# Photoreductions of 3,17β-Estradiol

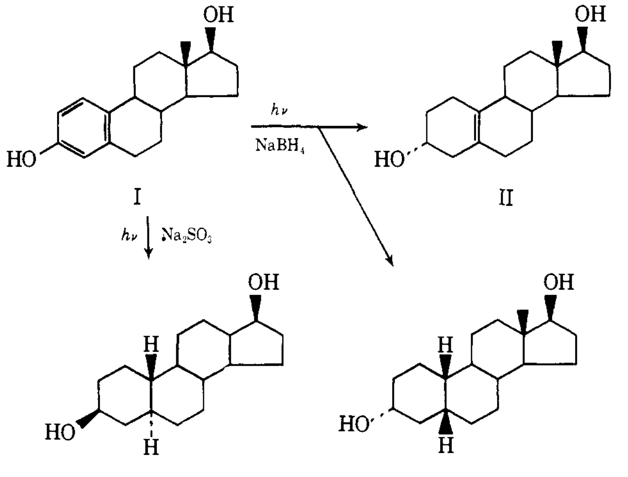
**James A. Waters and Bernhard Witkop**

*Contribution from the Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014.*
*Received September 26, 1966*

**Abstract:** The solvent-dependent photoreduction of 3,17β-estradiol (I) *in ethanol* with *sodium borohydride* gave 3α,17β-dihydroxy-5(10)-estrene (II), the A/B, *cis*-fused, 3α,17β-dihydroxy-5β,10β-estrane (III), and polymeric material. Photoreduction in *dioxane–water* led to a new isomer of 3,17β-dihydroxy-5(10)-estrene. By contrast, the novel photoreduction of 3,17β-estradiol (I) with *sodium sulfite* furnished the A/B, *trans*-fused, 3β,17β-dihydroxy-5α,10β-estrane (IV) as the predominant reduction product in addition to a by-product and polymeric material. While sodium bisulfite, sodium metabisulfite, and sodium hydrosulfite were also effective agents, if in lower yields, sodium dithionate and sodium thiosulfate failed to bring about photoreduction.

The photoreduction of the heterocyclic systems in uridine,[1] tryptophan,[2] and thymidine[3] by ultraviolet irradiation in the presence of sodium borohydride has been extended to aromatic phenolic compounds. In this paper we describe photoreductions with 3,17β-estradiol, which are of interest in connection with new routes to 19-norsteroidal hormones. Birch[4] has extensively investigated the reduction of estradiol and related phenolic ethers by sodium and alcohol in liquid ammonia to yield dihydro derivatives, which are readily converted to the corresponding α,β-unsaturated ketones. Recently the electrochemical reduction of aromatic systems to dihydro and tetrahydro derivatives[5] has been applied to estrone 3-methyl ether.[6]

**Photoreductions with Sodium Borohydride.** 3,17β-Estradiol (I) in ethanol containing a 4 *M* excess of sodium borohydride was irradiated with a 450-w Hanovia medium-pressure mercury lamp. Aliquots of the reaction mixture were removed periodically, and the ultraviolet absorption at 288 mμ was recorded. The reaction mixture obtained after a 34-hr irradiation period contained reduced monomers in 24% yield and polymeric material. Photoreduced compounds II and III and polymers (mol wt 828 and 1718) were isolated by extensive column and thin layer chromatography.



I II IV III

The tetrahydro derivative II was obtained as colorless plates, mp 206–208°, $[\alpha]^{24}\mathrm{D}$ +167.1° ($CHCl_3$). A lack of olefinic proton absorption in the nmr spectrum suggested either a compound unsaturated at the C-5(10) position or a saturated estrane derivative. Confirmation of the former was obtained from the mass spectrum which displayed a mass peak at 276 and additional peaks at *m/e* 199 and 131. Comparison of II with authentic 3α,17β-dihydroxy-5(10)-estrene,[7] mp 205–207°, $[\alpha]\mathrm{D}$ +186° ($CHCl_3$), established their identity (mixture melting point, infrared spectra, glpc retention time). The diacetate of II melted at 119–120°, $[\alpha]^{21}\mathrm{D}$ +145.7° ($CHCl_3$) [lit.[8] mp 119–120°, $[\alpha]\mathrm{D}$ +130° ($CHCl_3$)].

The *m/e* 199 ion of II is derived by fission of ring D (42 + 17)[9] and loss of water from ring A. The *m/e* 131 peak comes about by typical fragmentation at ring C plus elimination of water from the 3-hydroxy group.[10]

The mass spectrum of III, the minor monomeric reduction product, displayed peaks analogous to II (two additional mass units) at $M^+$ 278, *m/e* 201 and 133, suggestive of a saturated estrane derivative. Compound III, mp 202–204°, $[\alpha]^{22}\mathrm{D}$ +25.2° ($CHCl_3$), was identical with 3α,17β-dihydroxy-5β,10β-estrane [lit. mp 207–208°, $[\alpha]^{25}\mathrm{D}$ +29.8° ($CHCl_3$),[11] and mp 211–212°, $[\alpha]^{25}\mathrm{D}$ +10.2° ($CH_3OH$)[12]], with regard to mixture melting point, glpc, and tlc.

