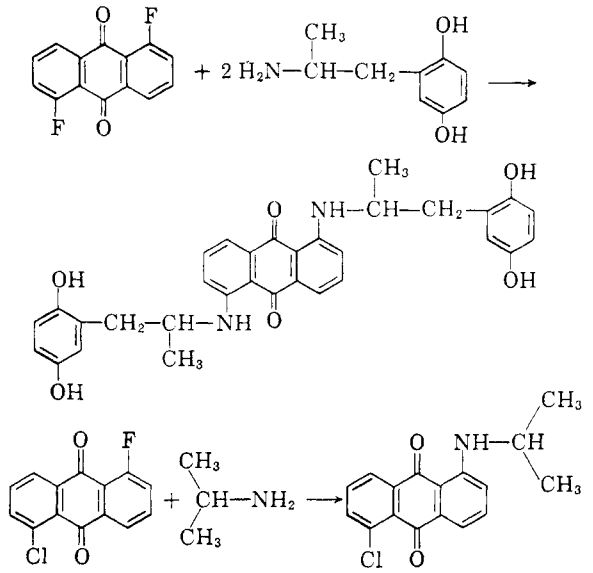
we have found that α-fluoroanthraquinones react with aliphatic amines under extremely mild conditions to give the corresponding aminoanthraquinones. This reactivity is particularly useful where the amine involved is heat-sensitive, or where the reactive α-nitroanthraquinones cannot be used because of redox reactions with substituents on the amine. Both of these conditions are successfully met in our preparation of 1,5-bis[β-(2′,5′-dihydroxyphenyl)α-methylethylamino] anthraquinone.



The selective replacement of fluorine in 1-chloro-5-fluoroanthraquinone[1] illustrates the difference in reactivity between the two halogens in these positions. Chlorine replacement does not occur to any appreciable extent below 100°.

EXPERIMENTAL

1,5-Bis(2′,5′-dihydroxyphenylisopropylamino)anthraquinone. A de-aerated mixture of 12.4 g. of 2-(2′-aminopropyl)-1,4-dihydroxybenzene hydrobromide (0.05*M*), 2.65 g. of anhydrous sodium carbonate (0.025*M*), and 50 ml. of pyridine was warmed until carbon dioxide evolution ceased. To this was added 1.3 g. (0.0053*M*) of 1,5-difluoroanthraquinone[2] and the mixture was stirred and heated on the steam bath for 4.5 hr. Most of the pyridine was blown off with nitrogen, then the reaction was quenched in 150 ml. of 3*N* hydrochloric acid. The precipitate was filtered, washed with warm water, and refiltered. Yield of magenta solid, m.p. 218–225°, λ = 526, 552, ε = 13,200, 11,800 (Methyl Cellosolve) was 2.3 g. (64.5%).

Anal. Calcd. for $C_{32}H_{30}N_2O_6$: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.98; H, 5.50; N, 5.27.

1-Chloro-5-isopropylaminoanthraquinone. A mixture of 0.4 g. of 1-chloro-5-fluoroanthraquinone and 20 ml. of isopropylamine was stirred at room temperature overnight. Excess amine was evaporated in vacuum, and the residual red solid was crystallized from 30 ml. of ethanol to give 0.3 g. of red needles, m.p. 138–139° (56%).

(1) Prepared from 1-chloro-5-aminoanthraquinone *via* the Schiemann reaction, yellow crystals m.p. 201–203°, from ligroin.

(2) French Patent 1,250,130.

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: Cl, 11.8; N, 4.7. Found: Cl, 12.3; N, 4.7.

RESEARCH DIVISION
POLAROID CORP.
CAMBRIDGE 39, MASS.

16-Hydroxylated Steroids. XXIII.[1] 21-Chloro-16α-hydroxycorticoids and Their 16α, 17α-Acetonides

SEYMOUR BERNSTEIN, ROBERT B. BROWNFIELD, ROBERT H. LENHARD, SIDNEY MAUER, AND IRA RINGLER

Received August 31, 1961

In this note we wish to record some observations regarding the effect of 16α,17α-acetonide formation on the biological activities of 21-chloro-16α-hydroxycorticoids.

