on the estradiol-17β [1,3,5(10)-estratriene-3,17β diol] molecule. It is the purpose of this note to report the synthesis of 2-nitroestradiol-17β (I), 4-nitroestradiol-17β (II), and 2,4-dinitroestradiol-17β (III). Two routes were investigated for the synthesis of the mononitroestradiols.

The first route involved the direct nitration of estrone to 2-nitroestrone and 4-nitroestrone by a known procedure[3] followed by the selective reduction of the pure compounds to the corresponding mononitroestradiols I and II, respectively. Sodium borohydride was chosen as the reagent for the reduction, because it is known to reduce estrone stereospecifically to estradiol-17β[4] and because it does not attack nitro groups under the mild conditions required for the reduction of a carbonyl group.[5] The products required only recrystallization for purification.

The second route involved the direct nitration of estradiol-17β. The products were separated by chromatography. The nitroestradiols, I and II, obtained by this procedure were identical to the products obtained by the sodium borohydride reduction of 2-nitroestrone and 4-nitroestrone, respectively. Although the first method involved two steps (nitration of estrone followed by reduction), it is preferred over the second method, because the 2- and 4-nitroestrones are more easily separated than a mixture of 2- and 4-nitroestradiols.

The sodium borohydride reduction of 2,4-dinitroestrone which was synthesized by the dinitration of estrone[3] gave III. The infrared spectrum[6] and physical properties were identical to those reported for the product obtained from the nitration of estradiol-17β with 2 moles of nitric acid.[7]

EXPERIMENTAL[8]

Reduction of nitroestrones. A solution of sodium borohydride (200 mg.) in 30 ml. methanol was poured into a solution of the nitroestrone (500 mg.) in 30 ml. of methanol and 0.2 ml. 20% sodium hydroxide. After standing overnight at room temperature, the solution was poured into 150 ml. of water and acidified with 6*N* hydrochloric acid. The precipitate was collected by filtration and recrystallized from ethanol.

2-Nitroestrone[3] (m.p. 180–182°; *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 68.55; H, 6.71; N, 4.44; Found: C, 68.74; H, 6.73; N, 4.48) gave the diol I, m.p. 164–167°. Yield: 480 mg. (96%). Recrystallization from ethanol gave the pure product, m.p. 167–168°, λ_{max}^{EtOH} 293 mμ (ε 8100), 364–366 mμ (ε 3690), and λ_{max}^{KBr} 2.85 (17—OH), 3.04 (3—OH), 6.12, 6.37, 6.56 (aromatic NO_2), 7.63, and 11.05 μ (isolated ring H).

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.11; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.21; N, 4.48.

4-Nitroestrone[3] (m.p. 272–278°; *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.57; H, 6.89; N, 4.40) gave 490 mg. (98%) of diol II, m.p. 253–254°. Recrystallization from ethanol gave the pure product, m.p. 255° (dec.); λ_{max}^{EtOH} 278 mμ (ε 1810), and λ_{max}^{KBr} 2.81 (17—OH), 3.16 (3—OH); 6.14, 6.32, 6.55 (aromatic NO_2), 7.26, 12.16 μ (two adjacent ring H).

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.11; H, 7.30; N, 4.41. Found: C, 68.11; H, 7.21; N, 4.49.

2,4-Dinitroestrone[3] (m.p. 183–185°; *Anal.* Calcd. for $C_{18}H_{20}O_6N_2$: C, 59.99; H, 5.59; N, 7.78. Found: C, 60.26; H, 5.62; N, 7.77) gave 425 mg. (85%) of diol III, m.p. 255° (dec.); λ_{max}^{EtOH} 277 mμ (ε 6490), 352 mμ (ε 3430), 430 mμ (ε 1040), and λ_{max}^{KBr} 2.80 (17—OH), 3.16 (3—OH), 6.15, 6.35, 6.47 (aromatic NO_2), 7.60, and 11.03 μ (isolated ring H).

