A New Route to $\Delta^{1,3,5(10)}$-Estratriene-3-thiols and Related Compounds

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The availability of 19-norsteroids from 10-methyl steroids by the syntheses recently developed in several laboratories[1] prompted a reinvestigation of their conversion in ring A aromatic steroids. In pursuing our studies on the aromatization of β,γ-disubstituted 3-keto-19-norsteroids, we have devised a simple route to 3-thioestrogens.[2]

As previously reported,[3,4] 19-nor-3-ketones functionalized at either C-5 and C-10 or C-5 and C-6 undergo ready aromatization to phenolic steroid 3-ethers by treatment with acids in alcoholic solvents. The alkoxy moieties of the ethers originate from the medium. It could be reasonably assumed that the same reaction carried out in the presence of mercaptans would have given the corresponding sulfides.[5]

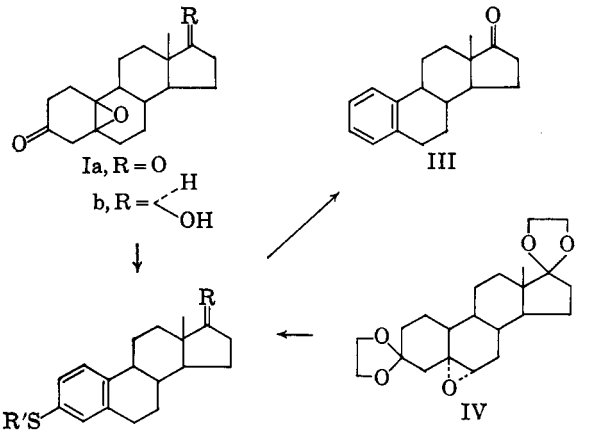
Actually, 5β,10β-oxido-19-norandrostane-3,17-dione (Ia),[3] refluxed in acetone with thiobenzyl alcohol and hydrochloric acid, gave 3-benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIa) in good yield. The product was easily identified by its elemental analysis, infrared spectrum, and ultraviolet spectrum which had a maximum at 258 mμ characteristic of an aromatic sulfide.[6] Finally, desulfurization of IIa with Raney nickel afforded $\Delta^{1,3,5(10)}$-estratrien-17-one (III).[7] Sulfide IIa was also obtained in a quite similar manner from 5α,6α-oxido-19-norandrostane-3,17-dione biscycloethylene ketal (IV).[8]

Treatment of Ia with ethylmercaptan or cyclopentylmercaptan in the presence of hydrochloric acid yielded ethylsulfide IIb or cyclopentylsulfide IIc, respectively, as expected.

Likewise, acid-catalyzed aromatization of 5β,10β-oxido-19-norandrostan-17β-ol-3-one (Ib)[9] in acetone–benzyl mercaptan gave 3-benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17β-ol (IId), which was also prepared by $NaBH_4$ reduction of IIa.

Benzyl sulfides IIa and IId appeared to be suitable intermediates for the preparation of free $\Delta^{1,3,5(10)}$-estratriene-3-thiols. Easy debenzylation of benzyl thioethers is well known, hydrogenolysis by metals in liquid ammonia being the procedure of choice.[10]

Accordingly, brief treatment of 3-benzylmercapto-



IIa, R = O; R′ = $C_6H_5CH_2$
b, R = O; R′ = CH_3CH_2
c, R = O; R′ = cyclopentyl
d, R = H, OH; R′ = $C_6H_5CH_2$
e, R = O; R′ = H
f, R = H, OH; R′ = H

$\Delta^{1,3,5(10)}$-estratrien-17-one (IIa) with sodium in liquid ammonia gave rise to a thiol promptly recognized as 3-mercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (3-thioestrone) (IIe) by its typical ultraviolet and infrared absorptions. A more prolonged treatment of IIa, as well as the reductive cleavage of benzyl thio ether IId, yielded 3-thioestradiol (IIf). The latter, also obtained by $NaBH_4$ reduction of IIe, was characterized as the disulfide, which proved to be identical with the product reported by Hecker.[2]

Experimental[11]

