.95; H, 9.46; O, 13.17%.

6α,16α-Dimethyl-17α-acetoxyprogesterone (IXc). The free compound, 6α,16α-dimethyl-17α-hydroxyprogesterone, IXb (0.6 g.) was acetylated with acetic anhydride (20 cc.) and *p*-toluenesulfonic acid (200 mg.) at room temperature for 65 hr. During this time the solution developed a pink color which later turned to brown. Addition of water and extraction with ethyl acetate followed by washing with sodium bicarbonate and evaporation gave a crude residue of the 3-enol acetate 17-acetate which had m.p. 197–200°, $[\alpha]_D$ −160°, λ_{max} 244 mμ, log ε 4.27 and ν_{max} 1755, 1738, 1715, 1250, 1210 cm.$^{-1}$ The enol acetate was converted into the Δ^4-3-ketone by refluxing for 1 hr. with aqueous hydrochloric acid (0.5 cc., concd.) in methanol (50 cc.). Water was then added and the mixture was extracted with ethyl acetate. After evaporation, the amorphous residue was chromatographed on washed alumina (30 g.) whence elution with hexane-benzene 2:1 gave crude 6α,16α-dimethyl-17α-acetoxyprogesterone, IXc, (200 mg.) with m.p. 166–167° which was purified by crystallization from ether-hexane: m.p. 170–172°, $[\alpha]_D$ +71.1°, λ_{max} 240 mμ, log ε 4.14, ν_{max} 1740, 1710, 1670, 1250 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06; O, 15.98%. Found: C, 74.46; H, 8.87; O, 16.44%.

6α,16α-Dimethyl-4-pregnene-17α,21-diol-3,20-dione 21-monoacetate (6α,16α-dimethyl-"compound S" acetate (XIa).

A. By direct 21-acetoxylation of 6α,16α-dimethyl-17α-hydroxyprogesterone (IXb). A mixture of 6α,16α-dimethyl-17α-hydroxyprogesterone (1 g.), methanol (4.5 cc.), tetrahydrofuran (7.5 cc. of peroxide containing solvent, 1 cc. equivalent to 10 mg. of iodine), iodine (1.5 g.), and calcium oxide (1.5 g.) was stirred for 3 hr. at room temperature. It was then poured into cold water containing sodium thiosulfate (0.5 g.), extracted with methylene chloride and washed with sodium thiosulfate and water. The solvent was removed under vacuum at 20° and it was noted that the solution became gradually violet. The residue was dissolved immediately in anhydrous acetone (500 cc.), anhydrous potassium acetate (5 g.) was added and the suspension was refluxed for 20 hr. Addition of water and extraction with ethyl acetate gave a crystalline residue showing a positive α-ketol reaction with triphenyltetrazolium chloride. Chromatography of this residue on silica-gel afforded in the benzene-ether 2:1 eluates crystalline 6α,16α-dimethyl-"Compound S" 21-acetate (700 mg.), m.p. 188–190° in 60% yield. Two crystallizations from acetone–ether gave material with m.p. 191–192°, $[\alpha]_D$ +102.5°, λ_{max} 240–242 mμ, log ε 4.23, ν_{max} 3400, 1750, 1720, 1640, 1590, 1230 cm.$^{-1}$. This compound was found to be identical in all respects (mixed melting point and infrared comparisons) with 6α,16α-dimethyl "S" 21-acetate prepared as described below in B.

B. By dehydration of 6β,16α-dimethylpregnane-5α,17α,21-triol-3,20-dione (Xb) *with acid.* The saturated ketone Xb (50 mg. m.p. 212–213°, $[\alpha]_D$ +8°) dissolved in acetic acid (20 cc.) was treated with aqueous concentrated hydrochloric acid (3 drops) at room temperature for 20 hr. Water was then added and the compound was extracted with ethyl acetate. The solution was washed with sodium bicarbonate and, after evaporation, the residue was chromatographed on silica-gel. Elution with benzene-ether 2:1 furnished crystals with m.p. 183–185° and after purifying by crystallization from acetone–ether, 6α,16α-dimethyl "S" 21-acetate was obtained: m.p. 190–192°, $[\alpha]_D$ +90°, λ_{max} 242 mμ, log ε 4.20, ν_{max} 3400, 1750, 1720, 1640, 1590, 1230 cm.$^{-1}$

It gave a positive α-ketol reaction with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71%. Found: C, 71.98; H, 8.88%.

6β,16α-Dimethylpregnane-3β,5α,17α,21-tetrol-20-one 21-monoacetate (Xa). Monobromination of 6β,16α-dimethylpregnane-3β,5α,17α-triol-20-one (VIIIb) (2.6 g., 0.0069 mole) in anhydrous dioxane (100 cc.) was carried out at room temperature with a 1.28*N* solution of bromine in dioxane (10.8 cc. molar ratio 1:1). The bromo compound was precipitated with water as an oil and the water was decanted. Crystallization of an aliquot from methanol-water gave needles with m.p. 120–125° dec., $[\alpha]_D$ −8°, −11°. The total crude bromo compound was dissolved in anhydrous acetone (400 cc.), sodium iodide (5 g.) was added and the suspension refluxed for 2 hr. Anhydrous potassium acetate (10 g.) was then added and heating was continued for 20 hr. more. Addition of water and extraction with ethyl acetate gave an amorphous residue. Chromatography of this residue on silica gel (150 g.) and elution with ether afforded silky fine needles (0.43 g.), m.p. 100–110° which were crystallized from ether to give pure 6β,16α-dimethylpregnane-3β,5α,17α,21-tetrol-20-one 21-monoacetate, m.p. 115–116° $[\alpha]_D$ −8.5°, ν_{max} 3350, 1745, 1720, 1230 cm.$^{-1}$ There was a positive reaction with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24; O, 21.99. Found: C, 68.62; H, 8.97; O, 22.59. Yield: 14% in pure material.