Anal. Calcd. for $C_{18}H_{22}O_6N_2$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.88; H, 6.05; N, 7.58.

Direct nitration of estradiol. Estradiol (1.5 g.) was dissolved in 45 ml. of hot acetic acid and allowed to cool to 45°. Then 0.34 ml. of nitric acid (sp. gr. 1.42) was added dropwise with stirring. After 24 hr. at room temperature it was poured slowly into 250 ml. of water with stirring. The mixture of mononitroestradiols was filtered, dried, and chromatographed on Merck alumna (acid washed). The column was eluted with benzene and benzene: acetic acid (99:1, 98:2, and 95:5, successively). The 4-nitroestradiol came off of the column first. Both products were recrystallized from 80% ethanol to give 490 mg. (28%) II, m.p. 255° (dec.) and infrared spectrum identical to II obtained by the reduction of 4-nitroestrone, and 512 mg. (29%) I, m.p. 166–167° and infrared spectrum identical to that of I obtained by the other procedure.

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[3] H. Werbin and C. Holoway, *J. Biol. Chem.*, **223**, 651 (1956).

[4] J. H. Biel, *J. Am. Chem. Soc.*, **73**, 847 (1951).

[5] S. W. Chaikin and W. B. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

[6] R. A. Pickering and H. Werbin, *J. Am. Chem. Soc.*, **80**, 680 (1958).

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[8] Melting points are uncorrected. The author wishes to acknowledge the assistance of Almeria Thompson for the ultraviolet spectra.

Epoxidation of Butadiene Sulfone

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The reaction of performic acid (generated *in situ* from formic acid and hydrogen peroxide) with an olefin almost invariably gives the α-glycol or its monoformate as the final product.[1] Only a handful of compounds have been oxidized by this strongly acidic reagent to an isolatable epoxide.[2–4] We have found that butadiene sulfone reacts with a mixture of formic acid and hydrogen peroxide under fairly strenuous conditions (formic acid at 50°) to give the epoxide (I) as the only product in 30% yield. The structure of I was established by the sequence of reactions outlined below. It is interesting to note

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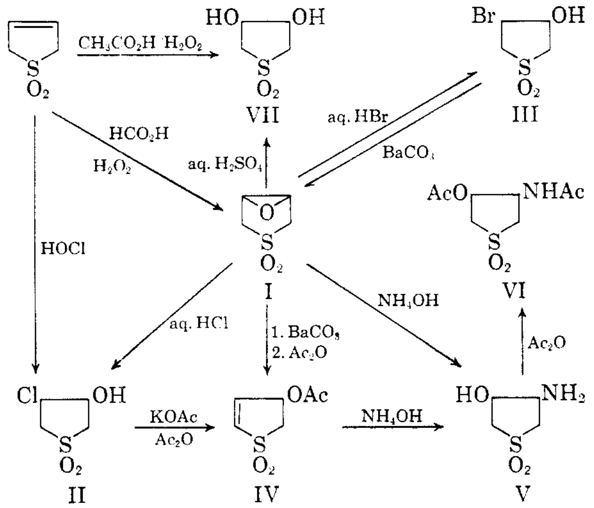
[1] D. Swern, Chapter on "Oxidation of Olefins with Peracids," in *Org. Reactions*, **Vol. VII**, John Wiley & Sons, Inc., New York, 1951.

[2] A. Byers and W. J. Hickinbottom, *J. Chem. Soc.*, 1328 (1948).

[3] U. S. Patent, **2,485,160** (W. D. Niederhauser and J. E. Koroky, to Rohm & Haas).

[4] G. Storck, *et al.*, *J. Am. Chem. Soc.*, **73**, 3546, 4496 (1951).

that the performic oxidation yielded the epoxide, while peracetic acid has been reported to oxidize butadiene sulfone to the 3,4-dihydroxytetramethylene sulfone, VII,[5,6] a fact we have verified experimentally. This is the reverse of what might be expected, since formic acid is considered to be much more destructive of the epoxide ring system, to form α-glycol derivatives,[1] than is acetic acid.