It has been reported by the Squibb group[2] that 21-chloro-9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione in a liver glycogen assay was inactive at a dose level ten times the minimum effective dose of cortisone acetate. This was surprising in view of their observation that the activities of 21-fluorocorticoids lie between those of the corresponding 21-hydroxy and 21-deoxy derivatives. We have found that both 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione[3] (II) and 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (V) are inactive in a thymus involution assay at 30 times the minimum effective dose of hydrocortisone. However, the acetonides (VII, IX) of both 21-chloro-16α-hydroxy compounds were found to be highly active.[4] In Table I are given the biological activities of the 21-chloro compounds, along with those for 9α-fluoro-16α-hydroxyhydrocortisone (I) and triamcinolone (III) which have been included for comparative purposes.

The 21-chloro analog (VII) of 9α-fluoro-16α-hydroxyhydrocortisone acetonide apparently possesses a thymolytic activity which surpasses that of the parent 21-hydroxyacetonide (VI). It was also of interest to find that the 21-chloro-Δ^4-acetonide VII has a higher activity than the corresponding 21-chloro-$\Delta^{1,4}$-acetonide IX.

(1) Paper XXII, M. Heller, S. M. Stolar, and S. Bernstein, *J. Org. Chem.*, in process of publication.

(2) J. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956); J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

(3) S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **82**, 3680 (1960).

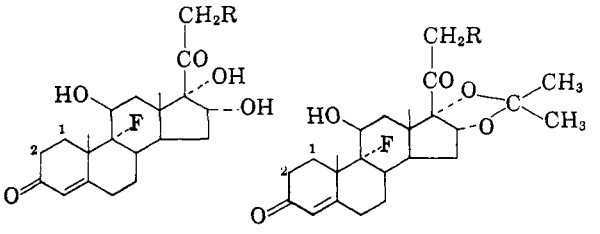
(4) A related finding has been reported by J. Fried (*Biological Activities of Steroids in Relation to Cancer*, ed. by G. Pincus and E. P. Vollmer, Chapt. 2, Academic Press, New York, 1960, page 9) with 12α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione with an activity of <0.1 × hydrocortisone whereas its acetonide had an activity of 10 × hydrocortisone.

TABLE I

BIOLOGICAL ACTIVITIES: THYMUS INVOLUTION ASSAY[a]

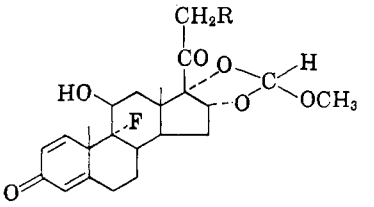
Compound	Free Steroid	Derivative: 21-Hydroxy-16,17-acetonide	Derivative: 21-Chloro-16,17-diol	Derivative: 21-Chloro-16,17-acetonide
9α-Fluoro-16α-hydroxyhydrocortisone	2	10	<0.1[b]	35
9α-Fluoro-16α-hydroxyprednisolone (triamcinolone)	4	27	<0.1[c]	5

[a] Activities are relative to hydrocortisone = 1. The assay was performed with intact immature female rats given a single subcutaneous injection of steroid suspended in a modified carboxymethylcellulose vehicle. Forty-eight hours after injection the rats were autopsied, at which time thymus and body weights were determined. [b] Inactive at a dose level of 6.4 mg. per rat. [c] Inactive both orally and subcutaneously at a dose level of 6.4 mg. per rat.



I. R = OH
II. R = Cl
III. Δ¹, R = OH
IV. Δ¹, R = OMs
V. Δ¹, R = Cl

VI. R = OH
VII. R = Cl
VIII. Δ¹, R = OH
IX. Δ¹, R = Cl



X. R = OH
XI. R = OMs

The 21-chloro compounds (II, V, VII, and IX) did not induce sodium retention in salt-loaded adrenalectomized rats. At a comparable dose level deoxycorticosterone induced a marked retention.

