68.70°. Recrystallization from methanol furnished the analytical sample, m.p. 74–75°, $[\alpha]_D$ +58°.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.85; H, 9.92. Found: C, 84.73; H, 9.90.

Reaction of 2-Hydroxymethyl-5α-androst-2-en-17β-ol 17-Acetate (VIIIb) with the Reagent I.—A solution of 1.73 g. (5 mmoles of 2-hydroxymethyl-5α-androst-2-en-17β-ol acetate (VIIIb, 1.0 g., 5 mmoles) of the reagent I, and dry tetrahydrofuran (20 ml.) was warmed gently on the steam bath for 10 min. Solvent was removed by evaporation under reduced pressure and the residual oil was adsorbed from hexane onto Florisil (100 g.). Elution with hexane–ether (9:1) afforded the mixed fluorinated products (see Discussion) (1.13 g., 65%), m.p. 110–117°, m.p. 115–117° after recrystallization from methanol, $[\alpha]_D$ +40°. Further elution with the same solvent system yielded the ether XXVII (0.59 g., 38%), m.p. 180–183°, raised to 203–205° by recrystallization from ethyl acetate; $[\alpha]_D$ +61°; ν_{max} 1738 and 1255 cm.$^{-1}$ (acetate).

Anal. Calcd. for $C_{44}H_{66}O_5$: C, 78.31; H, 10.16. Found: C, 78.45; H, 10.05.

Acknowledgment.—The authors are indebted to Professor C. Djerassi for the mass spectra and for consultations on their significance.

Steroids. CCLVII.[1] 5,10-Disubstituted Estranes

ALEXANDER D. CROSS, E. DENOT, R. ACEVEDO, R. URQUIZA, AND A. BOWERS

The Research Laboratories of Syntex, S. A., Apartado 2679, Mexico, D. F., Mexico

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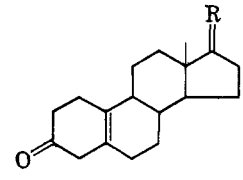
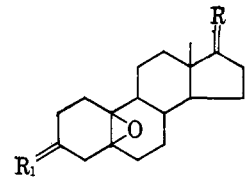
Epoxidations of various 3,17-disubstituted estr-5(10)-enes have been effected. Additions to the 5β,10β-epoxides, with ring opening, gave a variety of 5,10-disubstituted estranes including some stereoisomeric 3,5,10,17-tetrols and their derivatives. Assignment of configuration in estran-3α-ol 5β,10β-epoxide 3-acetates was facilitated by the occurrence of an intramolecular acetylation to give 5α-acetates.

Although strenuous efforts have been directed to the synthesis of 19-norsteroids bearing a 10β-hydrogen,[2] relatively little has been reported concering 19-norsteroids derived by electrophilic addition to estr-5(10)-enes. Rapala and Farkas described the hydrogenation of the latter compounds[3] and, with co-workers, converted a series of estr-5(10)-en-3-ones to estra-4,9-dien-3-ones by addition of bromine across the 5(10)-double bond followed by dehydrohalogenation.[4] An earlier communication from the Syntex laboratories revealed the conversion of 17β-hydroxyestr-5(10)-en-3-one (Ia) to the corresponding 5β,10β-epoxide (IIa).[5] Isomerization of the latter (IIa) with base afforded 10β-hydroxy-19-nortestosterone (IIIa), whose stereochemical identity had been established previously by optical rotatory dispersion studies.[6] Cleavage of the epoxide (IIa) by boron trifluoride led to the corresponding 5α-fluoro-10β-hydroxy derivative.[5] β-Addition of osmium tetroxide to the estra-5(10)-ene (Ia) is described in the patent literature, but no constants are given for the product.[7] Another patent claims that peracid oxidation of estr-5(10)-ene-3,17-dione (Ib) leads to a mixture of 10α- and 10β-hydroxyestr-4-ene-3,17-dione.[8] No firm evidence for the formation of the 10α-hydroxy compound is provided.

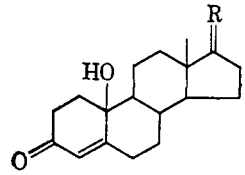
In view of the pre-eminent position occupied by estrane derivatives in the realm of ovulation inhibition by oral administration, we continued researches into electrophilic additions to nonconjugated 5(10)-double bonds.[9]



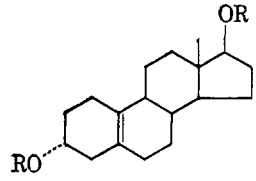
Ia, R = α-H, β-OH
b, R = O



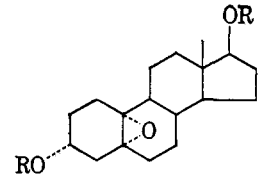
IIa, R = α-H, β-OH; R_1 = O
b, R = R_1 = O
c, R = R_1 = α-H, β-OH
d, R = α-H, β-OH; R_1 = α-OH, β-H
e, R = α-H, β-OAc; R_1 = α-OAc, β-H
f, R = R_1 = α-H, β-OAc
g, R = O; R_1 = α-OH, β-H



IIIa, R = αH, βOH
b, R = O



IVa, R=H
b, R=Ac



Va, R=H
b, R=Ac

Peracid oxidation of estr-5(10)-ene-3,17-dione (Ib) afforded the corresponding 5β,10β-epoxide (IIb).[11]

(1) Steroids CCLVI: I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

(2) For reviews see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 18; F. J. Kakis, "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 6; A. Bowers, *Drug Trade News*, 39 (Sept. 16, 1963).