Irradiation of 3,17β-estradiol in dioxane–water (9:1) under similar conditions gave comparable yields of monomeric and polymeric material. The major photoreduced monomer from this reaction, mp 206.5–208.5°, had a glpc retention time identical with that of II, and similar spectral data. However, on admixture

---

(1) P. Cerutti, K. Ikeda, and B. Witkop, *J. Am. Chem. Soc.*, **87**, 2505 (1965).

(2) O. Yonemitsu, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3941 (1966).

(3) G. Ballé, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3946 (1966).

(4) A. J. Birch, *Quart. Rev.* (London), 4, 69 (1950).

(5) R. A. Benkeser and E. M. Kaiser, *J. Am. Chem. Soc.*, **85**, 2858 (1963); R. A. Benkeser, E. M. Kaiser, and R. F. Lambert, *ibid.*, **86**, 5272 (1964).

(6) A. F. Fentiman, Jr., and R. H. Poirier, *Chem. Ind.* (London), 813 (1966).

(7) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963). The authors wish to express their gratitude to Dr. Levine for supplying a sample of this compound and also the epimeric 3β,17β-dihydroxy-5(10)-estrene.

(8) A. D. Cross, E. Denot, R. Acevedo, R. Urquiza, and A. Bowers, *J. Org. Chem.*, 29, 2195 (1964).

(9) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 339.

(10) Reference 9, p 345.

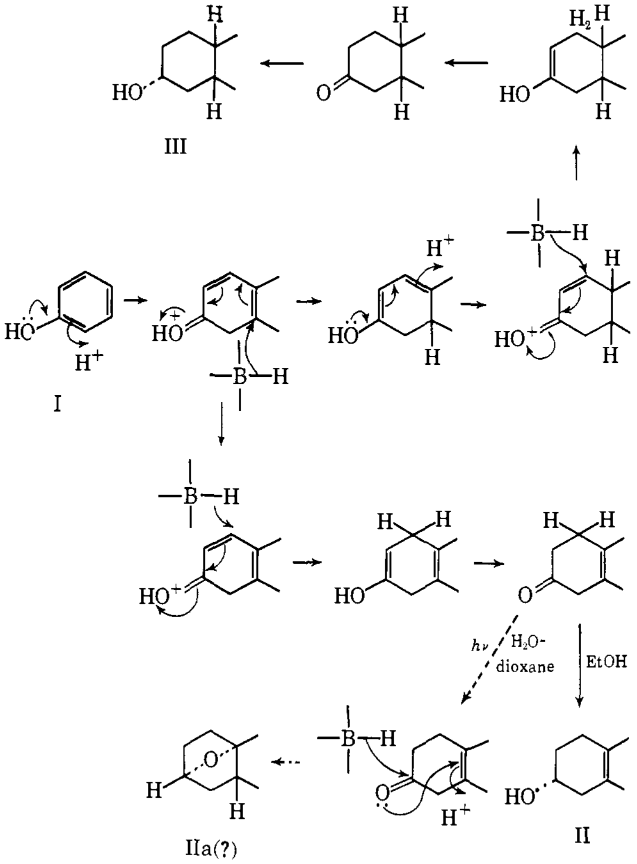
(11) R. E. Counsell, *Tetrahedron*, **15**, 202 (1961).

(12) R. T. Rapala and E. Farkas, *J. Am. Chem. Soc.*, **80**, 1008 (1958). The authors wish to express their gratitude to Dr. Rapala for supplying a sample of this compound.

of this compound with estrene II, a distinct melting point depression of 183–202° was observed. The mass spectrum showed peaks at $M^+$ 276, $m/e$ 199 and 131. Furthermore, the entire fragmentation pattern was identical with that of 3α,17β-dihydroxy-5(10)-estrene (II). The epimeric 3β,17β-dihydroxy-5(10)-estrene[7] could be immediately excluded by its low melting point of 130–132°.

Pending further investigation a possible structure for this isomer of II may be a valence (if not a "switch-bond") isomer, such as IIa, as shown in the hypothetical reaction scheme, in which the phenol I may equally well be represented by the phenoxide ion, and the photoaddition of hydride ion may well be the addition of H· to a radical intermediate. The scheme shows clearly that the estrene II is the end product of a separate sequence and cannot be an intermediate on the way to the estrane III.

In order to make a direct comparison with the Birch reduction,[13] 3,17β-estradiol 3-methyl ether was subjected to photoreduction. However, the reaction was not encouraging. The irradiation mixture contained five monomers in addition to polymeric material (56%).