The 21-chloro-16α,17α-acetonides (VII and IX) were prepared in the usual manner from the corresponding 16α,17α-diols (II and V) with acetone and perchloric acid. 21-Chloro-9α-fluoro-11β,16α,-17α-trihydroxy-1,4-pregnadiene-3,20-dione (V) was prepared in the following manner. 9α-Fluoro-11β,21 - dihydroxy - 16α,17α - methoxymethylenedioxy-1,4-pregnadiene-3,20-dione (X)[5] in pyridine was treated with methanesulfonyl chloride to give the 16α,17α-methoxymethylenedioxy-21-mesylate XI. Reaction of the latter in methanol with dilute hydrochloric acid removed the orthoformate protective grouping to give the 21-mesylate IV. Treatment with lithium chloride in dimethylformamide gave the desired 21-chloro compound V.[6]

EXPERIMENTAL

Melting points. All melting points are uncorrected.

Absorption spectra. The ultraviolet absorption spectra were determined in methanol. The infrared absorption spectra are for pressed potassium bromide.

21-Chloro-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (VII). A mixture of 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-4-pregnene-3,20-dione (II, 0.5 g.) in acetone (25 ml.) containing perchloric acid (70–72%; 0.05 ml.) was stirred for 3 hr.; complete solution occurred after about 10 min. The product was isolated by extraction with ethyl acetate and purified by recrystallization from acetone–petroleum ether (b.p. 60–70°); m.p. 264–265° dec., λ_{max} 238 mμ (ε 16,400); ν_{max} 3425, 1725, 1660, 1620, and 860 cm.$^{-1}$; $[\alpha]_D^{25}$ + 155° (chloroform).

Anal. Calcd. for $C_{24}H_{32}O_5ClF$ (454.95): C, 63.36; H, 7.09; Cl, 7.79; F, 4.18. Found: C, 63.91, 63.79; H, 7.32, 7.37; Cl, 8.02; F, 4.27.

9α-Fluoro-11β-hydroxy-16α,17α-methoxymethylenedioxy-21-methanesulfonyloxy-1,4-pregnadiene-3,20-dione (XI). Methanesulfonyl chloride (3.31 g.) was added slowly and with stirring to a solution of 9α-fluoro-11β,21-dihydroxy-16α,17α - methoxymethylenedioxy - 1,4 - pregnadiene - 3,20-dione (X, 9.63 g.) in dry pyridine (100 ml.) cooled in an ice-water bath. The reaction mixture was stirred at ice-bath temperature for 1 hr. and then kept at −10° overnight when it was poured into ice water with stirring. The solid product was separated by filtration and was washed successively with water, dilute hydrochloric acid, and water. This afforded 11.03 g. of XI, m.p. 201.5–202.5° dec. An analytical sample was obtained by recrystallization from methanol; m.p. 202.5–203.5° dec., λ_{max} 238 mμ (ε 16,500); ν_{max} 3390, 1730, 1650, 1610, 1358, 1175, 1125, 1053, and 1000 cm.$^{-1}$; $[\alpha]_D^{25}$ + 114° (Methyl Cellosolve).

Anal. Calcd. for $C_{24}H_{31}O_9SF$ (514.58): C, 56.02; H, 6.07; S, 6.23; F, 3.69. Found: C, 56.21; H, 6.34; S, 6.30; F, 3.45.

