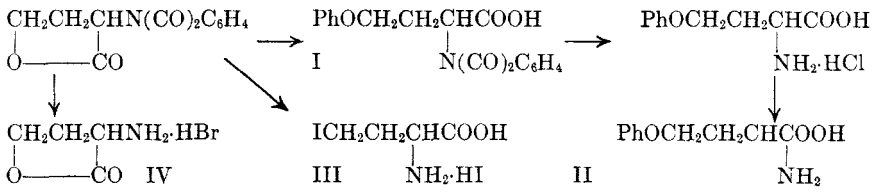

salt filtered off as a dark hygroscopic mass, which was dissolved in water and purified by repeated treatments with Norit and filtrations. 18% hydrochloric acid was introduced dropwise under cooling and stirring within two hours into the filtrate, to acidic reaction. The reaction mixture containing an oily, heavy precipitate was kept in the refrigerator for 1 day. After decantation, the semisolid acid (I) was purified by solution in boiling acetic acid, addition of a small amount of water, and treatment with Norit. To the cooled, vigorously stirred filtrate water was added slowly, causing precipitation of the acid (I). The dried crystals weighed 40 g. (62%), m.p. 122°. On recrystallisation from benzene–petroleum ether, m.p. 124°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 66.5; H, 4.6; N, 4.3. Found: C, 66.6; H, 4.7; N, 4.3.

*O-Phenyl-*DL*-homoserine hydrochloride (α-amino-γ-phenoxybutyric acid hydrochloride).* 300 ml. of 18% hydrochloric acid was added to a solution of α-phthalimido-γ-phenoxybutyric acid (I) (13 g., 0.04 mole) in 10 ml. of acetic acid, and the mixture refluxed for 3 hr. After concentration and cooling, phthalic acid was filtered off and the solution purified by treating with Norit. The crude hydrochloride, obtained on evaporation in vacuo, was dissolved in a small amount of water, freed from the rest of the phthalic acid by filtration and the solution concentrated again in vacuo. The dry residue was dissolved in water-ethanol, precipitated with ether, and dried in vacuo (P_2O_5). The almost colourless crystals (7 g., 76%) melted at 214°.

Anal. Calcd. for $C_{10}H_{14}NO_3Cl$: C, 51.7; H, 6.1; N, 6.1; Cl, 15.3. Found: C, 51.5; H, 6.3; N, 6.2; Cl, 15.5.

*O-Phenyl-*DL*-homoserine (α-amino-γ-phenoxybutyric acid) (II).* Triethylamine was added dropwise to a solution of O-phenyl-DL-homoserine hydrochloride (1 g., 0.0043 mole) in 10 ml. of 50% aqueous ethanol until *p*H 7–8. The precipitated free acid (II) was filtered off and washed with portions of ethanol. After drying in vacuo (P_2O_5), the crystals (0.8 g., 95%) melted at 230°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.3; H, 6.9; N, 7.2.

*N-Benzoyl-O-phenyl-*DL*-homoserine.* The *N*-benzoyl derivative was prepared in the usual way by benzoylation of the acid hydrochloride in 3*N* sodium hydroxide. After recrystallization from ethyl acetate–petroleum ether it melted at 145°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: N, 4.7. Found: N, 4.6.

α-Amino-γ-iodobutyric acid hydroiodide (III). (a) From α-phthalimido-γ-butyrolactone: Powdered α-phthalimido-γ-butyrolactone[3] (23 g., 0.1 mole) was refluxed with 110 ml. of 55% hydroiodic acid during 2 hr. 500 ml. of toluene was added and refluxing continued for 3 hr. The aqueous hydroiodic acid was removed from the stirred mixture by azeotropic distillation. After cooling, the toluenic layer, containing the phthalic acid, was removed by decantation and the residue of crude, dark hydroiodide (III) was washed with ether. White yellow crystals (35 g., 98%) were obtained by extraction with dry ether in a Soxhlet apparatus, m.p. 195–198°.

Anal. Calcd. for $C_4H_9NO_2I_2$: N, 3.9; I, 71.1; Found: N, 4.0; I, 71.2. Since hydrolysis and γ-iodination of α-phthalimido-γ-butyrolactone proceeds quantitatively, the yield of the hydroiodide (III) equalled that of α-phthalimido-γ-butyrolactone (75–80%), prepared from α-bromo-γ-butyrolactone. Uncrystallized lactone could be used giving similar yield; overall yield based on γ-butyrolactone *via* α-bromo-γ-butyrolactone and α-phthalimido-γ-butyrolactone was 64–72%. (*b*) *From α-benzamido-γ-butyrolactone:* α-benzamido-γ-butyrolactone[1] (20.5 g., 0.1 mole) was refluxed with 110 ml. of 55% hydroiodic acid. The mixture was worked up as described above, yielding 95% of the hydroiodide (III); based on γ-butyrolactone via α-bromo-γ-butyrolactone and α-benzamido-γ-butyrolactone the yield was 48–51%.

Anal. Found: N, 4.0; I, 71.3.

α-Amino-γ-butyrolactone hydrobromide (IV). Powdered α-phthalimido-γ-butyrolactone (2.3 g., 0.01 mole) was refluxed with 50 ml. of 24% hydrobromic acid for 3 hr. The solution was cooled and the phthalic acid which separated out was filtered off. The mother liquor was evaporated in vacuo; the dry residue was dissolved in 10 ml. of water and freed from traces of phthalic acid by filtration. Water was distilled off and the product washed with ethanol-ether. After drying in vacuo (P_2O_5), the crystals (1.7 g., 93%) melted at 225°.

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.7; Br, 43.9. Found: N, 7.6; Br, 44.1.

DL*-Homoserine (α-amino-γ-hydroxybutyric acid).* Powdered α-phthalimido-γ-butyrolactone (9.2 g., 0.04 mole) was dispersed in 50 ml. of 50% sulphuric acid, and the mixture refluxed for 3 hr. to dissolution of the lactone. The solution was left to cool to room temperature, then in ice-water. The phthalic acid was filtered off and the solution, containing the α-amino-γ-butyrolactone sulphate, was diluted, treated with Norit and filtered. 45 g. of calcium hydroxide was added and the mixture stirred on a steam bath for 1 hr. Calcium sulphate was filtered off and the solution, containing the calcium salt of DL-homoserine, concentrated to 20–25 ml. Diluted sulphuric acid was dropped in until neutral, and precipitated calcium sulphate filtered off. The solution was purified with Norit, the filtrate concentrated in vacuo to 10–15 ml., 20 ml. of ethanol, followed by 100 ml. of acetone were added and the mixture was kept in the freezer until complete separation of crude DL-homoserine (4.3 g., 91%). When recrystallized from a small amount of water and an excess of 1:5 ethanol-acetone, the crystals (3.8 g., 80%) melted at 182–183°.

Anal. Calcd. for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.8. Found: C, 40.1; H, 7.6; N, 11.7.

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The Synthesis of Nitroestradiols[1,2]

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As part of an investigation concerned with the relationship of molecular structure to estrogenic activity, new compounds are being synthesized by introducing substituents at various positions

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(2) Supported by a grant, CY-2873, from the National Cancer Institute, U. S. Public Health Service.

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 $C_{18}H_{21}O_4N$: 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).

(7) H. Werbin, *J. Org. Chem.*, **21**, 1532 (1956).

(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

(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).