Irradiation of 3α,17β-dihydroxy-5(10)-estrene (II) gave only starting material, thus excluding the possibility of II being the intermediate in the reduction to the estrane III. The absence of α,β-unsaturated ketone or dienone absorption in the ultraviolet suggests that a $\pi \rightarrow \pi^*$ transition is operative in these reactions. The formation of solvated electrons in the photolysis of phenolate ion in aqueous solutions was found to arise from an internal $\pi \rightarrow \pi^*$ excitation.[14]

## Discussion

The reducing species in this and related reactions[3] still has to be established. Hydrogen atoms generated by mercury-photosensitized reactions of hydrogen are regarded as typical "radical" reagents.[15] The large amount of polymer formation in our photolyses *a priori* need not imply a free radical mechanism, since polymer formation in the photoisomerization of dialkylbenzenes did not appear to be a free-radical recombination process.[16]

The preferential attack of hydrogen atoms at the photoexcited C-1 to C-4 positions of estradiol and the secondary attack at the more highly substituted C-5 and C-10 positions is in accord with addition of hydrogen atoms to olefins.[17] The reactivity of radicals with multiple bonds can be treated by the free-valence theory[18] or by localization energies.[19] Both concepts permit no clear predictions, however.[20]

**Photoreductions with Sodium Sulfite.** The novel photoreduction of the heterocyclic ring of kynurenic acid to the dihydroquinolone derivative, *i.e.*, kynurenine yellow, in aqueous solution containing *sodium sulfite*[21] prompted us to determine whether this method was capable of reducing phenolic systems and whether the sulfite reduction would be milder than catalytic hydrogenations at elevated pressures.[12,22]

A solution of 3,17β-estradiol ($2.7 \times 10^{-3}$ *M*) and sodium sulfite ($2.2 \times 10^{-1}$ *M*) in ethanol–water (1:2) was irradiated with a Hanovia medium-pressure mercury vapor lamp, 679A-36, equipped with a Vycor filter. Again, the disappearance of the ultraviolet absorption band at 288 mμ was recorded at intervals during the reaction period (24 hr). Extraction of the aqueous alcoholic solution with chloroform gave a white solid in 40–58% yield. The rate of the reaction and the yield of photoreduced product were not affected appreciably by change in the sulfite concentration employed, *i.e.*, $0.55 \times 10^{-1}$ to $2.2 \times 10^{-1}$ *M* (Table I). Concentration of the aqueous layer, followed by acidification, and then extraction with chloroform gave no additional product. A gas–liquid chromatogram of the crude material indicated the presence of two photoreduced monomers (*ca.* 44% of the chloroform-soluble extract).

The major photoreduced monomer IV was isolated by repetitive column chromatography of the crude product. 3β,17β-Dihydroxy-5α,10β-estrane (IV) was obtained as white flakes, mp 175–177°, $[\alpha]^{22}\text{D}$ +32.2° (lit.[11] mp 171–173°, $[\alpha]^{26}\text{D}$ +26°). Acetylation of the estranediol IV with pyridine–acetic anhydride gave 3β,17β-diacetoxy-5α,10β-estrane, mp 145–147° (lit.[11] mp 142–145°).

A minor amount of a second reduction product accompanying the estrane IV was not isolated. Its glpc retention time was similar to the estrene standard,

---

(13) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

(14) J. Jortner, M. Ottolenghi, and G. Stein, *ibid.*, **85**, 2712 (1963).

(15) R. J. Cvetanovic, *Advan. Photochem.*, **1**, 163 (1963).

(16) K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, **86**, 2307 (1964).

(17) Reference 15, p 157.

(18) B. Pullman and A. Pullman, *Progr. Org. Chem.*, **4**, 31 (1958).

(19) F. H. Burkitt, C. A. Coulson, and H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **47**, 553 (1951).

(20) K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, **21**, 174 (1953).

(21) T. Tokuyama, S. Senoh, T. Sakan, K. S. Brown, Jr., and B. Witkop, *J. Am. Chem. Soc.*, **89**, 1017 (1967).

(22) C. Chen, *Tetrahedron*, **3**, 43 (1958).

**Table I.** Comparison of Sulfites and Other Sulfur-Containing Salts as Partners in the Photoreduction of 3,17β-Estradiol

| Salt | Concn, $M$ | | Yields, % | | | Photoreduced monomers |
|---|---|---|---|---|---|---|
| | Salt, $10^{-1}$ | 3,17β-Estradiol, $10^{-3}$ | $CHCl_3$ extract | Photoreduced monomers | Polymers | |
| Sodium sulfite ($Na_2SO_3$) | 0.55 | 5.4 | 50 | 22 | 28 | Estrane IV (+ unidentified estrene) |
| | 1.1 | 2.7 | 40 | 17 | 23 | |
| | 2.2 | 2.7 | 58 | 25 | 33 | |
| Sodium bisulfite ($NaHSO_3$) | 1.1 | 2.7 | 13 | 6 | 7 | Estrane IV (+ estrene) |
| | 2.2 | 2.7 | 31 | 14 | 17 | |
| Sodium metabisulfite ($Na_2S_2O_5$) | 1.1 | 2.7 | 17 | 7 | 10 | Estrane IV |
| Sodium hydrosulfite ($Na_2S_2O_4$) | 1.1 | 2.7 | 12 | 5 | 7 | Estrane IV |
| Sodium thiosulfate ($Na_2S_2O_3$) | 1.1 | 2.7 | ... | 0 | ... | ... |
| Sodium dithionate ($Na_2S_2O_6$) | 1.1 | 2.7 | ... | 0 | ... | ... |

