158.0°. The chloroform recrystallizations gave poor recovery and did not appreciably improve the melting point.

1-Phenol-4-sulfonamides. General Method. N-Ethyl-1-phenol-4-sulfonamide (50).—To 29.7 g. (0.1 mole) of the benzoate of 1-phenol-4-sulfonyl chloride[14] in 100 ml. of 3 *N* NaOH cooled in an ice bath was added dropwise 4.5 g. (0.1 mole) of ethylamine. The mixture was stirred in the ice bath for 1.25 hr., heated on the steam bath for 1.25 hr., cooled to 25°, and acidified with concentrated HCl. The mixture was extracted with a total of 80 ml. of ether, the organic solution was washed with three 20-ml. portions of 20% K_2CO_3, then 20 ml. of water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 18.8 g. of viscous, brown liquid. Recovered benzoic acid from the aqueous wash liquids amounted to only a 71% yield, indicating some aminolysis of the ester linkage. The crude product was dissolved in 25 ml. of 3 *N* NaOH, and the solution was extracted with ether, yielding 2.2 g. of N-ethylbenzamide in the ether layer. The aqueous layer was acidified and extracted with ether. Evaporation of the solvent gave 14.5 g. of light brown liquid which slowly crystallized, m.p. 98°. Recrystallization from toluene–ethyl acetate gave 9.7 g. (48%) of white crystals with m.p. 105.0–106.5°.

Use of Excess Amine. N-Methyl-1-phenol-4-sulfonamide (49).—To approximately 75 ml. of methylamine at −75° was added slowly and in small portions the benzoate of 1-phenol-4-sulfonyl chloride[14] (29.7 g., 0.1 mole), followed by 100 ml. of ether. Stirring was continued at −75° for 0.5 hr., then at −1° (reflux) for 2.5 hr. Solvent and excess amine were distilled on the steam bath, 100 ml. of water was added to the residue, and the mixture was acidified with concentrated HCl and extracted with ether. The ethereal solution was washed with two 15-ml. portions of water and dried ($MgSO_4$), and the solvent was evaporated to give 27.9 g. of viscous, brown liquid. Addition of 3 *N* NaOH to the liquid precipitated crystals of N-methylbenzamide, m.p. 78.5–79.5° (8.8 g., 65%). Reacidification of the basic filtrate gave a paste, which was dried on a clay plate to give 5.2 g. of white crystals with m.p. 80–81.5°. Recrystallization from benzene–ethyl acetate gave 4.3 g. (23%) of product with m.p. 91.5–92.0°. This material is reported[15] to have m.p. 81–82°.

***p*-(Isopropylsulfamoyl)phenyl 1-Phenol-4-sulfonate (55).**—Isopropylamine (82.9 g., 1.4 moles) was added over a 5-min. period to a stirred slurry of the benzoate of 1-phenol-4-sulfonyl chloride[14] (416 g., 1.4 moles) in 1.4 l. of 3 *N* NaOH at 17°. The temperature was allowed to rise to 40° during 30 min. and maintained at 35–40° during an additional 30 min. The mixture was heated on the steam bath for 45 min., treated twice with activated carbon, and concentrated to two-thirds volume. The mixture was heated to 40°, sufficient water was added to effect homogeneous solution, and the solution was cooled to 10°. The crude sodium derivative of N-isopropyl-1-phenol-4-sulfonamide was filtered off, and the filtrate was acidified with concentrated HCl. The resulting precipitate was taken up in 300 ml. of ether, the ethereal solution was washed with 800 ml. of 20% $KHCO_3$, then with two 100-ml. portions of bicarbonate solution and 100 ml. of water, and the solvent was removed under reduced pressure. The solids were reprecipitated from 10% NaOH with HCl and recrystallized once from aqueous ethanol and three times from 6 *N* acetic acid to give 9.7 g. (3.7%) of white crystals with m.p. 164–165.5°.

Acknowledgment.—We wish to thank Dr. G. Rohrbacher, of these laboratories, and Dr. R. Hewitt, of Lederle Laboratories, for the determination of the biological data.

