trifluoro-3,5-dinitrotoluene in the distillate. The deep yellow residue from the steam distillation was recrystallized from methanol to give 12 g. (50%) of α,α,α-trichloro-3,5-dinitrotoluene, m.p. 76.5–77.5°.

Anal. Calcd. for $C_7H_3Cl_3N_2O_4$: Cl, 37.26. Found: Cl, 37.08.

α,α,α-Trichloro-3-chloro-5-nitrotoluene. A mixture of α,α,α-trifluoro-3-chloro-5-nitrotoluene (7.5 g., 0.033 mole) and acetyl chloride (10 g., 0.128 mole) was stirred gently while anhydrous aluminum chloride (5 g., 0.038 mole) was added slowly in small portions. The mixture was heated to 70° and stirring was continued until the mixture became a viscous mass. The mixture was treated with water and extracted with ether. Evaporation of the dried ether gave a residue which was distilled through a 6-in. helices-packed column to give 2 g. of unchanged starting material, b.p. 96–97° (10 mm.) and 4.5 g. (50%) of α,α,α-trichloro-3-chloro-5-nitrotoluene, b.p. 150–154° (3 mm.).

Anal. Calcd. for $C_7H_3Cl_4NO_2$: Cl, 51.58. Found: Cl, 51.55.

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Fluorosulfanilanilides

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Although 4′-fluorosulfanilanilide[1] is not a useful therapeutic agent, it was of interest to determine the effect on antibacterial activity of further substitution of fluorine. An increase in activity[2] due to increased amide acidity was expected. Condensation of 4-nitrobenzenesulfonyl chloride with eight fluoroanilines[3] in pyridine-acetone solution produced the fluorinated 4-nitrobenzenesulfonanilides listed in Table I; catalytic reduction of these intermediates gave the corresponding sulfanilanilides, Table II, in good yield.

Greater activity[4] against Gram-positive organisms *in vitro* was shown by 2′,4′- and 3′,5′-difluorosulfanilanilide than by the monofluoro analogs or sulfanilanilide itself. This increase in activity compared with the parent anilide or the monofluoro compounds is accompanied by an increase in acidity. Thus, 2′,4′- and 3′,5′-difluorosulfanilanilides in 30% aqueous acetone have pK_a values of 8.5 and 8.1, respectively, compared with 9.6 for sulfanilanilide (*cf.* 2-sulfanilamidopyridine, 8.4, and 2-sulfanilamidopyrimidine, 6.6, under the same conditions). However, no promising activity[5] *in vivo* was observed: the 2′, 4′- and 3′,5′-difluoro derivatives were only about one sixty-fourth as active as 2-sulfanilamidopyrimidine[6] against a lethal infection with *staphylococcus aureus*, strain Smith, in mice. The remaining compounds in Tables I and II were less active.

TABLE I

4-NITROBENZENESULFONANILIDES[a]

Compound	Yield, %	M.P. Corr.	Calcd., % / Found, % C	H	N	F
2′-F	78	163–165	48.7	3.1	—	6.4
			48.3	3.3	—	6.1
3′-F	65	131–132	48.6	3.1	9.5	6.4
			48.7	3.2	9.4	6.4
4′-F	97	182–183	48.6	3.1	—	6.4
			48.3	3.1	—	6.7
2′-CH_3-5′-F	26	147–148	50.3	3.5	—	6.1
			50.4	3.6	—	6.1
2′,4′-F_2	87	151–152	45.9	2.6	—	12.1
			46.2	2.5	—	12.6
2′,5′-F_2	98	139–140	45.9	2.6	8.9	12.1
			46.1	2.8	9.0	12.1
3′,5′-F_2	87	149–150	45.9	2.6	8.9	12.1
			46.1	2.9	9.0	12.0
3′-CF_3	58	148–149	45.1	2.6	—	16.5
			45.3	2.8	—	16.2

[a] The 4-nitrobenzenesulfonanilides were prepared by the condensation of *p*-nitrobenzenesulfonyl chloride with the corresponding fluoroaniline in pyridine-acetone solution by the procedure given for the preparation of 3′,5′-difluoro-4-nitrobenzenesulfonanilide. The 4-nitrobenzenesulfonanilides were dissolved as their sodium salts and precipitated with dilute acid; no further purification was necessary.