*i.e.*, 3α,17β-dihydroxy-5(10)-estrene (II), obtained from the borohydride reduction. The remaining solid from the chloroform extract (*ca.* 56%), obtained from more polar solvent elution of the chromatographic column, was judged to be polymeric material on the basis that it was not detected by glpc.

Sodium bisulfite, sodium metabisulfite, and sodium hydrosulfite were also found to be effective in this reduction (Table I). However, the yields were not comparable to the sodium sulfite reduction. A twofold increase in the sodium bisulfite concentration increased the yield of photoreduced material considerably. The fully oxygenated salts, sodium thiosulfate and sodium dithionate, were found to be ineffective as reducing agents.

In initial experiments, sodium hydroxide was added to the already basic reaction medium to increase the solubility of estradiol. However, complete solution of estradiol and sodium sulfite was possible with ethanol–water (1 : 2) without additional base. The presence of additional sodium hydroxide appeared to have no effect on the course of irradiation.

## Discussion

The formation of saturated *trans*-estrane IV as the predominant compound in the sulfite photoreduction differs from the borohydride reduction in which the 5(10)-estrene II is the major and the *cis*-estrane III the minor reduction product. The difference in the stereochemistry at the A/B ring juncture of the estrane compounds from the sulfite reduction (*trans:* 5α,10β) and the borohydride reduction (*cis:* 5β,10β) strongly suggests a different mechanism is operative in each case.

The photoreduction of estradiol may proceed through a sulfinate intermediate. The sulfinate group could be cleaved photolytically, followed by attack of hydrogen abstracted from solvent, or by hydrolysis of the sulfinate group, to give the reduced compound. Such addition–reductions are known to occur with heterocycles *in the ground state*. For example, the dithionite reduction of DPN[23] and N-benzylnicotinamide[24] proceeds *via* a sulfinate, followed by hydrolysis to the 1,4-dihydropyridine and sulfite. Sulfinate intermediates of estradiol or estradiol cleavage products, which are not photolyzed or are unreactive to solvent, may account for the large amount of water-soluble material present in this reaction. Further work on the mechanism of this photoreduction is in progress.

High-dilution technique might be employed for the suppression of polymerization. However, even dilution may not be a safeguard against photochemical dimerization, as has been observed in the case of B-norcholestadiene.[25]

## Experimental Section

**Apparatus.** Melting points were obtained on a Kofler hot stage and are uncorrected. The ultraviolet spectra were obtained in ethanol or 33% aqueous ethanol on a Cary 15 spectrograph. The glpc data were obtained on a Barber-Colman Series 5000 gas chromatograph using a 1% (4%) SE-30 column on Gas Chrome P, 100–120 mesh, column temperature 190° (200°), 30 psi. The irradiations were performed with a 450-w Hanovia mercury-vapor lamp, 679A-36, using a water-cooled, quartz immersion well equipped with a Vycor filter. Nitrogen was passed through the solution during the entire irradiation period. The molecular weights of the polymers were determined on a Mechrolab osmometer, Model 301A, in dioxane. The infrared spectra were obtained on a Perkin-Elmer spectrometer (Model 21) in chloroform, the nmr spectra on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as the internal standard, and the mass spectra on a mass spectrometer AEI MS 9 at 70 ev.

**Photoreduction of 3,17β-Estradiol in Ethanol.** A solution of 4.1 g (0.015 mole) of 3,17β-estradiol and 2.27 g (0.06 mole) of sodium borohydride in 1 l. of absolute ethanol was irradiated by a 450-w Hanovia medium-pressure, mercury-vapor lamp. The disappearance of the aromatic absorption band in the ultraviolet at 288 mμ was recorded using optical density units at the following times (in hours): 0, 1.46; 1, 1.13; 2, 0.97; 3, 0.86; 4, 0.77; 5, 0.71; 7, 0.60; 10, 0.45; 13, 0.36; 16, 0.30; 19, 0.28; 34, 0.15. On completion of the 34-hr reaction period, the solvent was removed under reduced pressure and the brown solid distributed between 50 ml of chloroform and 50 ml of water. The aqueous extract was washed with chloroform, and the combined chloroform extracts were washed with water and saturated sodium chloride solution and then dried over sodium sulfate. Removal of the solvent gave 3.86 g of tan solid. A glpc spectrum (4% SE-30 column, 200°) of the crude product showed four peaks at 7.3, 9.5, 10.9, and 12.7 min (approximately 10, 5, 20, and 65%), respectively, by area under peak method. The crude product was subjected to column chromatography (230 g of Woelm alumina, grade 1, 800 ml of solvent per fraction). Two similar irradiations and chromatographic separations were carried out to give the combined total amounts of material from each fraction (Table II). Glpc of each of the fractions indicated a total of 24% monomers and 76% polymers were present in the crude reaction mixture. The fraction notations used in Table II will be used in the experiments to be described.