(3) R. T. Rapala and E. Farkas, *J. Org. Chem.*, **23**, 1404 (1958).

(4) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(5) J. Pérez Ruelas, J. Iriarte, F. A. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(6) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(7) R. L. Pederson and J. C. Babcock, U.S. Patent 2,806,862 (1957).

(8) F. B. Colton, U. S. Patent 2,729,654 (1956).

(9) During the final stages of our work, we became aware of independent and simultaneous studies by Dr. S. G. Levine in this field. Very few of our results overlap with his and, generally, the two separate studies utilized different substituents at C-17. We wish to acknowledge a most friendly exchange of information with Dr. Levine and express thanks for a copy of his recent communication[10] prior to publication.

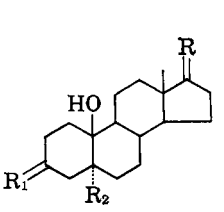
(10) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).

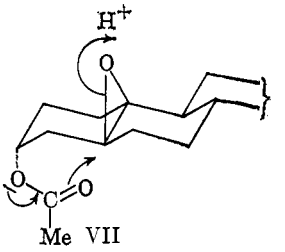
(11) After completion of our work (1962), R. Gardi, C. Pedrali, and A. Ercoli [*Gazz. chim. ital.*, **93**, 1503 (1963)] reported bromination and epoxidation of estr-5(10)-enes.

Sodium borohydride reduction of the latter furnished estrane-3β,17β-diol 5β,10β-epoxide (IIc), also obtained by borohydride reduction of the related 3-ketone IIa.[5] A 3β-orientation of the hydroxyl is expected since the β-epoxide function should hinder β-face approach of the reagent to the 3-keto group. When estr-5(10)-ene-3,17-dione or the monoketone Ia[5] was first reduced to a diol (shown in the sequel to be IVa) then subjected to peracid oxidation, estrane-3α,17β-diol 5β,10β-epoxide (IId) was obtained. The derived diacetate IIe was different from that (IIf) prepared from the first diol epoxide IIc. Alkaline hydrolysis of the 3α,17β-diacetate IIe regenerated the diol IId, thus demonstrating the stability of the 3α-hydroxy 5β,10β-epoxide system to mild base treatment. In a further structural correlation estr-5(10)-ene-3α,17β-diol (IVa) was converted to the diacetate IVb and epoxidation carried out to yield the same 5β,10β-epoxide 3α,17β-diacetate IIe as was obtained by the alternative reaction sequence outlined above.

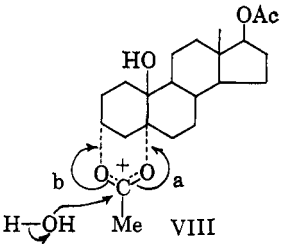
This additional correlation was deemed advisable since, although additions to 5(10)-double bonds normally proceed predominantly from the β-face[5,10] to give products containing the anti-5,9,10-backbone, a homoallylic 3α-hydroxyl might lead to a stereochemically controlled α-face epoxidation,[12] in which case the corresponding 3α-acetate would be expected to give a different epoxide though being a much less effective stereochemically controlling neighboring group.[13] Moreover, the epoxide resulting from oxidation of the 3α,17β-diacetate IVb proved to be different from estrane-3α,17β-diol 5α,10α-epoxide diacetate (Vb) described later in this work. Further chemical proof of the β-orientation of the epoxide in both diols IIc and IId stemmed from conversion (*vide infra*) of each to 10β-hydroxyestr-4-en-3-one derivatives. The epoxide configuration being established, the only possible structural difference rested in the orientation of the 3-hydroxyl group formed by reduction of 5β,10β-epoxy 3-ketones (II) and $\Delta^{5(10)}$-3-ketones (I), respectively. The formation of a 3α-hydroxyl in borohydride[16] reduction of the latter system I was proven convincingly by the following series of reactions.

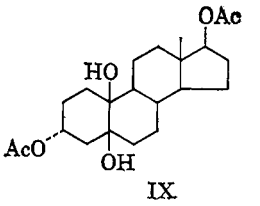
Treatment of estrane-3α,17β-diol 5β,10β-epoxide (IId) with 2 *N* sulfuric acid–ether two-phase system at room temperature (1.5 hr.) led to the expected tetrol VIa which was converted by chromic acid reagent[17] to the corresponding dione VIb (ν_{max} 1740 and 1705 cm.$^{-1}$). Methanolic potassium hydroxide effected dehydration of this 5α-hydroxy 3-ketone VIb with formation of 10β-hydroxyestr-4-ene-3,17-dione[8,11] (IIIb) which was indistinguishable from an authentic sample.[6,8] In striking contrast exposure of estrane-3α,17β-diol 5β,10β-epoxide diacetate (IIe) to the same