(14) (a) S. Magnusson, J. E. Christian, and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **36**, 257 (1947); (b) M. Schreinemakers, *Rec. trav. chim.*, **16**, 422 (1897).

(15) W. Steinkopf, *J. prakt. Chem.*, [2] **117**, 58 (1927).

Notes

Spiro-3-oxiranyl-5α-androstan-17β-ols

H. G. LEHMANN, O. ENGELFRIED, AND R. WIECHERT

Research Laboratories, Schering AG, Berlin, Germany

Received November 21, 1964

The publication of Wolff, Ho, and Kwok[1] describing the spiro-3β-oxiranyl formation from steroid 3-ketones of the allo series with dimethylsulfoxonium methylide prompts us to record our own results in this area.

After the introduction of the methylenation method by Corey and Chaykovsky[2] we have methylenated 5α-androstan-17β-ol-3-one (I) and in agreement with Wolff and co-workers[1] a spiro-3-oxiranyl-5α-androstan-17β-ol, m.p. 171–173° (uncor.), $[\alpha]_D$ +1.93° (*c* 0.94, $CHCl_3$), was obtained. These authors assume that the 3β-oxiranyl compound (II) with an equatorial epoxy oxygen is formed by attack of the reagent from the back side of the molecule. However, according to our results, the 3α-oxiran (III) is formed with sulfoxonium methylide from I. Our assignment is based on the lithium aluminum hydride reduction of III resulting in the formation of the 3β-methyl-5α-androstane-3α 17β-diol (IV).[3] On the other hand, we have obtained the 3β-oxiran (II), m.p. 190.5–191° (uncor.), $[\alpha]^{26}D$ + 28.8° (*c* 0.90, $CHCl_3$), from the 3-cyanohydrin *via* trimethyl(3β,17β-dihydroxy-5α-androstan-3α-ylmethyl) ammonium iodide (V) by pyrolysis of the free base. The lithium aluminum hydride reduction of II afforded 3α-methyl-5α-androstane-3β,17β-diol (VI).[3] Oxidation of the diols IV and VI led to the 17-ketones VII and VIII[3a] which on acetylation gave the corresponding 3-acetates (IX and X).

As expected, all 3β-oxygenated compounds possessed higher dipole moments[4] than their 3α-epimers (see Table I). The fact that the 3α-acetate IX showed

TABLE I

Compd.	μ calcd.	μ found
II	2.50	2.61 dioxane
III	2.33	2.24 dioxane
VII	3.32	3.55 benzene
		3.73 dioxane
VIII	2.26	2.75 dioxane

complex acetoxy bands in the 8-μ region of the infrared whereas the 3β-acetate X had a single band[5] confirms our assignment of the configuration at C-3. Neither epimeric spiro-3-oxirane showed anabolic or androgenic activity after subcutaneous application in rats in the Hershberg assay.