**3α,17β-Dihydroxy-5(10)-estrene (II).** A glpc chromatogram of fraction 5 showed two main peaks with retention times of 10.9 and

---

[23] M. B. Yarmolinsky and S. P. Colowick, *Biochim. Biophys. Acta*, **20**, 177 (1956).

[24] W. S. Caughey and K. A. Schellenberg, *J. Org. Chem.*, **31**, 1978 (1966).

[25] W. G. Dauben, *Chem. Weekblad*, **60**, 381 (1964).

**Table II**

| Fraction | Solvent | Amount, g |
|---|---|---|
| 1 | Ether | |
| 2 | 0.1% methanol in ether | 0.10 |
| 3 | 0.25% methanol in ether | |
| 4 | 0.5% methanol in ether | 0.81 |
| 5 | 1% methanol in ether | 1.17 |
| 6 | 2.5% methanol in ether | 1.17 |
| 7 | 5% methanol in ether | 2.27 |
| 8 | 10% methanol in ether | 2.71 |
| 9 | 25% methanol in ether | 2.59 |
| 10 | 50% methanol in ether | 0.43 |

12.7 min (9 and 85%, respectively). The fraction was chromatographed on alumina (70 g). Elution with 0.5 and 1% methanol in ether gave 804 mg of colorless solid which was enriched with the higher retention-time compound (glpc). This material was recrystallized from acetone–methanol to give 163 mg of white plates, mp 195–200°. Additional crystalline crops, slightly less pure, could be obtained from the mother liquors. A second recrystallization from acetone–methanol raised the melting point to 206–208°, $[\alpha]^{24}\mathrm{D}$ +167.1° (CHCl$_3$) [lit. for 3α,17β-dihydroxy-5(10)-estrene, mp 205–207°, $[\alpha]\mathrm{D}$ +186° (CHCl$_3$),[7] and mp 208–209°, $[\alpha]\mathrm{D}$ +122.5° (CHCl$_3$)[26]]. A mixture melting point with an authentic sample[7] was 205–208° (no depression); glpc retention time and infrared spectrum of both samples were identical; nmr spectrum: no olefinic proton absorption; mass spectrum: M$^+$ 276, *m/e* 199 and 131.

The diacetate of II (37.8 mg) was prepared with 0.4 ml of acetic anhydride and 3 ml of pyridine. The solution was kept at room temperature for 12 hr, followed by heating for 1 hr at 60°. The cooled solution was added, with stirring, to 15 ml of cold 5% sodium carbonate. The colorless solid was removed by filtration and then washed with water. Recrystallization of the dried product from methanol–dichloromethane gave 22 mg of colorless needles, mp 118–120°. A second recrystallization raised the melting point to 119–120°; $[\alpha]^{21}\mathrm{D}$ +145.7° (CHCl$_3$) [lit.[8] mp 119–120°, $[\alpha]\mathrm{D}$ +130° (CHCl$_3$)].

The colorless solid obtained from the recrystallization mother liquors of II was repeatedly crystallized to determine if any of the epimeric 3β,17β-dihydroxy-5(10)-estrene[7] was present. None of the lower melting epimer, mp 130–132°, was obtained.

**3α,17β-Dihydroxy-5β,10β-estrane (III).** A glpc chromatogram of fraction 6 displayed two main peaks (same as fraction 5) with retention times of 10.9 and 12.7 min (46 and 41%, respectively). To obtain the lower retention time compound in pure form, the fraction (1.17 g) was chromatographed on 70 g of alumina (grade 1). Elution with 1% methanol in ether (120 ml) gave 303 mg of colorless solid (30% contamination with the 12.7-min compound). Further purification of this material was achieved by chromatography on silica gel (100–200 mesh; 15 g). Elution with ether–benzene (1:1) and ether gave 242 mg of colorless solid, which was subjected to two more column chromatographic separations (alumina) to give 62 mg of colorless solid, highly enriched in the desired compound according to glpc. However, this material could not be crystallized from a number of solvent systems, apparently owing to a small amount of contamination. The material was then subjected to preparative tlc (silica gel G, *n*-hexane–acetone–ether, 6:2:2; continuous development for 2 hr). Inspection of the plate under short-wave ultraviolet light showed a purple zone. Elution of this zone with acetone gave 42 mg of colorless solid which was recrystallized from acetone–methanol to give colorless clusters, mp 200–202°, with transformation into needles at 175–180°. A second recrystallization from the same system gave 3α,17β-dihydroxy-5β,10β-estrane (III) as colorless needles, mp 202–204°, $[\alpha]^{22}\mathrm{D}$ +25.2° (CHCl$_3$) [lit. mp 207–208°, $[\alpha]^{25}\mathrm{D}$ +29.8° (CHCl$_3$),[11] and mp 211–212°, $[\alpha]^{25}\mathrm{D}$ +10.2° (CH$_3$OH)[12]]. The mixture melting point with an authentic sample,[12] mp 206.5–207.5°, was 202–204.5° (no depression). The tlc and glpc retention time of both samples were identical. Spectral investigations showed: infrared spectrum at 3600, 1455, 1380, 1132, 1050, 1028, and 952 cm$^{-1}$; mass spectrum at M$^+$ 278, *m/e* 201 and 133.