The epoxide I was refluxed with dilute hydrochloric acid to give a chlorohydrin II, identical with that from the addition of hypochlorous acid to butadiene sulfone. Reaction of II with potassium acetate in acetic anhydride gave the cyclic olefin–sulfone acetate, IV, by elimination of HCl. Compound IV, when warmed for one hour with aqueous ammonia, gave the same amino alcohol, V, that resulted from I by the action of aqueous ammonia at room temperature for 24 hours. Epoxide I reacted with hydrobromic acid to give the bromohydrin, III, which regenerated I by treatment with barium carbonate. Refluxing 10% sulfuric acid converted the epoxide I to the same diol, VII, as obtained by peracetic acid oxidation of butadiene sulfone. (All disubstituted compounds are believed to be *trans* isomers from the known stereochemical course of most of the reactions involved.)

The epoxide I has been described previously as having been prepared from the 3-hydroxy-4-bromotetramethylene sulfone (III) by the action of pyridine.[7] The reported melting point was 130°. The melting point of I as we obtained it was 159–160°, which, strangely enough, is exactly that of the diol VII. A mixed melting point between our I and VII was depressed 50°. Analysis and chemical reactivity clearly showed that each had the structure assigned to it. Our epoxide I gave a negative test with periodic acid, was recovered unchanged from refluxing acetic anhydride, and showed no hydroxyl absorption in the infrared. The diol VII, prepared by either route, gave a positive periodic acid test, a diacetate from acetic anhydride, and strong hydroxyl absorption. The 130° melting point reported for I[7] is thought to be in error.[8]

EXPERIMENTAL

Epoxide I. Reaction of butadiene sulfone with formic acid and hydrogen peroxide. To 850 ml. of 98% formic acid was added 170 g. of purified butadiene sulfone, m.p. 64–65°, (recrystallized from chloroform-ether). Then 214 g. of 30% hydrogen peroxide was added. Considerable heat was evolved and the reaction was cooled in ice to keep the temperature at 50°. The reaction was allowed to stand at room temperature over a weekend. Excess ferrous ammonium sulfate was added to destroy the remaining peroxides, and the solution distilled at water aspirator pressure. When most of the solvent had been removed, a solid began to form. This was filtered, triturated with water to remove the red iron salts, and recrystallized from acetone to give shiny needles, m.p. 159.5–160°, after thorough drying. The yield was 56.5 g. (30%).

Anal. Calcd. for $C_4H_6O_3S$: C, 35.82; H, 4.47; S, 23.89. Found: C, 35.9, 35.8; H, 4.6, 4.5; S, 24.4, 24.4.

Reaction of I *with HCl* (II). Two grams of I was refluxed 8 hr. with 44 ml. of 9% hydrochloric acid. On cooling, 2.4 g. (95% yield) of white crystals were obtained, which, after washing with water and drying without further purification, melted sharply at 167–168°. On admixture with I, a depression of the m.p. to 140–144° occurred. With authentic 3-chloro-4-hydroxy-tetramethylene sulfone, prepared below, no melting point change occurred. [Ref. (7) reports the m.p. of II as 160°].

Anal.: Calcd. for $C_4H_7ClO_3S$: C, 28.23; H, 4.11. Found: C, 28.6, 28.50; H, 4.1, 4.2.

3-Chloro-4-hydroxy-tetramethylene sulfone (II). To a stirred, ice-cooled solution of 59 g. butadiene sulfone in 300 ml. water was added a solution of HOCl, as prepared in *Org. Syntheses*, **Coll. Vol. 1**, 158, until no more HOCl was taken up (KI-HCl test). A solid separated during the course of the addition, which, after filtering, was recrystallized from acetone and then methanol, followed by vacuum drying. It had a m.p. of 167–168°; the m.p. was not depressed by the product from the preceding paragraph. The yield was 68 g.