3-Benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIa). A.—A solution of 500 mg. of 5β,10β-oxido-19-norandrostane-3,17-dione (Ia)[3] in a mixture of 10 ml. of acetone and 4 ml. of benzyl mercaptan was treated with 2 drops of concentrated hydrochloric acid and refluxed for 1 hr. The mixture was then cooled and the acetone was removed under vacuum. The oily residue was treated with 50 ml. of 1 *N* sodium hydroxide and the mixture was extracted with ether. The ethereal extracts were washed with water and dried, and the solvent was removed to give a residue, which was chromatographed on alumina. Elution with ether afforded 425 mg. of 3-benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIa), m.p. 125–127°, which on recrystallization from methanol melted at 131–132°: $[\alpha]_D$ +117° ($CHCl_3$); λ_{max}^{EtOH} 258 mμ (ϵ 8700); ν_{max}^{Nujol} 1733, 1590, 1558, 1498 (shoulder), 1258, 1050, 808, 770, 715, and 691 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{28}OS$: C, 79.74; H, 7.49; S, 8.52. Found: C, 79.63; H, 7.46; S, 8.62.

B.—5α,6α-Oxido-19-norandrostane-3,17-dione biscycloethylene ketal (IV)[8] (500 mg.), treated with benzyl mercaptan according to the above procedure, yielded 360 mg. of IIa: m.p. 130–131°, $[\alpha]_D$ +117° ($CHCl_3$), λ_{max}^{EtOH} and ν_{max}^{Nujol} as reported above.

By reaction of 5β,10β-oxido-19-norandrostane-3,17-dione (Ia) with ethyl mercaptan and with cyclopentyl mercaptan, carried out according to the above described procedure, the following compounds were prepared.

3-Ethylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIb) had m.p. 93–94°; $[\alpha]_D$ +146° ($CHCl_3$); λ_{max}^{EtOH} 258 mμ (ϵ 8800); ν_{max}^{Nujol} 1736, 1593, 1556, 1498 (shoulder) 1256, 1049, 821, and 776 cm.$^{-1}$.

(1) (a) R. Gardi and C. Pedrali, *Gazz. chim. ital*, **91**, 129 (1961); **93**, 514 (1963); (b) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **84**, 1496 (1962); (c) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *ibid.*, **84**, 3204 (1962); (d) K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein,, *Experientia*, **18**, 464 (1962).

(2) Preparation of 3-thioestradiol from the corresponding 3-amine has been recently described by E. Hecker, *Ber.*, **95**, 977 (1962).

(3) R. Gardi, C. Pedrali, and A. Ercoli, *Gazz. chim. ital.*, **93**, 1503 (1963).

(4) R. Gardi and C. Pedrali, *Steroids*, **2**, 387 (1963).

(5) This was supported also by a consideration on the reaction mechanism, which very likely involves, as key steps, alcohol addition to protonated ketone and subsequent water removal.[3]

(6) *Cf.* E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949).

(7) E. Caspi, E. Cullen, and P. K. Grover, *J. Chem. Soc.*, 212 (1963).

(8) R. Gardi, C. Pedrali, and A. Ercoli, *Gazz. chim. ital.*, **93**, 525 (1963).

(9) J. P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(10) *Cf.* R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935); J. Baddilly and E. M. Thain, *J. Chem. Soc.*, 800 (1952); *cf.* also *Biochem. Prep.*, **5**, 93 (1957).

(11) Melting points are uncorrected. The ultraviolet spectra were determined on an Optica CF$_4$ spectrophotometer and the infrared spectra on a Perkin-Elmer Model 21 instrument. We are indebted to Dr. Sergio Cairoli for the microanalyses.

Anal. Calcd. for $C_{20}H_{26}OS$: C, 76.38; H, 8.33; S, 10.20. Found: C, 76.55; H, 8.38; S, 10.35.

3-Cyclopentylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIc) had m.p. 102–103°; $[\alpha]_D$ +131° ($CHCl_3$); λ_{max}^{EtOH} 260–261 mμ (ε 8900); ν_{max}^{Nujol} 1733, 1590, 1556, 1496 (shoulder) 1258, 1046, 809, and 770 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}OS$: C, 77.91; H, 8.53; S, 9.04. Found: C, 78.20; H, 8.48; S, 9.22.