VIa, R = α-H, β-OH; R_1 = α-OH, β-H; R_2 = OH
b, R = R = O; R_2 = OH
c, R = α-H, β-OAc; R_1 = α-OAc, β-H; R_2 = OH
d, R = α-H, β-OAc; R_1 = α-OH, β-H; R_2 = OAc
e, R = α-H, β-OAc; R_1 = O, R_2 = OAc
f, R = R_1 = α-H, β-OAc; R_2 = OH
g, R = R_1 = α-H, β-OH; R_2 = Me
h, R = R_1 = O; R_2 = Me
j, R = α-H, β-OAc; R_1 = α-OAc, β-H; R_2 = Me





two-phase acid reagent furnished the expected estrane-3α,5α,10β-17β-tetrol 3α,17β-diacetate (VIc) as the minor product and a second diactate in abundance. The unknown diacetate was identified as estrane-3α,5α,10β,17β-tetrol 5α,17β-diacetate (VId) by virtue of its chemical properties and from the nuclear magnetic resonance (n.m.r.) spectrum[18] of the ketone VIe which was formed by oxidation of VId with chromic acid reagent.[17] The ketone VIe showed singlet resonances at 49.5 (13β-methyl) and 120.6 c.p.s. (two acetates). However, at lower fields resonance was observable at *ca.* 277 c.p.s., equivalent to only *one* proton in the environment H–C–OAc, and this had the ill-resolved triplet pattern typical of a 17α-proton in steroid 17β-acetates.[19] This information, when coupled with the fact that the ketone VIe underwent facile β-elimination of an acetate with concomitant generation of the 10β-hydroxy-4-en-3-one chromophore, as in III (λ_{max} 236–238 mμ), established that acid treatment of the epoxy diacetate IIe induced acyl migration (3α → 5α) leaving an oxidizable 3-hydroxyl group. An indication of the existence of 1,3-diaxially oriented hydroxyl and acetate group was derived from the infrared spectrum of the diacetate VId which shows acetate carbonyl stretching absorption frequencies at 1730 and 1755 cm.$^{-1}$. The latter frequency must arise from the 5α-acetate where the alcoholic oxygen is hydrogen bonded to 3α-hydroxyl leaving the carbonyl with more double bond character. Consideration of the mechanics of this reaction suggests that only when the acetate is oriented 3α does internal participation of the acetate in acid-catalyzed

(12) Henbest and Wilson have demonstrated stereochemical control of epoxidation by allylic hydroxyl,[13] but absence of such an effect with certain homoallylic alcohols.[14] However, cases have been reported where homoallylic hydroxyls can exercise stereochemical control in electrophilic additions to the proximate double bond (*e.g.*, Simmons–Smith reaction[15]).

(13) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(14) H. B. Henbest and B. Nicholls, *ibid.*, 4608 (1957).

(15) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **81**, 3235 (1961).

(16) Levine and collaborators[9] reported reduction of the 3-keto group in the system I by tritertiarybutoxy aluminum hydride to give a 3α-hydroxyl group whose orientation was established in a different manner from that reported here.

(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

(18) N.m.r. spectra were recorded at 60 Mc. for 5–8% w./v. solutions in deuteriochloroform containing a little tetramethylsilane as an internal reference standard. Chemical shifts, ν, are quoted as c.p.s. from the reference and are accurate to ±1 c.p.s. Coupling constants, *J*, also expressed in c.p.s., are accurate to ±0.5 c.p.s. We thank the Universidad Nacional Autónoma de México for time on the Varian A-60 spectrometer.

(19) *Cf.* N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 353.

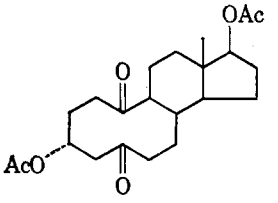
5β,10β-epoxide opening become feasible. Thus, with acid the epoxy diacetate (IIe = VII) affords a charged species VIII which can collapse through the intervention of solvent water, routes a and b, to yield *two* diacetates, VIc and VId, respectively.[20] It was established in a separate experiment that androstane-3α,17β-diol diacetate is insensitive to the mild acid conditions employed in the rearrangement. With lithium aluminum hydride the diacetate VId gave the tetrol Ia (*vide supra*) which was also arrived at by a similar reduction of the disecondary diacetate VIc. Subsequently, acetyl migration followed by oxidation to give VIe was wrought upon the epoxy diacetate IIe in one reaction through the medium of a two-phase chromic acid oxidative system.[21] Alkaline treatment of VIe led to the development of an ultraviolet absorption maximum at 236–238 mμ. The 17-ketone IIIb derived from IIIa by chromic acid oxidation[17] was indistinguishable from a specimen obtained by alkaline treatment of the epoxydione IIb.

When estrane-3β,17β-diol 5β,10β-epoxide diacetate (IIf) was subjected to dilute acid in a water–ether two-phase system, the sole isolable product was estrane-3β,5α,10β-17β-tetrol 3β,17β-diacetate (VIf), resistant to attack by chromic acid reagent.[17] Thus no internal acyl migration was effected in this case, as was expected for the 3β-oriented ester group.