**Photoreduced Polymers of 3,17β-Estradiol.** Fraction 8 (2.71 g), undetected by glpc, was chromatographed on 160 g of alumina. Elution with 10% methanol in ether gave 1.8 g of brown solid. The trimer was crystallized two times from acetone to give a light brown solid, mp 235–240°.

*Anal.* Found: C, 75.52; H, 9.90; mol wt, 828 (osmometer).

Fraction 9 was chromatographed on 156 g of alumina. Elution with 25% methanol in ether gave 1.7 g of brown solid. Two crystallizations of the hexameric product from acetone–methanol afforded a tan solid, mp >300°.

*Anal.* Found: C, 75.83; H, 9.93; mol wt, 1718 (osmometer).

**Irradiation of 3α,17β-Dihydroxy-5(10)-estrene (II).** A solution of 45 mg of pure 3α,17β-dihydroxy-5(10)-estrene (II) and 227 mg of sodium borohydride in 100 ml of absolute ethanol was photolyzed in the manner described above for 24 hr. Work-up of the reaction mixture in the usual manner gave 42 mg of colorless solid, the glpc retention time of which was identical with that of the starting material. Recrystallization of the product from acetone–methanol gave 31 mg of colorless crystals, mp 207–209°. A mixture melting point with II showed no depression.

**Photoreduction of 3,17β-Estradiol in Dioxane–Water.** A solution of 4.1 g (0.015 mole) of 3,17β-estradiol and 2.27 g (0.06 mole) of sodium borohydride in 1 l. of dioxane–water (9:1) was photolyzed under the conditions previously described. The irradiation was stopped after 22 hr (OD$_{288\mathrm{m}\mu}$ 0.17) and worked up in the usual manner. A glpc chromatogram of the crude product displayed peaks at 7.3, 9.5, 10.9, and 12.7 min (10, 15, 10, and 65%, respectively). Elutions with 2.5, 5, 10, and 25% methanol in ether gave polymeric material (3.02 g, 75% of total product). Elution with 1% methanol in ether gave 340 mg of colorless gum which was chromatographed two more times to give 39 mg of product. Two crystallizations from acetone–methanol gave a colorless crystalline solid (2.6 mg), mp 202–205°. A third recrystallization raised the melting point to 206.5–208.5°. A mixture melting point with 3α,17β-dihydroxy-5(10)-estrene (II), mp 206–208°, showed a distinct depression, mp 181–202°. The mass spectrum showed M$^+$ 276, *m/e* 191 and 131; the entire fragmentation pattern was identical with that of compound II obtained from the photoreduction in ethanol.

**Photoreduction of 3,17β-Estradiol 3-Methyl Ether.** To 10.0 g of 3,17β-estradiol in 150 ml of 95% ethanol was added an excess of ethereal diazomethane (from 22.4 g of N-methyl-N′-nitro-N-nitroguanidine) and the reaction mixture stirred overnight. The crude product was recrystallized from 80% ethanol to yield 9.7 g of the 3-methyl ether, mp 119–121° (lit.[13] 120.5–121.5°). A solution of 9.7 g of 3,17β-estradiol 3-methyl ether in 2.4 l. of absolute ethanol containing 5.14 g of sodium borohydride was photoreduced as previously described. The ultraviolet absorption band at 278 mμ was recorded using optical density units at the following times (in hours): 0, 1.48; 1, 1.38; 2, 1.29; 3, 1.25; 4, 1.23; 5, 1.19; 7, 1.14; 24, 0.71; 48, 0.27; 65, 0.09; 80, 0.01. On completion of the 80-hr reaction period, the crude product was obtained in the usual manner. Column chromatography of the material and glpc of the fractions obtained showed five monomers (44% of total) and the remainder was polymeric material.

**Photoreductions of 3,17β-Estradiol (I) With Sodium Sulfite. A. Na$_2$SO$_3$ 1.1 × 10$^{-1}$ *M* and 3,17β-Estradiol 2.7 × 10$^{-3}$ *M*.** As a control experiment a solution of 272 mg of 3,17β-estradiol and 80 mg of sodium hydroxide in 375 ml of dilute ethanol (33%) was irradiated for a period of 19 hr.