3-Benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17β-ol (IId). A.—A solution of 500 mg. of 5β,10β-oxido-19-norandrostan-17β-ol-3-one (Ib) in a mixture of 10 ml. of acetone and 4 ml. of benzyl mercaptan was treated with 2 drops of concentrated hydrochloric acid and refluxed for 1 hr. The mixture was then cooled and the product was isolated as described for IIa. The crude product (410 mg.), recrystallized from methanol and dried under vacuum at 80° for 5 hr., afforded 360 mg. of benzyl sulfide IId: m.p. 107–108°; $[\alpha]_D$ +58° ($CHCl_3$); λ_{max}^{EtOH} 258 mμ (ε 8300); ν_{max}^{Nujol} 3540, 1588, 1556, 1496 (shoulder) 1038, 1005, 806, 768, 714, and 690 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{30}OS$: C, 79.31; H, 7.99; S, 8.47. Found: C, 79.18; H, 8.03; S, 8.58.

B.—Sodium borohydride (50 mg.) in 2 ml. of water was added to a solution of 250 mg. of 3-thioestrone benzyl ether (IIa) in 10 ml. of tetrahydrofuran and the whole was stirred at room temperature for 8 hr. Water was added and the mixture was extracted with ether. After washing the collected extracts with water, evaporation of the solvent yielded 45 mg. of IId, m.p. 96–98°, which after crystallization from methanol and careful drying showed m.p. 107–108°, $[\alpha]_D$ +58° ($CHCl_3$), λ_{max}^{EtOH} and ν_{max}^{Nujol} as reported above.

$\Delta^{1,3,5(10)}$-Estratrien-17-one (III).—Raney nickel W2 (2 ml.) was added to a solution of 250 mg. of 3-thioestrone benzyl ether (IIa) in 10 ml. of absolute ethyl alcohol and the mixture was heated under reflux for 8 hr. After cooling, the catalyst was removed by filtration and washed with ethyl alcohol; afterwards the solution was evaporated to give 148 mg. of a product, m.p. 135–137°. Two recrystallizations from methanol yielded $\Delta^{1,3,5(10)}$-estratrien-17-one (III): m.p. 139–140°; $[\alpha]_D$ +166° (dioxane)[12]; λ_{max}^{EtOH} 214 mμ (ε 8200), 267 (470), and 274 (490); ν_{max}^{Nujol} 1735, 1601, 1574, 1494, 1050, 815, 750, and 741 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.25; H, 8.72.

3-Mercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (3-Thioestrone) (IIe).—To 120 ml. of anhydrous liquid ammonia contained in a flask cooled in a Dry Ice–acetone bath, sufficient metallic sodium was added so that the blue color finally persisted for at least 10 min. (about 200 mg.). The air was displaced by nitrogen and a solution of 600 mg. of 3-benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIa) in a mixture of 20 ml. of anhydrous ether and 10 ml. of anhydrous dioxane (both solvents were freed of peroxides) was rapidly added. The blue color disappeared and was regenerated by the addition of a small amount of sodium. The mixture was then stirred for 10 min. and the reaction was terminated with ammonium chloride. The cooling bath was removed and the ammonia was allowed to evaporate. After dilution with ice-cold water and acidification with diluted hydrochloric acid the mixture was extracted with peroxide-free ether. The ether extract was washed with 3% sodium bicarbonate solution and then with water until neutral, dried with anhydrous magnesium sulfate, and concentrated under vacuum. The crude product, 360 mg., m.p. 200–202°, was purified by dissolution in 0.5 *N* sodium hydroxide and reprecipitation with diluted hydrochloric acid. Crystallization from acetone gave IIe (needles), m.p. 205–207°; $[\alpha]_D$ +164° (dioxane); λ_{max}^{EtOH} 213 mμ (ε 23,200), 242 (10,300), and 285 (1070); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 16,000); ν_{max}^{Nujol} 2520 (very weak), 1732, 1591, 1556, 1493, 1253, 1116, 1047, 1002, 807, and 769 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}OS$: C, 75.48; H, 7.74; S, 11.20. Found: C, 75.51; H, 7.73; S, 11.36.