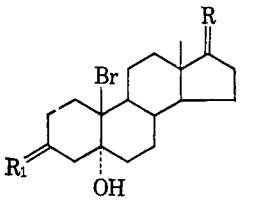
Osmium tetroxide oxidation of estr-5(10)-ene-3α,-17β-diol diacetate (IVb) led to a new tetrol diacetate which we formulate as the 5β,10β-diol IX. Lead tetraacetate cleavage then gave the 5,10-seco-5,10-dione X.

Attention was turned next to the action of methyl Grignard reagent upon the 5β,10β-epoxides. Such treatment of estrane-3β,17β-diol 5β,10β-epoxide (IIc), followed by acetylation, furnished an oily product which was hydrolyzed to the crystalline triol VIg. Oxidation led to the diketone VIh in which a new angular methyl group was disclosed by a second three-proton singlet at 74.4 c.p.s. in the n.m.r. spectrum,[16] in addition to that at 53.0 c.p.s. for the 13β-methyl. Analyses were in agreement with a C-19 structure. The corresponding 3α-alcohol IId afforded with methyl Grignard and then acetylation a triol diacetate VIj which showed three-proton singlet resonances[16] at 48.4 and 68.8 c.p.s., equivalent to *two* methyl groups attached to quaternary carbon as well as acetate proton resonance at 121.8 c.p.s. (two acetates). Accordingly, we formulate this Grignard reaction product at the 5α-methyl-10β-hydroxy derivative VIj. Insufficient material was obtained for further investigation. The 5α-methyl structures are favored since the products then possess the most stable stereochemistry of rings A, B, and C.

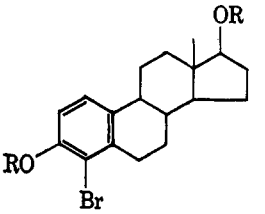
Various 10-bromo analogs were prepared and studied. Additions to the 5(10)-double bond are considered to proceed by β-face attack of a positively charged species.[5] Over-all *trans* diaxial addition is then expected to give 5α,10β-adducts. Estr-5(10)-ene-3α,17β-diol diacetate (IVb) readily added hypobromous acid leading to the 10β-bromo derivative XIa. The bromohydrin XIa on exposure to methanolic sodium methoxide underwent an internal displacement of bromide with formation of the 5α,10α-epoxide Va, purified through the diacetate Vb. Similarly estr-5(10)-ene-3,17-dione (Ib) was converted to the crude bromohydrin XIb. However, reaction of the latter with methoxide and chromatography of the product over silica gel led to only a small amount of solid showing strong ultraviolet absorption at 232–234 mμ, tentatively considered to be 10β-bromoestr-4-ene-3,17-dione. Hydrochloric acid–acetic acid reagent promoted dehydration of this unsaturated ketone to afford estrone. In an attempt to obtain more of the α-epoxide Va, oily impure fractions containing some bromohydrin XIa were subjected to methoxide ion. Chromatography of the crude product over silica gel led to an amorphous solid. Acetylation of the latter furnished a new crystalline compound giving a positive Beilstein reaction. Formulation of this compound as 4-bromoestradiol diacetate (XIIa) stems primarily from spectral analyses and is supported by elemental analyses of both the diacetate and the derived diol XIIb. Both the diacetate and diol showed ultraviolet and infrared spectral characteristics of a nonconjugated aromatic ring. In the n.m.r. spectrum the diacetate XIIa showed three-proton resonance singlets at 48 (13β-methyl), 122 (17β-acetate), and 139 c.p.s. (phenolic acetate), and an AB quartet centered at 426 c.p.s. ($\Delta\nu$ 24 c.p.s., J = 8.5 c.p.s.) for the adjacent C-1 and C-2 protons. Since no further aromatic proton resonance was visible, the compound is substituted at both C-3 and C-4. Mechanistically, 4-bromoestradiol derivatives may arise from the bromohydrin XI by hydrolysis and dehydration to a Δ^4-steroid followed by further addition of hypobromous acid to furnish a 4β,10β-dibromo-3α,5α,17β-triol. Elimination of quaternary bromine and hydroxyl would lead to a sensitive diene which requires only oxidation to give 4-bromoestradiol.



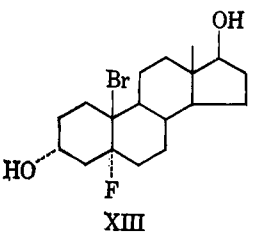
X



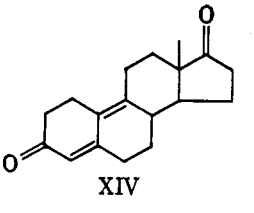
XIa, R = α-H, β-OAc;
R_1 = α-OAc, β-H
b, R = R_1 = O



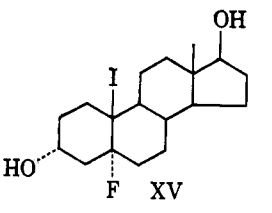
XIIa, R=Ac
b, R=H



XIII



XIV



XV

(20) Excellent evidence for the existence of charged intermediates such as VIII was reported very recently by J. W. Blunt, M. P. Hartshorn, and D. N. Kirk [*Chem. Ind.* (London), 1955 (1963)] who isolated the perchlorate salt of such an ion in the cholestane series.