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(6) S. F. Birch and D. T. McAllan, *J. Chem. Soc.*, 2556 (1951).

(7) O. E. van Lohuizen and H. J. Backer, *Rec. trav. chim.*, **68**, 1137 (1949).

(8) Since this paper was submitted, M. Prochaska and V. Horak, *Coll. Czech. Chem. Comm.*, **24**, 1509 (1959), have reported the preparation of epoxide I by the method of Ref. (7). They obtained a melting point of 124.5–6°. They also describe a number of derivatives of the epoxide which correspond in melting point to those reported here and in Ref. (7). In addition, Prochaska and Horak find that treatment of their epoxide with barium carbonate gives the olefin-alcohol corresponding to IV, above, which is then acetylated to IV. We find that our epoxide, I, melting at 159–160°, undergoes the same sequence of reactions, leading to IV, identical to the compound obtained from the potassium acetate/acetic anhydride treatment of the chlorohydrin II. Prochaska and Horak report almost exactly the same reaction of the chlorohydrin, with sodium acetate and acetic anhydride in two steps, to give IV also. It is difficult to explain the wide variance in melting point of epoxide I between that reported in Ref. (7) (130°) and by Prochaska and Horak (124.5–126°), and that found by us (159–160°). It may be a matter of two crystalline modifications; thus far, we have been unable to transform the 159–160° melting compound to any other form by recrystallization from various solvents.

(77%) of crude product. Only a slight loss occurred on recrystallization.

Reaction of I *with HBr* (III). Five g. I was refluxed with 39 ml. 10% HBr for 8 hr. On cooling, the solid which formed was of high apparent purity, and on washing with water and drying it melted sharply at 192–193°. The yield was 5.5 g. (69%).

Anal.: Calcd. for $C_4H_7BrO_3S$: C, 22.3; H, 3.25; Br, 37.2. Found: C, 22.5, 22.3; H, 3.2, 3.2; Br, 37.2, 37.8.

Reaction of III *with $BaCO_3$.* Five and two-tenths g. of the bromohydrin from above was heated for 2 hr. on the steam bath with 2.4 g. $BaCO_3$ in 20 ml. water. The solution became almost completely clear. It was filtered of some residual solid and the filtrate cooled in ice. The solid that formed was recrystallized from ethanol/ethyl acetate; m.p. 158–159°, yield, 2.1 g. (65%). On admixture with Compound I there was no depression of melting point.

Anal.: Calcd. for C_4HO_3S: C, 35.88; H, 4.51; S, 23.89. Found: C, 35.6, 35.9; H, 4.2, 4.3; S, 24.5, 24.41.

Reaction of I *with Ammonia* (V). In 250 ml. of 28% aqueous ammonia was placed 10 g. of I. It was allowed to stand at room temperature for 24 hr. A small amount of a crystalline solid was filtered off that melted (dec.) at 260°. The filtrate was evaporated, and the solid residue triturated with ether, acetone, and ethyl acetate. After drying, it had a m.p. of 198–199°; yield, 7.4 g. (64%).

Anal.: Calcd. for $C_4H_8NO_3S$: C, 31.81; H, 5.92; N, 9.28; S, 21.20. Found: C, 31.9, 31.9; H, 6.3, 6.1; N, 9.4, 9.3; S, 21.4, 21.4.

Acetylation of V (VI). To a mixture of 50 ml. acetic anhydride and 3 ml. acetic acid was added 2.5 g. of V. The mixture was refluxed for 3 hr. The excess anhydride and acid was distilled under vacuum and the residual solid recrystallized from methanol; m.p. 149–150° after drying; yield 3.8 g. (93%).

Anal.: Calcd. for $C_8H_{13}NO_5S$: C, 40.85; H, 5.53; N, 5.95; S, 13.59. Found: C, 40.5, 40.5; H, 5.6, 5.5; N, 5.8, 5.8; S, 13.3, 13.2.