3-Thioestradiol (IIf). A.—Benzyl sulfide (IIa, 600 mg.) was treated with sodium in liquid ammonia as reported for the preparation of IIe, except that the reaction time was extended to 1 hr. The reduction gave 340 mg. of 3-thioestradiol (IIf), m.p. 97–99°, which, after purification as reported for IIe (taking care of using solvents freed of peroxides), recrystallization from hexane, and drying at 80° under vacuum for 10 hr., showed m.p. 106–107.5°[13]; $[\alpha]_D$ +78° (dioxane); λ_{max}^{EtOH} 214 mμ (ε 22,000), 242 (9800), and 286 (980); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 16,600); ν_{max}^{Nujol} 3550, 2520, 1592, 1556, 1496, 1244, 1065, 1049, 1005, 809, and 770 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}OS$: C, 74.95; H, 8.39; S, 11.12. Found: C, 75.06; H, 8.27; S, 10.98.

B.—Benzyl sulfide IId, reduced as above, yielded IIf identical with the product prepared according to A.

C.—3-Thioestrone (IIe, 250 mg.) was reduced with 50 mg. of sodium borohydride in aqueous tetrahydrofuran for 8 hr. at room temperature. Isolation and purification of the product with the aforementioned care afforded 200 mg. of IIf, m.p. 106–107.5°, $[\alpha]_D$ +78.5° (dioxane), identical with the product prepared according to A and B.

17β-Hydroxy-$\Delta^{1,3,5(10)}$-estratrien-3-yl Disulfide.—A solution of 50 mg. of 3-thioestradiol (IIf) in ethanol (2 ml.) was treated with a solution of 100 mg. of $FeCl_3 \cdot 6H_2O$ in ethanol (1 ml.) and allowed to stand at room temperature for 2 hr. Dilution with water gave a crude product, which was recrystallized from methanol to give 40 mg. of the disulfide: m.p. 194–196°[2]; $[\alpha]_D$ +96° (dioxane); λ_{max}^{EtOH} 235–240 mμ (ε 22,000); ν_{max}^{Nujol} 3410, 1590, 1500 (shoulder), 1245, 1132, 1068, 1050, 1005, 876, 808, and 769 cm.$^{-1}$.

Anal. Calcd. for $C_{36}H_{46}O_2S_2$: C, 75.21; H, 8.07; S, 11.16. Found: C, 74.97; H, 8.18; S, 11.08.

Reduction of the product with sodium in liquid ammonia in the conventional manner gave 3-thioestradiol.

(12) For III, lit.[7] m.p. 135–136°, $[\alpha]_D$ +400°(?) (dioxane).

(13) Hecker[2] reported for IIf partially different data: m.p. 98–100°; λ_{max} 241 mμ (ε 9350), 273.5 (1330), and (295) (750); $\lambda_{max}^{0.1\ N\ NaOH}$ 267 mμ (ε 16,000); ν_{max}^{KBr} 3356 and 2551 cm.$^{-1}$.

The Aldol Condensation of Methylene Bis(ethyl sulfone). A Novel Synthesis of Benzofurans

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Although a few 1,1-bisalkylsulfonyl-1-alkenes (**2**) are known,[1,2] a Knoevenagel condensation[3] between a methylenebis(alkyl sulfone) and an aldehyde which proceeds directly to 1,1-bisalkylsulfonyl-1-alkenes has not been described. The β-hydroxy sulfones (**1**), the

$$\underset{\mathbf{1}}{RCH(OH)CH(SO_2Et)_2} \qquad \underset{\mathbf{2}}{RCH{=}C(SO_2Et)_2}$$

expected intermediates by this procedure, are known to undergo the retro-aldol reaction common to such substances.[1,4] However, it was anticipated that the efficient removal of water from the reaction and the use of a catalyst of the type recommended by Cope[3] would suppress this side reaction. Accordingly, when an equimolar mixture of aldehyde and methylenebis(ethyl sulfone) (**3**) was heated in refluxing toluene in the presence of a trace of piperidine acetate, the desired 1,1-bis(ethylsulfonyl)-2-substituted ethylenes were obtained in moderate yield (Table I).

When salicylaldehydes were employed in the reaction sequence, a slight excess of the equimolar quan-

(1) D. L. MacDonald and H. O. L. Fischer, *J. Am. Chem. Soc.*, **74**, 2087 (1952).

(2) L. C. Rinzema, J. Stoffelsma, and J. F. Arens, *Rec. trav. chim.*, **78**, 354 (1959); A. L. Barney, U. S. Patent 2,641,594 (June 9, 1953).

(3) E. Knoevenagel, *Ber.*, **29**, 172 (1896); **31**, 730 (1898); A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

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