(21) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

N-Bromoacetamide–hydrofluoric acid halogenated the 5(10)-double bond of the diol IVa to yield the 10β-bromo-5α-fluoro derivative XIII. The latter was oxidized with chromic acid[17] to the corresponding 3,17-dione which, without purification, was dehydrohalogenated through the agency of sodium methoxide in methanol to obtain estra-4,9-diene-3,17-dione (XIV).

Finally, the 5(10)-enediol (IVa) was converted to the 5α-fluoro-10β-iodo derivative XV by means of N-iodosuccinimide–hydrofluoric acid.

Levine and co-workers[9] have already discussed the conformational factors which lead to a predominance of 3α-alcohol in the reduction of estr-5(10)-en-3-ones (I).

Experimental[22]

Estrane-3,17-dione 5β,10β-Epoxide (IIb).—To an ice-cold solution of estr-5(10)-ene-3,17-dione (Ib, 6 g.) in methylene dichloride (100 ml.) was added cold ethereal 3.6 *N* monoperphthalic acid (100 ml.), and the whole was stored at 0° for 16 hr. After being diluted with ethanol, the solution was extracted with 10% aqueous sodium bicarbonate, washed with water, dried, and evaporated. Crystallization of the residual solid from acetone–hexane yielded the the 5β,10β-epoxide (3.5 g.). A pure sample showed m.p. 145–147°, $[\alpha]_D$ +39°, ν_{max} 1712 and 1740 cm.$^{-1}$; lit.[11] m.p. 155–156° for a sample recrystallized from methanol, $[\alpha]_D$ +39°.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 75.05; H, 8.54; O, 16.52.

Estrane-3β,17β-diol 5β,10β-Epoxide (IIc).—Reduction of the above dione epoxide IIb (1 g.) dissolved in methanol (70 ml.) with a methanolic solution of sodium borohydride (400 mg. in 17 ml.) during 0.75 hr. at room temperature and work-up in the normal manner gave the diol IIc (340 mg.), recrystallized from acetone–hexane to obtain a pure specimen, m.p. 149–150°, $[\alpha]_D$ +89°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.42. Found: C, 73.89; H, 9.46; O, 16.28.

The diacetate epoxide IIf was obtained by treatment of the above diol IIc with cold acetic anhydride–pyridine followed by work-up in the usual manner. A sample recrystallized from methylene chloride–hexane showed m.p. 108–110°, $[\alpha]_D$ −11°, ν_{max} 1740 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.25. Found: C, 69.81; H, 8.67; O, 21.31.

Estr-5(10)-ene-3α,17β-diol (IVa).—A suspension of estr-5(10)-ene-3,17-dione (Ib, 8 g.) in methanol (300 ml.) was mixed with a solution of sodium borohydride (8 g.) in the same solvent (150 ml.) and kept at room temperature for 0.75 hr. Dilution with water precipitated a solid which was collected (7.1 g.) and crystallized from methanol–acetone to furnish the diol IVa (5 g.), m.p. 203–208°. Further recrystallizations gave the analytical sample, m.p. 210–212°, $[\alpha]_D$ +178° (ethanol), ν_{max} 3210 cm.$^{-1}$; lit.[23] m.p. 208–209°, $[\alpha]_D$ + 122.5° (chloroform).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; O, 11.58. Found: C, 78.19; H, 10.28; O, 11.56.

The corresponding diacetate IVb was prepared by exposure of the diol IVa to warm acetic anhydride–pyridine and work-up in the normal manner. Crystallizations of the product from methylene chloride–methanol afforded a pure specimen, m.p. 119–120°, $[\alpha]_D$ +130°, ν_{max} 1740 and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.39; H, 9.07; O, 17.74.

Estrane-3α,17β-diol 5β,10β-Epoxide (IId).—Peracid oxidation of estr-5(10)-ene-3,17β-diol (IVa) by the procedure described above led to the corresponding 5β,10β-epoxide IId, m.p. 159–161°, $[\alpha]_D$ +79°, after crystallization from acetone–hexane; lit.[11] m.p. 154–155°, $[\alpha]_D$ +78°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.42. Found: C, 73.62; H, 9.78; O, 16.75.

Estrane-3α,17β-diol 5β,10β-Epoxide Diacetate (IIe). A.—Acetylation of the above diol epoxide (IId) with acetic anhydride–pyridine and work-up in the normal manner afforded the diacetate derivative IIe which, after chromatography over silica and recrystallization from methylene dichloride–hexane, had m.p. 173–174°, $[\alpha]_D$ +54°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.25. Found: C, 70.29; H, 8.41; O, 21.11.

B.—Peracid oxidation of estr-5(10)-ene-3α,17β-diol diacetate (IVb) by the procedure described above led to the 5β,10β-epoxide IIe, purified by recrystallization from methylene dichloride–hexane to furnish a sample, m.p. 172–174°, indistinguishable from that prepared by the above alternative route on the basis of comparative infrared spectra and mixture melting point (no depression).

The epoxide diacetate IIe (1.2 g.) was dissolved in methanol (50 ml.) containing potassium hydroxide (2 g.), and the soluton was kept under reflux during 1 hr. Neutralization was then effected by adding acetic acid. To the residue remaining after evaporation to dryness was added water, and the insoluble material (820 mg.) was filtered off and recrystallized from acetone–hexane to give the above diol IId, m.p. 99–101° and 159–161°, $[\alpha]_D$ +80°.

