

New Compounds: Steroidal Spiroethers

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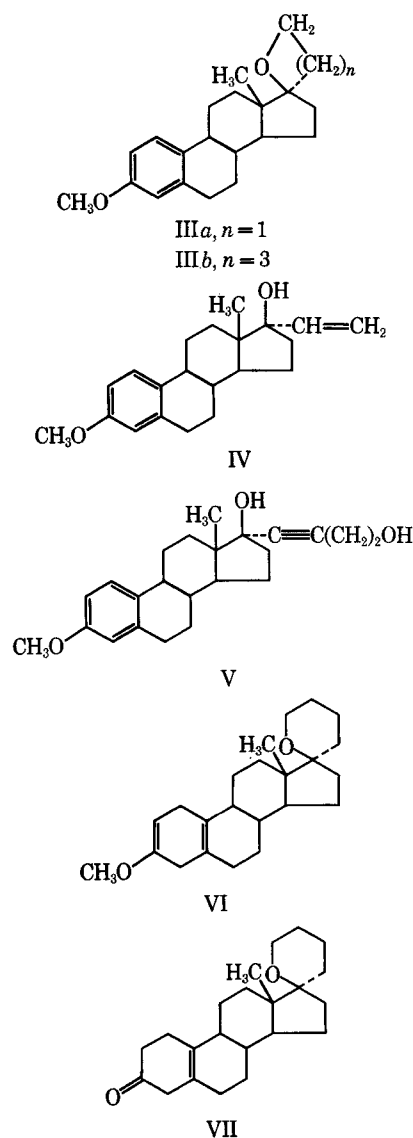
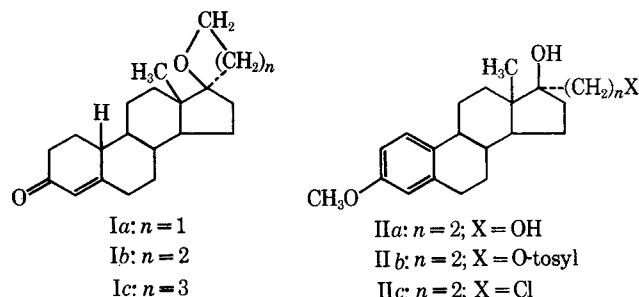
Abstract □ 3-Methoxyspiro[estra-1,3,5(10)-triene-17,2'-oxetane] (17 β -O) (IIIa) and tetrahydro-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'-pyran](17 β -O) (IIIb) were synthesized from 3-methoxy-19-nor-17 α -pregna-1,3,5(10),20-tetraen-17-ol (IV) and 17-(4-hydroxy-1-butynyl)-3-methoxyestra-1,3,5(10)-trien-17 β -ol (V). Additionally, IIIb was transformed into tetrahydrospiro[estr-5(10)-ene-17,2'-pyran]-3-one (17 β -O) (VII) via tetrahydro-3-methoxyspiro[estra-2,5(10)-diene-17,2'-pyran] (17 β -O) (VI).

Keyphrases □ Steroidal spiroethers—synthesis □ Antiestrogens—synthesis, steroidal spiroethers □ Spiroethers, steroidal—synthesis □ NMR spectroscopy—structure

The disclosure by Brown (1) concerning the synthesis of the spiroether Ic and the attempted synthesis of the spiroether Ia prompted the authors to report the results obtained in their laboratory. Their interest in this area stemmed from the reported potent antiestrogenic activity of the spiroether Ib (2). The intermediates, IIa and IIc, were prepared by different routes than those utilized by Brown (1). Hydroboration (3) of 3-methoxy-19-nor-17 α -pregna-1,3,5(10),20-tetraen-17-ol (4) gave the diol IIa, which was converted to the tosylate IIb by means of *p*-toluenesulfonyl chloride in pyridine at 0–5° overnight. Brown (1) reported that at room temperature a mixture of IIb and IIc was isolated. The catalytic hydrogenation of 17-(4-hydroxy-1-butynyl)-3-methoxyestra-1,3,5(10)-trien-17 β -ol (V) (5) afforded the diol IIc. Treatment of IIc with *p*-toluenesulfonyl chloride in pyridine at 0–5° gave the tosylate IIe which could not be crystallized. The cyclizations of IIb to IIIa and of IIc to IIIb were effected with sodium hydride in refluxing tetrahydrofuran. The yields of IIIa and IIIb appear to be much better than those reported by Brown (1), who utilized potassium *tert*-butoxide in refluxing *tert*-butyl alcohol. Since the observations on the transformation of IIIb to Ic and the attempted preparation of Ia parallel those of Brown (1), they will not be duplicated here; however, VII [not reported by Brown (1)] was prepared by the oxalic acid hydrolysis of VI [not characterized by Brown (1)].