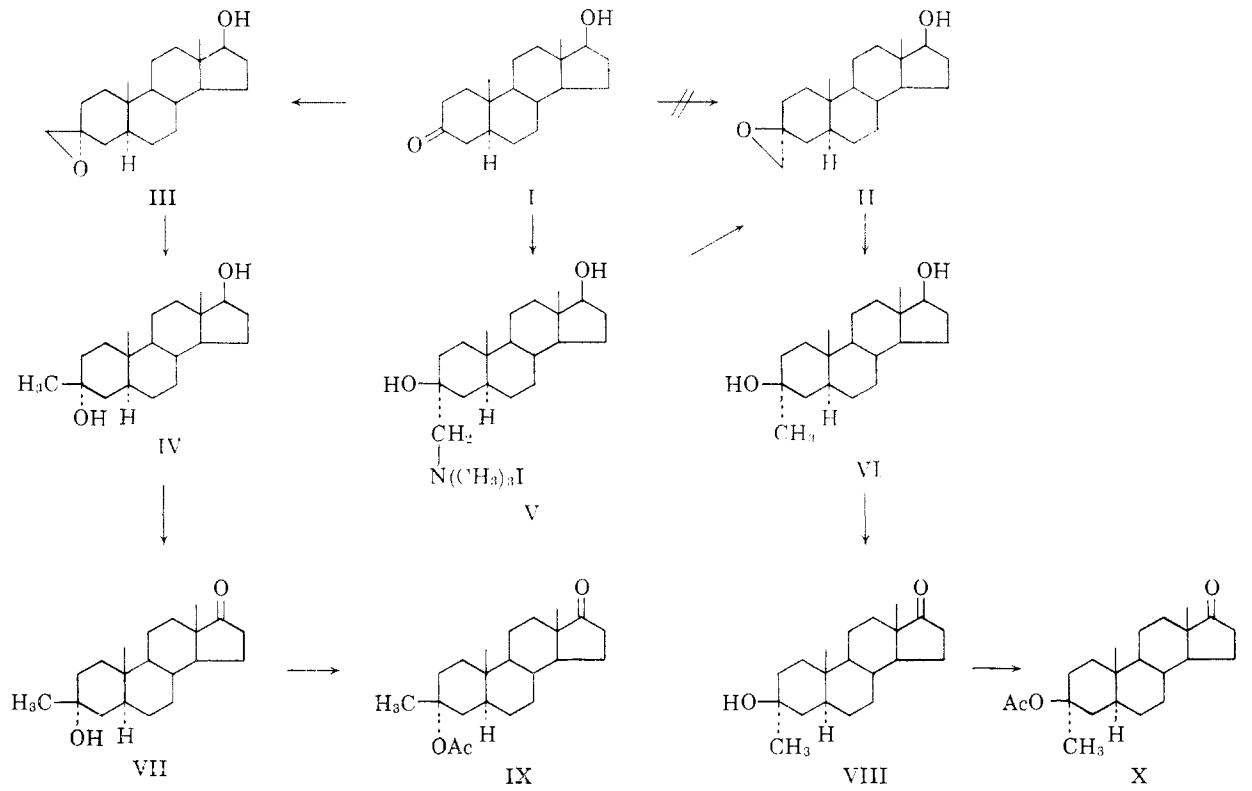
(1) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

(2) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

(3) (a) J. Kathol, Schering AG, German Patent 881,945 (April 7, 1951); *Chem. Zentr.*, 10329 (1955); (b) B. Pelc, *Collection Czech. Chem. Commun.*, **25**, 1624 (1960).

(4) For a description of the calculation and measurement of dipole moments, see W. Neudert and H. Röpke, "Steroid Atlas," Springer-Verlag, Berlin, 1965.

(5) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951); H. Rosenkrantz and P. Skogstrom, *ibid.*, **77**, 2237 (1955).



Experimental

All melting points were taken in the apparatus of Tottoli, unless otherwise stated, and are uncorrected.

Spiro-3β-oxiranyl-5α-androstan-17β-ol (II).—A solution of 4.92 g. of V in methanol was passed through a 50-ml. Amberlite IRA-400-OH resin column which had been washed free of alkali with water and methanol before use. The methanol eluate was dropped into a flask immersed in a bath at 100° and evaporated. Crystallization of the residue from methanol yielded 2.06 g. of II, m.p. 192.5–193°, $[\alpha]^{26}D$ +28.8° (*c* 0.9, $CHCl_3$), dipole moment 2.61 μ in dioxane (calcd. 2.58 μ). A second crop of 0.18 g. (total yield 73%), m.p. 190.5–191°, was obtained.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59; O, 10.51. Found: C, 78.70; H, 10.44; O, 10.70.

Spiro-3α-oxiranyl-5α-androstan-17β-ol (III).—This compound was prepared from 5α-androstan-17β-ol-3-one in the same way as described by Wolff, *et al.*[1]; m.p. 171–173°, $[\alpha]^{26}D$ +1.93° (*c* 0.93, $CHCl_3$), dipole moment 2.24 μ in dioxane (calcd. 2.30 μ).