A solution containing 109 mg of 3,17β-estradiol, 40 mg of sodium hydroxide, and 2.0 g of sodium sulfite in 150 ml of dilute ethanol (33%) and a similar solution containing no base were placed in the dark for 20 hr.

Each of the three above experiments showed no change in starting material by glpc, tlc, and ultraviolet spectra.

A solution of 544 mg (2 mmoles) of 3,17β-estradiol and 160 mg (4 mmoles) of sodium hydroxide in 250 ml of ethanol was added to a solution of 10.0 g (0.08 mole) of sodium sulfite (Na$_2$SO$_3$) in 500 ml of water. The resulting clear solution was irradiated for 24 hr. The disappearance of the aromatic absorption band at 297 mμ in the ultraviolet was recorded using optical density units at the following times (in hours): 0, 1.97; 2, 1.55; 18, 0.11. On completion of the 24-hr reaction period, the solution was extracted five times with 75-ml portions of chloroform. The combined chloroform extracts were washed two times with water and dried over sodium sulfate to yield 215 mg of a colorless solid (*ca.* 40%). Evaporation of the aqueous solution, acidification with 20% hydrochloric acid (to congo red), and extraction with chloroform gave no appreciable amount of additional material. A glpc chromatogram (1% SE-30 column, 190°) of the chloroform-soluble extract indicated the presence of two photoreduced monomers at 3.4 (major compound) and 4.5 min (minor). The major peak at 3.4 min had

---

[26] J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955).

an identical retention time with a saturated estrane standard, *i.e.*, 3α,17β-dihydroxy-5β(10β)-estrane (III), and the minor compound a glpc retention time similar to a 3α,17β-dihydroxy-5(10)-estrene (II) standard.

**B. Na$_2$SO$_3$ 0.5 × 10$^{-1}$ *M* and Estradiol 5.4 × 10$^{-3}$ *M*.** This experiment represents a one-half decrease in sodium sulfite concentration and twofold increase in 3,17β-estradiol concentration in relation to the experiment described above. A solution of 1.306 g of 3,17β-estradiol and 384 mg of sodium hydroxide in 300 ml of ethanol was added to 6.0 g of sodium sulfite in 600 ml of water. The solution was irradiated and the ultraviolet absorption band at 297 mμ recorded using optical density units at the following times (in hours): 0, 2.09; 2, 1.85; 6, 1.41; 19, 0.58; 27, 0.28; 44, 0.04. The reaction mixture was worked up in the usual manner, the chloroform extract amounting to 664 mg of pale yellow solid (*ca.* 50%). The glpc chromatogram of the material showed the presence of two reduced compounds (3.4 and 4.5 min) in the same ratio as found in the foregoing experiment.

**C. Absence of Additional Base.** A solution of 653 mg (2.4 mmoles) of 3,17β-estradiol in 300 ml of ethanol was added to 24.0 g (0.19 mole) of sodium sulfite in 600 ml of water. The resulting clear solution was photoreduced for 24 hr. This disappearance of the aromatic absorption band at 288 mμ was recorded using optical density units at the following times (in hours): 0, 1.63; 1, 1.60; 2, 1.42; 4, 1.17; 7, 0.83; 12, 0.50; 18, 0.27; 24, 0.13. The chloroform-soluble extract gave 380 mg of colorless solid (*ca.* 58%). The glpc chromatogram showed peaks at 3.4 and 4.5 min as previously described. Ten similar irradiations were carried out. The combined chloroform extracts from each amounted to 3.76 g of crude photoreduced material which was chromatographed on 165 g of alumina (Woelm, neutral grade 1). Elution with 1.7 l. of 0.25% methanol in ether gave 474 mg of colorless solid enriched in the two photoreduced monomers. This material was chromatographed on 25 g of alumina. Elution with 0.17 and 0.25% methanol in ether gave 104 and 118 mg of photoproduct, respectively, whose glpc chromatograms showed a single peak at 3.4 min corresponding to the major photoreduced compound (*ca.* 70% of the total photoreduced monomers). The combined material (222 mg) was crystallized from acetone to give 177 mg of colorless flakes, mp 160–165°, sintering at 130°. Two recrystallizations from acetone–methanol gave 3β,17β-dihydroxy-5α,10β-estrane (IV), mp 175–177°, $[\alpha]^{22}\text{D}$ +32.2° (CHCl$_3$). Two additional recrystallizations from ethyl acetate did not raise the melting point [lit.[11] mp 171–173°, $[\alpha]^{26}\text{D}$ +26° (CHCl$_3$)].

*Anal.* Calcd for C$_{18}$H$_{30}$O$_2$: C, 77.65; H, 10.86. Found: C, 77.44; H, 10.90.