EXPERIMENTAL¹

3-Methoxy-19-nor-17 α -pregna-1,3,5(10)-triene-17,21-diol (IIa)—To an ice-cold solution of 62 g. of IV in 300 ml. of dry tetrahydrofuran was added 250 ml. of 1.0 *M* solution of disiamylborane in tetrahydrofuran. The resulting solution was allowed to stand at 0–10° for 72 hr. and was then stirred in an ice bath; 200 ml. of 3 *N* sodium hydroxide solution was added to it carefully, followed by the dropwise addition of 210 ml. of 30% hydrogen peroxide. Stir-



¹ Melting points were determined in open capillaries in an oil bath and are uncorrected. Optical rotations were determined using 1% solutions of the compounds in chloroform; UV spectra were recorded on a Cary model 11 spectrophotometer in 95% ethanol solutions. IR spectra were determined with 0.5% KBr pellets on a Perkin-Elmer model 21 spectrophotometer, and the NMR spectra were recorded in CDCl₃ solutions using trimethylsilane as the internal standard on a Varian model A-60 spectrometer.

ring was continued for another 2 hr., and then the unreacted hydrogen peroxide was destroyed by the addition of 40 ml. of a saturated solution of sodium bisulfite. The mixture was partitioned between chloroform and water. Evaporation of chloroform gave a white

residue which was crystallized from acetonitrile to yield 40 g. of IIa, m.p. 160–162° [lit. (1) m.p. 162–163°].

3-Methoxy-19-nor-17 α -pregna-1,3,5(10)-triene-17,21-diol 21- β -Toluenesulfonate (IIb)—A solution of 5.0 g. of IIa and 6.0 g. of *p*-toluenesulfonylchloride in 30 ml. of dry pyridine was left at 0–5° overnight and then poured into ice-cold water. The product was extracted with ether. The ethereal extract was washed with dilute hydrochloric acid to remove pyridine. After it was dried (MgSO₄), the solution was concentrated to crystallize 5.8 g. of IIb, m.p. 150–152° [lit. (1) m.p. 147–148°]; UV max. (95% EtOH) 224 nm. (21,000); $\lambda_{\text{max}}^{\text{KBr}}$ 2.86, 8.43, and 8.53 μ ; NMR signals at 390–480 (7 aromatic protons), 259 (t, —O₂SOCH₂—) and 145 Hz. (s, Ar—CH₃).

Anal.—Calcd. for C₂₈H₃₆O₅S: C, 69.40; H, 7.48; S, 6.61. Found: C, 69.62; H, 7.46; S, 6.58.

3-Methoxyspiro[estra-1,3,5(10)-triene-17,2'-oxetane] (17 β -O) (IIIa)—A mixture of 6.0 g. of IIb, 1.0 g. of sodium hydride, and 300 ml. of dry tetrahydrofuran was stirred under reflux for 120 hr. (the reaction was followed by TLC) and then allowed to cool to room temperature. The unreacted sodium hydride was destroyed by adding methanol (2 ml.), and the mixture was partitioned between ether and water. The ethereal extract was dried (MgSO₄) and then evaporated to give an oily residue, which was crystallized from *n*-pentane–ether to afford 3.5 g. of IIIa; m.p. 108–109°; NMR spectrum displayed peaks at 390–440 (aromatic protons), 223 (—OCH₃), 262 (m, —OCH₂—), and 47 Hz. (18—CH₃).