Estrane-3α,5α,10β,17-tetrol (VIa).—A solution of estrane-3α,17β-diol 5β,10β-epoxide (IId, 380 mg.) in ether (75 ml.) was stirred vigorously at room temperature with 3.5% aqueous sulfuric acid (3 ml.) for 2 hr. After dilution with water the two-phase system was extracted with ethyl acetate. The extracts were washed with water to neutrality and dried (Na_2SO_4), and the residue was crystallized from acetone–hexane and acetone–methanol to yield the tetrol VIa (70 mg.), m.p. 243–244°, $[\alpha]_D$ −11° (in ethanol), ν_{max} 3330 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74; O, 20.62. Found: C, 69.35; H, 9.92; O, 20.46.

5α,10β-Dihydroxyestrane-3,17-dione (VIb).—The tetrol VIa (50 mg.) in cold acetone (5 ml.) was treated dropwise with chromic acid reagent[17] until an excess of oxidant was present. Care was taken to maintain the reaction temperature at or below 10°. Addition of water caused precipitation of a solid which was collected and recrystallized from ether–hexane, thereby affording the diketone VIb (25 mg.), m.p. 223–225°; $[\alpha]_D$ +118° (in ethanol); ν_{max} 3480, 3550, 1740, and 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.13; O, 21.31. Found: C, 70.38; H, 8.41; O, 21.39.

A small sample of the dione VIb in alkaline methanol developed strong ultraviolet absorption at 238–240 mμ indicative of formation of 10β-hydroxyestr-4-ene-3,17-dione (IIIb). On a larger scale, dilution of the alkaline alcoholic solution with water and filtration yielded a crystalline solid which, after purification, proved to be identical with authentic specimen of the enone IIIb.[6,8]

Acid-Catalyzed Rearrangement of Estrane-3α,17β-diol 5β,10β-Epoxide Diacetate (IIc).—A solution of the 3α,17β-diacetate 5β,10β-epoxide IIe (450 mg.) in ether (100 ml.) was stirred vigorously with 3.5% aqueous sulfuric acid (4 ml.) at room temperature for 2 hr. Work-up of the reaction mixture as outlined above furnished a solid (430 mg.) from which was obtained by several crystallizations from methylene chloride–hexane a pure sample of estrane-3α,5α,10β,17β-tetrol 5α,17β-diacetate (VId), m.p. 229–232°; $[\alpha]_D$ +27° (in dioxane); ν_{max} 3460, 1755 (5α-OAc), 1730 (17β-OAc), and 1245 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.35; H, 8.76; O, 23.98.

From the mother liquors of the diacetate VId was isolated, by chromatography over silica, an isomeric product. Several crystallizations from methylene chloride–hexane gave a pure specimen of estrane-3α,5α,10β,17β-tetrol 3α,17β-diacetate (VIc), m.p. 191–192°; $[\alpha]_D$ −28°; ν_{max} 3630, 3550, 1740, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.25; H, 8.75; O, 24.08.

Reduction of the tetrol 5α,17β-diacetate VId (140 mg.) in tetrahydrofuran (30 ml.) at reflux for 2 hr. with lithium aluminum hydride (100 mg.) and work-up in the usual manner led to the 3α,5α,10β,17β-tetrol VIa (120 mg.), m.p. 243–245°, undepressed by admixture with the sample described above.

Reduction of the tetrol 3α,17β-diacetate VIc (60 mg.) by the same procedure led to the same product VIa (25 mg.).

(22) Except where stated otherwise, melting points are uncorrected, optical rotations are for chloroform solutions, ultraviolet spectra were obtained with ethanol solutions, and infrared spectra were run with potassium bromide disks. Microanalyses were performed either by Mid-West Micro Laboratories, Indianopolis 20, Ind., or by Dr. A. Bernhardt, Mulheim (Ruhr), Germany.

(23) J. A. Hartman [*J. Am. Chem. Soc.*, **77**, 5151 (1955)] obtained this compound but assigned the incorrect[16] stereochemistry at C-3.

5α,10β,17β-Trihydroxyestran-3-one 5α,17β-Diacetate (VIe). A.—Estrane-3α,17β-diol 5β,10β-epoxide diacetate (IIe, 150 mg.) was dissolved in ether (50 ml.). A solution of chromic acid (134 mg. of sodium chromate in 0.6 ml. of 35% aqueous sulfuric acid) was added and the two-phase system[21] was stirred for 2 hr. at room tempe.ature then diluted with water and ether. The ether layer was washed with aqueous bicarbonate and with water to neutrality, dried, and evaporated to yield a solid residue, m.p. 160–170° (85 mg.). Recrystallization from methylene chloride–hexane furnished an analytical specimen of 5α,10β,17β-trihydroxyestran-3-one 5α,17β-diacetate (VIe), m.p. 178–183°; $[\alpha]_D$ +29°; ν_{max} 3430, 1738, 1712, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.29; H, 8.48.