Reaction of II *with acetic anhydride and potassium acetate* (IV). Seventeen g. of II was added to a solution of 10.0 g. KOAc in 200 ml. Ac_2O and 20 ml. HOAc. This mixture was heated on the steam bath overnight, then refluxed 2 hr. further. An inorganic solid was filtered, the filtrate evaporated under vacuum and the solid residue taken up in methanol. Again, some inorganic solid was filtered. The methanol solution was cooled and the crystalline solid recrystallized from methanol. The product weighed 12 g. (68%); m.p. 110–111°.

Anal.: Calcd. for $C_6H_8O_4S$: C, 40.85; H, 4.55; S, 18.18. Found: C, 40.9, 41.1; H, 4.6, 4.67; S, 18.5, 18.7.

Reaction of IV *with ammonia* (V). A mixture of 5.5 g. IV and 90 ml. 28% aq. ammonia was heated on the steam bath for 1 hr. The liquid was distilled under vacuum and the residue recrystallized from ethanol-water after trituration with ethyl acetate; m.p. 197–198°, yield 2.5 g. (48%). Mixed melting point with V from I plus NH_4OH was not depressed.

Reaction of I *with aqueous H_2SO_4* (VII). A solution of 10 g. of I in 50 ml. of 10% H_2SO_4 was refluxed overnight. The acid was neutralized with solid sodium carbonate and the mixture evaporated to dryness. The solid residue was taken up in absolute alcohol, filtered, and the alcohol filtrate cooled. The solid that separated was recrystallized twice from absolute alcohol. After drying it had a m.p. of 159–160°. It depressed the melting point of starting material almost 50° on admixture. It did not depress the m.p. of authentic 3,4-dihydroxytetramethylene sulfone, prepared below.

Dihydroxylation of butadiene sulfone (VII). Butadiene sulfone was dihydroxylated according to the method of Ref. (6) (where 2,5-dihydrothiophene was the starting material) using peracetic acid. The diol VII was the product in 75% yield. It was identical with VII prepared from I by acid hydrolysis (above). The procedure involves finally refluxing the acetic acid solution for 3 hr. to destroy excess peroxide. When I is refluxed in 98% formic acid for 3 hr., it is recovered unchanged.

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Lithium Aluminum Alkoxide Catalyzed Transesterification of Primary Alcohols with Ethyl Acetate

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In the course of another investigation, it was necessary to convert 3-butyl-3-propyloctanoic acid (I) to 3-butyl-3-propyl-1-octanol (II). The reduction was carried out by using an excess of lithium aluminum hydride, followed by destruction of the excess hydride with ethyl acetate, prior to hydrolysis, according to conventional procedures.[1–3]

Upon examining the reaction mixture, it was found that extensive transesterification had taken place, and that a mixture of the expected alcohol (II) and 3-butyl-3-propyl-1-octyl acetate (III) was obtained. Reduction of I to pure II was accomplished successfully by the procedure of Nystrom and Brown[4] by destroying the excess lithium aluminum hydride with dilute sulfuric acid.

As no particular care had been taken to hydrolyze the original reduction mixture immediately after the excess lithium aluminum hydride had been destroyed with the ethyl acetate, it was interesting to examine the reaction system further. A series of reductions of the acid (I) was carried out in which variations were made in the period of time which the reaction mixtures were allowed to stand in contact with a large excess of ethyl acetate before hydrolysis. The mixtures of alcohol (II) and acetate (III) were analyzed by gas chromatography and the results are summarized in Table I. It is noteworthy that even when the reaction mixture was acidified immediately following the introduction of the ethyl acetate, 31% of ester (III) was obtained. The rapidity of the transesterification appeared to be unusual because of the low temperatures involved and the hindered structure of the alcohol (II).

In order to determine if the observed rate of transesterification were peculiar to the structure of the alcohol (II), four reductions of caprylic acid

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