3β-Methyl-5α-androstane-3α,17β-diol (IV).—Lithium aluminum hydride (450 mg.) was added to a refluxing solution of the spiro-3α-oxiran (III) (304 mg.) in anhydrous ether by extraction. The heating was continued for 2.5 hr. To decompose the excess hydride the cooled mixture was treated with ethyl acetate and with aqueous methanol. After filtration and washing of the inorganic residue with hot methanol, the extract was evaporated. IV (210 mg., 68%) was obtained, m.p. 165–166°. After recrystallization from ethyl acetate it melted at 167–167.5°, and was identical in all respects with a sample prepared from I with methylmagnesium bromide.[3]

N,N,N-Trimethyl-N-(3β,17β-dihydroxy-5α-androstan-3α-ylmethyl)ammonium Iodide (V).—3-Cyano-5α-androstane-3,-17β-diol, m.p. 176–178°, was prepared and hydrogenated according Goldberg and Kirchensteiner[6] to give 3-aminomethyl-5α-androstane-3,17β-diol, m.p. 220–221° (from methanol).

Anal. Calcd. for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36; O, 9.95. Found: C, 74.71; H, 11.04; N, 4.30; O, 10.16.

This amine (3.2 g.) was refluxed with a mixture of 30 ml. of anhydrous methanol and 6 ml. of methyl iodide under an atmosphere of nitrogen. A methanol solution of sodium methoxide, prepared from 440 mg. of sodium and 20 ml. of absolute methanol, was added within a 2-hr. period. Refluxing was continued for 1 hr. and after addition of 1 ml. of methyl iodide the reaction mixture was left at room temperature overnight. After evaporation, the residue was washed with a small amount of cold water. The yield of methiodide (V) was 2.71 g. (55%), m.p. 283–285° dec. For analysis it was recrystallized from methanol; the melting point remained unchanged.

Anal. Calcd. for $C_{23}H_{42}INO_2$: I, 25.82; N, 2.85. Found: I, 26.18; N, 2.86.

3α-Methyl-5α-androstane-3β,17β-diol (VI).—A 100-mg. sample of the spiro-3β-oxiran (II) was reduced with lithium aluminum hydride in the same manner as described for the epimer IV. A total of 38% of VI, m.p. 190.5–191.5°, was obtained after two recrystallizations from ethyl acetate, and VI was identical with an authentic sample.[3]

3β-Methyl-5α-androstan-3α-ol-17-one (VII).—The diol IV was oxidized with chromic acid[3a] to give the 17-ketone VII, m.p. 147–148°, $[\alpha]^{26}D$ +88.3° (*c* 1.0, $CHCl_3$), dipole moment 3.55 μ in benzene, 3.73 μ in dioxane (calcd. 3.32 μ).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.90; H, 10.56.

3α-Methyl-5α-androstan-3β-ol-17-one (VIII).—The diol VI was oxidized with chromic acid[3a] to give the 17-ketone VII, m.p. 185–186°, $[\alpha]^{25}D$ +96.6° (*c* 1.0, $CHCl_3$), dipole moment 2.75 μ in dioxane (calcd. 2.26 μ).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.00; H, 10.75.

3β-Methyl-5α-androstan-3α-ol-17-one Acetate (IX).—VII (0.5 g.) was refluxed in 4 ml. of pyridine and 1 ml. of acetic anhydride under nitrogen for 6 hr. The cooled mixture was poured into water, collected, and washed with water. A yield of 365 mg. of IX was obtained, m.p. 181–182° (Kofler apparatus) (from methanol and hexane), $[\alpha]^{19}D$ +88.6° (*c* 1.025, $CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.40; H, 10.00.

3α-Methyl-5α-androstan-3β-ol-17-one Acetate (X).—VIII (0.5 g.) was refluxed in 4 ml. of pyridine and 1 ml. of acetic anhydride under nitrogen for 9 hr. After the same work-up procedure as above, recrystallization from methanol and hexane yielded 480 mg. of X, m.p. 158–159° (Kofler apparatus), $[\alpha]^{19}D$ +86.4° (*c* 0.985, $CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.20; H, 10.10.

Acknowledgment.—The authors wish to thank Dr. W. Neudert for calculation and determination of dipole moments and Mr. J. Huber for microanalytical results.

(6) M. W. Goldberg and H. Kirchensteiner [*Helv. Chim. Acta*, **26**, 288 (1943)] describe the preparation of the cyanohydrin and its hydrogenation (for the 17-acetates).