B.—Estrane-3α,5α,10β,17β-tetrol 5α,17β-diacetate (VId, 50 mg.) in cold acetone (10 ml.) solution was treated dropwise with chromic acid solution[17] until an excess of reagent was apparent. Dilution with water caused precipitation of a solid (35 mg.), m.p. 170–178°, from which was obtained by crystallizations from methylene chloride–hexane a sample of the 3-ketone VIe, indistinguishable from that described above.

With acid or alkali the 5α-acetoxy 3-ketone VIe developed strong ultraviolet absorption at 236–238 mμ.

Action of Ether–Aqueous Acid on Androstane-3α,17β-diol Diacetate.—To a solution of androstane-3α,17β-diol diacetate (30 mg.) in ether (30 ml.) was added aqueous sulfuric acid (0.3 ml. of 35%) and the whole was stirred at room temperature for 4 hr. Dilution with water and extraction with ether led, by evaporation of the washed ether extracts, to recovered starting material. Examination of the mother liquors from crystallization revealed only traces of by-products.

Acid-Catalyzed Hydration of Estrane-3β,17β-diol 5β,10β-Epoxide Diacetate (IIf).—A solution of the 5β,10β-epoxide 3β,17β-diacetate IIf (1 g.) in ether (50 ml.) was treated with aqueous sulfuric acid (1 ml. of 35%) by the method previously outlined. There resulted an amorphous solid (800 mg.) from which was obtained by chromatography over silica gel (100 g.) and elution with hexane–ether estrane-3β,5α,10β,17β-tetrol 3β,17β-diacetate (VIf, 200 mg.). Recrystallization from acetone–hexane gave a pure sample, m.p. 233–235°; $[\alpha]_D$ −15°; ν_{max} 3510, 1730, and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.42; H, 8.59; O, 24.28.

A solution of this diacetate VIf in acetone did not decolorize Jones reagent.[17]

Estrane-3α,5β,10β,17β-tetrol 3α,17β-Diacetate (IX).—Osmium tetroxide (1.0 g.) was added to a solution of estr-5(10)-ene-3α,17β-diol diacetate (IVb, 1.0 g.) in a mixture of chloroform (30 ml.) and pyridine (30 ml.). After 6 days at room temperature, the reaction mixture was diluted with ethyl acetate (75 ml.). Hydrogen sulfide was then bubbled through the solution for 30 min. when the insoluble salts were removed by filtration over Celite. Removal of the solvent gave a product which was adsorbed from benzene onto alumina (50 g.). Elution with benzene–ether (70:30, 600 ml.) afforded estrane-3α,5β,10β,17β-tetrol 3α,17β-diacetate (IX, 330 mg.), m.p. 165–172° raised by crystallizations from acetone–hexane to 187–189°, $[\alpha]_D$ +31°.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.34. Found: C, 67.31; H, 8.70; O, 23.95.

3α,17β-Dihydroxy-5,10-secoestrane-5,10-Dione Diacetate (X).—Lead tetraacetate (1.46 g.) was added with stirring to a solution of estrane-3α,10β,5β,17β-tetrol 3α,17β-diacetate (IX, 1.0 g.) in dry benzene (85 ml.) and glacial acetic acid (85 ml.) at room temperature. After 15 min. the reaction mixture was poured into ice–water and the product was isolated by extraction with benzene. The combined benzene solutions were washed several times with water and dried over sodium sulfate. Removal of the solvent and crystallization from acetone–hexane gave 3α,17β-dihydroxy-5,10-secoestrane-5,10-dione acetate (X, 810 mg.), m.p. 139–142° raised by several crystallizations from the same solvent mixture to 147–149°, $[\alpha]_D$ −43°.

Anal. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22; O, 24.46. Found: C, 67.27; H, 8.13; O, 24.25.

5α-Methylestrane-3β,10β,17β-triol (VIg).—A solution of estrane-3β,17β-diol 5β,10β-epoxide (IIc, 1 g.) in benzene (50 ml.) was treated with methyl Grignard reagent (20 ml. of a 3 *N* ethereal solution) at reflux during 18 hr. under a nitrogen atmosphere. The cooled reaction mixture was then treated with ammonium chloride and extracted with ethyl acetate, washing with 2% aqueous sulfuric acid and with water to neutrality. Evaporation of the dried (Na_2SO_4) solution yielded an amorphous solid (960 mg.) which was promptly acetylated with acetic anhydride (2 ml.) and pyridine (10 ml.) at 0° in the normal manner. There was obtained a solid acetylated derivative which was chromatographed over silica. Elution with hexane–ether (90:10) afforded 550 mg. of a solid. This material was treated under reflux for 1 hr. with methanolic potassium carbonate (200 mg. in 20 ml.). Dilution with water, extraction with ethyl acetate as usual, and recrystallization of the resultant solid (170 mg.) from acetone–hexane gave a product considered to be 5α-methylestrane-3β,10β-17β-triol (VIg, 110 mg.), m.p. 237–240°, $[\alpha]_D$ +29° (in ethanol), ν_{max} 3280 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46; O, 15.56. Found: C, 73.76; H, 10.48; O, 15.60.