Dihydroxy-5α,10β-estrane (15.3 mg) was acetylated with 0.2 ml of acetic anhydride and 1.0 ml of pyridine. The solution was heated for 2 hr at 80° and then kept at room temperature overnight. The reaction mixture was slowly added, with stirring, to 10 ml of ice water. The colorless solid was removed by filtration and washed with water. The product was crystallized from ethanol–water to give 3β,17β-diacetoxy-5α,10β-estrane as colorless flakes, mp 145–147° (lit.[11] mp 142–145°).

The minor monomeric photoreduction product (4.5-min glpc retention time) was found to be present in the 0.5 and 1% methanol–ether elutions of the initial chromatographic separation. The compound (*ca.* 30% of total monomer yield) was not isolated in pure form.

Elution of the chromatographic column with more polar solvent (5, 25, and 50% methanol in ether) gave polymeric material (*ca.* 56% of the chloroform-soluble extract) which was not detected by glpc.

**Photoreduction of 3,17β-Estradiol. A. With Sodium Bisulfite.** A solution of 544 mg (2 mmoles) of 3,17β-estradiol and 160 mg of sodium hydroxide in 250 ml of ethanol was added to a solution of 8.3 g (0.08 mole) of sodium bisulfite (NaHSO$_3$) in 500 ml of water. A small amount of bisulfite precipitated which was removed by filtration. The solution was irradiated for 18 hr. An aliquot of the solution showed no aromatic ultraviolet absorption at 297 mμ. The chloroform extract gave 70 mg (*ca.* 13%) of colorless solid. A glpc chromatogram of the product showed a single peak at 3.4 min, identical with the retention time of 3β,17β-dihydroxy-5α,10β-estrane (IV).

An increase in yield of the chloroform-soluble extract (31%) was obtained by irradiation (20 hr) in which the sodium bisulfite concentration was increased twofold and in the absence of sodium hydroxide. The material consisted of two photoreduced monomers with identical glpc retention times as the compounds from the sodium sulfite reaction.

**B. With Sodium Metabisulfite.** A solution of 544 mg of 3,17β-estradiol and 160 mg of sodium hydroxide in 250 ml of ethanol was added to 15.2 g (0.08 mole) of sodium metabisulfite (Na$_2$S$_2$O$_5$) in 500 ml of water. The cloudy solution was irradiated for 18 hr. The ultraviolet absorption at 297 mμ of an aliquot of the solution had decreased to zero. The chloroform extract gave 92 mg (17%) of colorless solid, a glpc chromatogram of which indicated the presence of a single photoreduced monomer identical with estrane IV.

**C. With Sodium Hydrosulfite.** 3,17β-Estradiol was irradiated for 18 hr as described above in the presence of sodium hydrosulfite (Na$_2$S$_2$O$_4$). A glpc chromatogram of the chloroform-soluble extract (65 mg, 12%) displayed a single peak whose retention time corresponded to compound IV from the sodium sulfite reaction.

**Attempted Photoreductions. A. Sodium Thiosulfate.** 3,17β-Estradiol (544 mg) was photolyzed (18 hr) in the manner described above in the presence of 19.8 g (0.08 mole) of sodium thiosulfate (Na$_2$S$_2$O$_3$·5H$_2$O). The solution turned deep red in color after a few minutes of irradiation. The chloroform extract gave a dark brown solid (132 mg) consisting of starting material and no detectable amount of photoreduced monomer by glpc.

**B. Sodium Dithionate.** Irradiation of 3,17β-estradiol (544 mg) for 24 hr in the presence of sodium dithionate (19.4 g, 0.08 mole, Na$_2$S$_2$O$_3$·2H$_2$O) gave 348 mg of dark brown solid. The glpc chromatogram of the material indicated the absence of any reduced monomer.

**Acknowledgment.** The initial observations on the photoreduction of phenols were made by Dr. P. Cerutti, now Department of Chemistry, Princeton University, and Dr. James A. Moore, then Visiting Professor from the University of Delaware. Preliminary experiments on the photoreduction of estradiol were carried out by Dr. M. Chaykovsky. We are greatly indebted to Professor Robert M. Moriarty, Catholic University of America, for constructive criticism of the manuscript.

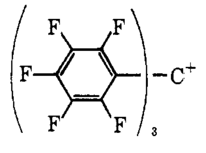
# Communications to the Editor

## Tris(pentafluorophenyl)methyl Cation

*Sir:*

We wish to report the preparation and spectroscopic detection of tris(pentafluorophenyl)methyl cation (I).

Tris(pentafluorophenyl)carbinol (II), mp 116–117° (cor), was prepared in 72% yield by reaction of decafluorobenzophenone[1] with pentafluorophenyllithium (from C$_6$F$_5$Br + *n*-BuLi) in *n*-hexane solution at −78° or preferably, in 60% yield, by reaction of pentafluorophenyllithium with ethyl pentafluorobenzoate in ether at −65° (*Anal.* Calcd for C$_{19}$HOF$_{15}$: C, 43.04; H,



I

---

[1] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 166 (1959).