6β,16α-Dimethylpregnane-5α,17α,21-triol-3,20-dione 21-monoacetate (Xb). Oxidation of 6β,16α-dimethylpregnane-3β,5α,17α,21-tetrol 21-monoacetate (Xa) (150 mg., m.p. 115–116°) was effected at 5° in acetone (40 cc.) solution by careful titration with 8*N* chromic acid.[13] Extraction with ethyl acetate followed by washing and evaporation gave crude material with m.p. 207–210° which after three crystallizations from acetone-ether furnished the pure-3-ketone (50 mg.) as needles with m.p. 211–213°, $[\alpha]_D$ +12°, ν_{max} 3600, 1750, 1725, 1710, 1245 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81; O, 22.10. Found: C, 69.38; H, 8.94; O, 21.53.

Purification of the mother liquors by chromatography on silica gel provided additional material (25 mg.) which was eluted with benzene-ether 1:1 and showed m.p. 205–210°, $[\alpha]_D$ +8°. Crystallization of this material from acetone-ether gave needles with m.p. 211–213°.

6α,16α-Dimethyl-4-pregnene-17α-21-diol-3,20-dione (6α,16α-dimethyl "compound S" (XIb). The free compound XIb was prepared by hydrolysis, at room temperature for 20 hr., of the 21-acetate XIa (40 mg.) dissolved in methanol-tetra-

hydrofuran (1:1, 50 cc.) containing potassium bicarbonate (200 mg. in 5 cc. of water). Water was then added (50 cc.) and the solution was neutralized with acetic acid. Free 6α, 16α-dimethyl-"S" crystallized slowly overnight (23 mg.) from the aqueous solution as needles with m.p. 181–183°, $[\alpha]_D$ +84°, λ_{max} 240–242 mμ, log ε 4.19, ν_{max} 3550, 1715, 1660, 1610 cm.$^{-1}$ Extraction of the mother liquors with ethyl acetate furnished additional material. Total yield 78%. The analytical specimen was prepared by recrystallization from acetone-ether, m.p. 185–187°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15%. Found: C, 74.29; H, 9.39%.

6α,16α-Dimethyl-4-pregnene-11β,17α,21-triol-3,20-dione (6α,16α-dimethyl- "hydrocortisone") (XIc). Incubation of free 6α,16α-dimethyl "Compound "S" (350 mg.) with fresh bovine adrenal glands[20] followed by extraction of the breis with acetone, concentration of the aqueous acetone solution *in vacuo*, extraction of the aqueous residue with methylene chloride, and removal of the solvent, provided a residue. This material was chromatographed directly, without previous removal of the fats, on silica gel (400 g.). The eluates obtained with ethyl acetate afforded 6α,16α-dimethylhydrocortisone as crystals purified from acetone-ether (80 mg.) m.p. 235–237°, $[\alpha]_D$ +98.4°, λ_{max} 242 mμ, log ε 4.15, ν_{max} 3500, 1720, 1660, 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.48. Found: C, 71.09; 71.27; H, 8.87, 8.96; O, 20.18, 20.19. Yield 22% in purified material.

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Thermal Decomposition and Electrophilic Arylations with Aryldiazonium Tetrachloroborates and Tetrabromoborates. Remarks on the Mechanism of the Schiemann Reaction

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Thermal decomposition of aryldiazonium tetrachloroborates to aryl chlorides, boron trichloride, and nitrogen proceeds similarly to the Schiemann reaction of aryldiazonium tetrafluoroborates. Under similar conditions, aryldiazonium tetrabromoborates yield aryl bromides. Ring arylation was observed when the reactions were carried out in the presence of aromatic hydrocarbons. Quantitative investigation of the isomers formed in the case of arylation of fluorobenzene is in accordance with an electrophilic substitution mechanism. An ionic mechanism based on the experimental data for the thermal decomposition of all aryldiazonium tetrahaloborates investigated is suggested.

In 1927[1] Balz and Schiemann reported the thermal decomposition of aryldiazonium tetrafluoroborates to give aryl fluorides

$$ArN_2^+ BF_4^- \longrightarrow ArF + N_2 + BF_3$$

The Schiemann reaction has since gained widespread application for the preparation of aromatic fluorine compounds.[2] The mechanism of the Schiemann reaction has been investigated in some detail but only tentative mechanisms involving either a radical or ionic type reaction have been suggested.[2] Nesmeianov and his co-workers[3] investigated the decomposition reaction of aryldiazonium tetrafluoroborates in nitrobenzene and found that *m*-nitrobiphenyl was formed in the reaction in addition to fluorobenzene. They concluded that an ionic type of decomposition reaction involving the $C_6H_5^+$ ion takes place. Phenyldiazonium chloride under similar conditions gave a mixture of *o*-, *m*- and *p*-dinitrodiphenyl pointing, in this case, to a radical type phenylation reaction.

The preparation of aryldiazonium tetrachloroborates and tetrabromoborates[4] now makes it possible to investigate the thermal decomposition and arylation reactions of these new stable diazonium salts.

The solid aryldiazonium tetrachloroborates when heated above their decomposition point (with obvious care to exclude moisture) decompose very vigorously (sometimes explosively) with strong boron trichloride evolution. The thermal decomposition reaction can be carried out, however, under controlled conditions when the diazonium salt is heated in the presence of an inert diluent, such as a higher boiling aliphatic hydrocarbon. Under these conditions a smooth decomposition to aryl chlorides, nitrogen, and boron trichloride takes place.

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