EXPERIMENTAL

3′,5′-Difluoro-4-nitrobenzenesulfonanilide. An exothermic reaction was observed on the addition of 48.7 g. (0.220 mole) of 4-nitrobenzenesulfonyl chloride to a solution of 25.8 g. (0.200 mole) of 3,5-difluoroaniline in 160 ml. of acetone and 32 ml. (0.40 mole) of reagent grade pyridine. After 10 min. the reaction was complete as indicated by arylamine analysis (Bratton-Marshall).[7] The solution was poured into 400 ml. of 0.6*N* hydrochloric acid, and a white precipitate was isolated. This material was dissolved in 200 ml. of 10% potassium hydroxide, and the orange solution then added to 400 ml. of 10% hydrochloric acid resulting in the isolation of 54.8 g. (87%) of white 3′,5′-difluoro-4-nitrobenzenesulfonanilide, m.p. 149–150° corr.

3′,5′-Difluorosulfanilanilide. A solution of 38.9 g. (0.124 mole) of 3′,5′-difluoro-4-nitrobenzenesulfonanilide in 150 ml. of acetone and 14.0 g. of Raney nickel in ethanol was shaken in a Parr hydrogenation apparatus under a pressure

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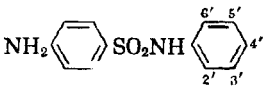
TABLE II

SULFANILANILIDES[a]



Compound	Yield, %	M.P. Corr.	Calcd., % / Found, % C	H	N	F
2'-F	92	190–191	54.1	4.2	10.5	7.1
			54.7	4.4	10.7	6.7
3'-F	98	167–168	54.1	4.2	10.5	7.1
			54.0	4.2	10.9	7.1
4'-F	89	162–163	—	—	—	—
2'-CH_3-5'-F	85	148–149	55.7	4.7	10.0	6.8
			55.9	5.0	10.1	7.0
2',4'-F_2	21	161–162	50.7	3.6	9.9	13.4
			51.1	3.8	10.1	12.6
2',5'-F_2	66	183–185	50.7	3.6	9.9	13.4
			50.9	3.6	10.1	13.7
3',5'-F_2	91	178–178.5	50.7	3.6	9.9	13.4
			50.8	3.8	9.9	12.7
3'-CF_3	55	115–117	49.4	3.5	8.9	18.0
			49.4	3.7	8.9	18.3

[a] The sulfanilanilides in Table II were prepared by the procedure used to reduce 3',5'-difluoro-4-nitrobenzenesulfonamide to the corresponding sulfanilanilide. These sulfanilanilides were crystallized analytically pure from the reduction solution, the melting point being unchanged by further purification.

of 45 p.s.i. of hydrogen. On termination of the reduction, the catalyst was removed, and the filtrate concentrated to obtain 31.9 g. (91%) of white crystalline 3',5'-difluorosulfanilanilide, m.p. 178–178.5° corr.

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The Synthesis of 9α-Hydroxy Steroids[1]

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This paper is concerned with the development of a chemical method for the introduction of a 9α-hydroxyl group into steroids.

One of the mechanisms of steroid degradation by microorganisms involves a 9α-hydroxylation reaction, followed by a 1,2-dehydrogenation (or *vice-versa*) with the formation of a 9,10-seco-steroid.[2,3] In order to study the enzymatic mechanism of the conversion of 9α-hydroxyandrostene-3,17-dione to 9,10-seco-3-hydroxy-1,3,5(10)-androstatriene-9,17-dione, a substantial quantity of 9α-hydroxyandrostene-3,17-dione was needed; it was solely for this reason that this work was undertaken.

The conventional method for the preparation of 9α-hydroxy steroids has been by microbiological methods. The yield of 9α-hydroxy steroids has been low in some cases and usually a number of other major hydroxylated products have been also produced to complicate the isolation processes.[4,5] In cases where the yield of 9α-hydroxy steroids have been relatively efficient.[3,6,7] The organisms used have not been available for general circulation and special equipment is needed for large scale fermentations.

4-Androstene-9α,11β-diol-3,17-dione,[8] 9α-hydroxycortisone acetate, 9α-hydroxyhydrocortisone acetate.[9,10] and 9α-hydroxyhydrocortisone[11] have been prepared by the acid catalysis of their corresponding 9β,11β-epoxides by chemical methods. However, 9α-hydroxy steroids devoid of oxygen functions at the 11- positions in these series have not been prepared to our knowledge. This method describes the synthesis of 9α-hydroxyandrostene-3,17-dione based on the reduction of its corresponding 9α,11α-epoxide with lithium aluminum hydride to the corresponding 9α-(axial) hydroxyl compound. 3β-Acetoxyergostan-9α-ol has been prepared by the reduction of 3β-acetoxy-9α,11α-epoxyergostane with lithium-ethylamine,[12] but apparently lithium aluminum hydride was unable to reduce this epoxide. The method herein described should also be applicable for the synthesis of other 9α-hydroxy steroids such as 9α-hydroxyprogesterone and 9α-hydroxycortexolone. The procedure developed is formulated as follows (I–VIII):

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