Anal.—Calcd. for C₂₁H₂₈O₂: C, 80.72; H, 8.97. Found: C, 81.01; H, 9.09.

17-(4-Hydroxybutyl)-3-methoxyestra-1,3,5(10)-trien-17 β -ol (IIc)—V, 20.5 g., was hydrogenated over 1.2 g. of 10% palladium on charcoal catalyst in 300 ml. of dry tetrahydrofuran. The theoretical amount of hydrogen was taken up in 3.5 hr. Crystallization from ether gave 19.2 g. of IIc, m.p. 124–126° [lit. (1) m.p. 127–128°].

Tetrahydro-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'-pyran] (17 β -O) (IIIb)—A solution of 3.8 g. of the diol IIc and 4.1 g. of *p*-toluenesulfonyl chloride in 35 ml. of dry pyridine was allowed to stand in an ice bath for 6.5 hr. and then was partitioned between ether and water. The ethereal extract was washed with dilute hydrochloric acid three times and finally with water. After it was dried (MgSO₄), the solution was evaporated to dryness to give 4.94 g. of IVe as a semisolid material which failed to crystallize and was used as such in the next step (TLC examination indicated only one spot).

A slurry of 4.9 g. of the tosylate IVe, 300 mg. of sodium hydride, and 150 ml. of dry tetrahydrofuran was refluxed for 24 hr. After cooling to room temperature, the unreacted sodium hydride was destroyed by adding a few drops of methanol, and the mixture was partitioned between ether and water. The ethereal solution was dried (MgSO₄) and then evaporated to dryness. The residue was crystallized from *n*-pentane–ether to afford 3.1 g. of IIIb; m.p. 106–108°; NMR 390–440 (3 aromatic protons), 222 (OCH₃), 218 (m, —OCH₂—), and 51 Hz. (18—CH₃).

Anal.—Calcd. for C₂₃H₃₂O₂: C, 81.13; H, 9.44. Found: C, 81.03; H, 9.28.

Tetrahydro-3-methoxyspiro[estra-2,5(10)-diene-17,2'-pyran] (17 β -O) (VI)—To a stirred solution of 16.7 g. of IIIb in 1600 ml. of dry ether and 1600 ml. of anhydrous liquid ammonia, held under reflux with a dry ice condenser, was added 20 g. of lithium wire over a period of 20 min. The resulting blue solution was further stirred for 30 min. At this stage, the reaction was quenched by the dropwise addition of 325 ml. of ethanol to give a colorless slurry. Ammonia was evaporated on a water bath, and the mixture was diluted with 800 ml. of water. The ethereal layer was decanted, dried (MgSO₄), and evaporated to dryness to give an oily residue which was crystallized from ether–*n*-pentane to afford 14.5 g. of VI, m.p. 140–142°; $\lambda_{\text{max}}^{\text{KBr}}$ 5.90 and 6.0 μ ; NMR 312 (m, C₂ proton), 212 (—OCH₂), 218 (m, OCH₂), and 51 Hz. (18—CH₃).

Anal.—Calcd. for C₂₃H₃₄O₂: C, 80.65; H, 10.01. Found: C, 80.80; H, 9.95.

Tetrahydrospiro[estr-5(10)-ene-17,2'-pyran]-3-one (17 β -O) (VII)—A solution of 7.8 g. of VI, 13 ml. of water, 8.0 g. of oxalic acid dihydrate, 20 ml. of methanol, and 200 ml. of tetrahydrofuran was stirred at room temperature for 1 hr. and then diluted with 400 ml. of water. The product was extracted with ether. After drying (MgSO₄), the ethereal solution was evaporated to dryness to afford a white residue which was crystallized from ether to give 6.2 g. of VII, m.p. 164–166°; $\gamma_{\text{max}}^{\text{KBr}}$ 5.81 μ ; NMR spectrum displayed peaks at 200 (m, —OCH₂), 163 (s, 2 protons), 146 (s, 4 protons), and 51 Hz. (18—CH₃).

Anal.—Calcd. for C₂₂H₃₂O₂: C, 80.44; H, 9.83. Found: C, 80.80; H, 9.82.

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