9α-Fluoro-11β,16α,17α-trihydroxy-21-methanesulfonyloxy-1,4-pregnadiene-3,20-dione (IV). A mixture of 9α-fluoro-11β - hydroxy - 16α,17α - methoxymethylenedioxy - 21 - methanesulfonyloxy-1,4-pregnadiene-3,20-dione [XI, 10.3 g. (20 mmoles)], methanol (500 ml.), and dilute hydrochloric acid [20 ml. (56.8 meq.)] was heated under reflux with stirring for 40 minutes, during which time solid separated. It was then refrigerated (5°) overnight when the solid was collected by filtration and washed with methanol, 8.27 g., m.p. 198–199.5° dec. Several recrystallizations from methanol afforded an analytical sample; m.p. 197–197.5° dec., λ_{max} 238 mμ (ε 15,100); ν_{max} 3450, 2940, 1732, 1660, 1620, 1342, 1172, 1133, 1087, 1070, and 1035 cm.$^{-1}$; $[\alpha]_D^{26}$ +55° (Methyl Cellosolve).

Anal. Calcd. for $C_{22}H_{29}O_8SF$ (472.54): C, 55.92; H, 6.19; S, 6.79; F, 4.02. Found: C, 55.62; H, 6.56; S, 6.93; F, 3.94.

21-Chloro-9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (V). A mixture of 9α-fluoro-11β,16α,17α-trihydroxy - 21 - methanesulfonyloxy - 1,4 - pregnadiene - 3,20-

(5) L. L. Smith and M. Marx, *J. Am. Chem. Soc.*, **82**, 4625 (1960).

(6) The preparation of this compound directly from triamcinolone by treatment with methanesulfonyl chloride in pyridine at room temperature (see ref. 3) was initially attempted. However, this procedure is markedly inferior to the one employed here wherein the reactive 16α-hydroxyl group is blocked by the orthoformate grouping.

dione (IV, 0.75 g.), lithium chloride (202 mg.), and dimethylformamide (30 ml.) was heated under reflux for 50 min., concentrated *in vacuo* to a small volume, and treated with water. The solid so obtained was separated by filtration and recrystallized from acetone–petroleum ether (b.p. 60–70°) and from isopropyl alcohol; wt. 278 mg., m.p. 261–263° dec. The sample for analysis was obtained by recrystallization from methanol which lowered the m.p. to 250–251° dec., λ_{max} 239 mμ (ε 15,300); ν_{max} 3330, 1739, 1678, 1627, and 1610 cm.$^{-1}$; $[\alpha]_D^{25}$ +83° (dioxane).

Anal. Calcd. for $C_{21}H_{26}O_5ClF$ (412.90); C, 61.09; H, 6.35; Cl, 8.59; F, 4.60. Found: C, 60.93; H, 6.62; Cl, 8.81; F, 4.90.

In other runs it was found that the reflux time may be successfully shortened to 8 minutes or that the reaction mixture may be simply stirred at room temperature for 45 min.

21-Chloro-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (IX). To a suspension of 21-chloro-9α-fluoro-11β,16α,17α-trihydroxy-1,4-pregnadiene-3,20-dione (V, 0.16 g.) in acetone (8 ml.) at room temperature was added 70% perchloric acid (2 drops), and the mixture was stirred for 1 hr. when 0.5 ml. of 5% sodium bicarbonate solution was added. The mixture was diluted with 5 ml. of water and cooled. The solid was collected by filtration, washed with methanol, and air-dried to give 147 mg. of IX, m.p. 297° dec. Recrystallization from aqueous dimethylformamide afforded the sample for analysis, m.p. 297–299° dec., λ_{max} 238 mμ (ε 16,100); ν_{max} 3340, 1740, 1666, 1623, 1607, and 857 cm.$^{-1}$; $[\alpha]_D^{25}$ +139° (dimethylformamide).

Anal. Calcd. for $C_{24}H_{30}O_5ClF$ (452.96): C, 63.64; H, 6.68; Cl, 7.83; F, 4.19. Found: C, 63.32; H, 6.90; Cl, 7.58; F, 4.10.

Acknowledgment. The elemental analyses were done by Mr. Louis M. Brancone and associates. Infrared and ultraviolet absorption spectra and optical rotations were done by Mr. William Fulmor and associates. Biological testing was done by Miss E. Heyder.

ORGANIC CHEMICAL AND EXPERIMENTAL THERAPEUTICS RESEARCH SECTIONS
AND PHARMACEUTICAL PRODUCT DEVELOPMENT SECTION
LEDERLE LABORATORIES
A DIVISION OF AMERICAN CYANAMID CO.
PEARL RIVER, N. Y.

Addition of Grignard Reagents to Hindered *N*-Sulfinylamines[1]

WALTER T. SMITH, JR., POO AN THIO, AND MICHAEL GRASLEY

Received August 31, 1961

The addition of a Grignard reagent to several *N*-sulfinylamines has been found to give good yields of sulfinamides.[2–4] Klamann, Sass, and Zelenka[4] used both aliphatic and aromatic *N*-sulfinylamines, with both aliphatic and aromatic Grignard reagents. Their yields ranged from 40 to 88%. Since sulfinamides are easily hydrolyzed in either acidic or basic solutions, the conditions for the hydrolysis of the intermediate Grignard complex are very critical. These investigators surveyed the usual reagents for this hydrolysis and determined that a dilute ammonium chloride solution was the most favorable. The low yield listed above was for the reaction of *N*-sulfinyl-*n*-butylamine with phenylmagnesium bromide when the intermediate Grignard complex was hydrolyzed under unfavorable conditions. When dilute (10%) ammonium chloride was used for hydrolysis of the intermediate, the yield was 85% for the same reaction.

In none of the previous work was a hindered *N*-sulfinylamine used. To what extent the addition of a Grignard reagent to an *N*-sulfinylamine is subject to steric influences is of considerable interest for the information it might provide about the structure of the —NSO group and about the nature of the Grignard addition.

We have studied the reaction of phenylmagnesium bromide with two *N*-sulfinylamines, each of which may be considered to possess a certain amount of hindrance around the functional group. These sulfinylamines are *N*-sulfinylmesidine and *N*-sulfinyl-*t*-butylamine. The ultraviolet spectrum of 2,6-dimethyl-*N*-sulfinylaniline indicates that two *ortho* methyl groups force the —NSO group out of the plane of the benzene ring as a result of considerable interference of the *ortho* methyl groups with the —NSO group.[5]

It would be expected that the above situation also exists with *N*-sulfinylmesidine and that this compound provides a good example of a hindered *N*-sulfinylamine. However, we have found that a 71% yield of the expected sulfinamide can be obtained from phenylmagnesium bromide and *N*-sulfinylmesidine. This result indicates that there is essentially no inhibition of the Grignard addition and therefore none of the addition of the Grignard reagent takes place at the nitrogen-sulfur bond. This confirms the earlier work of Gilman and Morris.[3]

The reaction of phenylmagnesium bromide with *N*-sulfinyl-*t*-butylamine gave the sulfinamide in a yield of only 7% under reaction conditions which give high yields (72–92%) of sulfinamides from unhindered aliphatic *N*-sulfinylamines.[6] These reactions were carefully worked up using the optimum conditions worked out by Klamann, Sass, and Zelenka.[4] Hence, the low yield cannot be ascribed to decomposition during the isolation procedure.

EXPERIMENTAL

N-Mesitylbenzenesulfinamide. Phenylmagnesium bromide was prepared according to Fieser[7] from 4 g. (0.164 g.-atom)

(1) This research was supported in part by the Directorate of Chemical Sciences, Air Force Office of Scientific Research.

(2) A. Sonn and E. Schmidt, *Ber.*, **57**, 1355 (1924).

(3) H. Gilman and H. Morris, *J. Am. Chem. Soc.*, **48**, 2399 (1926).

(4) D. Klamann, C. Sass, and M. Zelenka, *Ber.*, **92**, 1910 (1959).

(5) W. T. Smith, Jr., D. Trimnell, and L. D. Grinninger, *J. Org. Chem.*, **24**, 664 (1959).

(6) M. Grasley, M.S. thesis, University of Kentucky, 1960.