5α-Methyl-10β-hydroxyestrane-3,17-dione (VIh).—Oxidation of the above 3β,10β,17β-triol (VIg, 2 g.) in acetone (200 ml.) with chromic acid reagent[16] in the normal way yielded, after isolation of the product (1.8 g.), chromatography, and recrystallization from methylene chloride, a pure sample of the 3,17-dione VIh, m.p. 218–219°; $[\alpha]_D$ +128°; ν_{max} 3450, 1740, and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.77. Found: C, 74.78; H, 9.29; O, 15.86.

5α-Methylestrane-3α,10β,17β-triol 3α,17β-Diacetate (VIj).—Treatment of estrane-3α,17β-diol 5β,10β-epoxide (IId, 920 mg.) in benzene (75 ml.) with ethereal methyl magnesium bromide (50 ml. of 3 *N*) by the procedure described above furnished crude amorphous 5α-methylestrane-3α,10β,17β-triol (VIk, 918 mg.). By acetylation in the usual manner there could be isolated the corresponding diacetate VIj (835 mg.) which was chromatographed over silica (100 g.). A pure specimen separated as prisms from acetone–hexane and had m.p. 233–234°; $[\alpha]_D$ −12°; ν_{max} 3520, 1735, 1710, 1250, and 1265 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25; O, 20.38. Found: C, 70.58; H, 9.39; O, 20.50.

10β-Bromoestrane-3α,15α,17β-triol 3α,17β-Diacetate (XIa).—A solution of estr-5(10)-ene-3α,17β-diol diacetate (IV, 1.37 g.) in dioxane (12 ml.) was treated with aqueous perchloric acid (1.8ml. of 70%) and N-bromosuccinimide (700 mg.) at 10° with stirring during 0.75 hr. The precipitate which formed on dilution with water was collected and washed with water. This product, 820 mg., m.p. 98–105°, was placed on a column of silica (100 g.) and subjected to chromatographic separation, whereupon the 10β-bromo diacetate XIa (230 mg.) was obtained. A sample recrystallized from acetone–ether showed m.p. 157–159°; $[\alpha]_D$ −34°; ν_{max} 3560, 1740, and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}BrO_5$: C, 57.76; H, 7.27; Br, 17.47; O, 17.49. Found: C, 58.02; H, 6.99; Br, 17.78; O, 17.77.

Estrane-3α,17β-diol 5α,10α-Epoxide Diacetate (Vb).—The bromohydrin XIa (615 mg.) was dissolved in a mixture of methylene chloride and methanol (50 ml. of 1:5) and treated at 10° with a solution of methanolic sodium methoxide (3 ml. of 1 *N*) during 15 min. The mixture was then concentrated *in vacuo* to one-third its original volume and water was added. Ethyl acetate extracted the precipitated solid and this solution was washed with water to neutrality, dried (Na_2SO_4), and evaporated to leave estrane-3α,17β-diol 5α,10α-epoxide (Va) as an amorphous solid. Acetylation of the diol Va in the usual way with acetic anhydride–pyridine reagent led to the corresponding diacetate Vb. This was chromatographed over alumina and crystallized from methylene chloride–hexane giving 380 mg. of product, m.p. 117–122°. The pure specimen separated from methanol–water as prisms and had m.p. 124–125°, $[\alpha]_D$ +71°, ν_{max} 1735 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.75. Found: C, 70.2; H, 8.72; O, 21.66.

Conversion of Estr-5(10)-ene-3,17-dione to Estrone.—A solution of estr-5(10)-ene-3,17-dione (Ib, 1.59 g.) in dioxane (15 ml.) was treated with aqueous perchloric acid (12.1 ml. of 0.6 *N*) and N-bromoacetamide (345 mg.) at −5° as outlined above to form 10β-bromo-5α-hydroxyestrane-3,17-dione (XIb). The crude product (1.04 g.) was exposed to methanolic sodium methoxide (50 ml. of 1 *N*) during 15 min. at 10°, and worked up as described above. Thereby was obtained a small quantity of a product considered to be 10β-bromoestr-4-ene-3,17-dione. After recrystallization from methylene chloride–ether the crystals totaled 50 mg., m.p. 188–195°, λ_{max} 232–234 mμ (log ε 4.12). This supposed 10β-bromo-4-en-3--one (20 mg.) in acetic acid (2 ml.) was treated with hydrogen chloride gas and kept at room temperature during 18 hr. Dilution with water caused formation of a precipitate. The latter was collected and crystal-

lized from methylene chloride–hexane to afford estrone (5 mg.), m.p. 242–252°, showing an ultraviolet absorption maximum at 280–282 mμ (log ε 3.30) and an infrared spectrum essentially identical with that of authentic estrone.

4-Bromoestra-1,3,5(10)-triene-3,17β-diol Diacetate (XIIa).—Oily fractions totaling 1.2 g. containing the bromohydrin XIa were obtained from the column chromatography of this bromohydrin (*vide supra*) and from recrystallization of the mother liquors. Treatment with methanolic sodium methoxide (50 ml. of 1 *N*) during 15 min. at 10°, followed by work-up as described above, then acetylation in the normal manner (Ac_2O–pyridine) yielded an oily product (700 mg.), where solid 5α,10α-epoxide Vb had been obtained earlier. The oil was placed on a column of silica (100 g.) and elution with benzene–hexane (40:60) gave a new product (310 mg.), less polar than epoxy diacetate Vb which was eluted in later fractions. Recrystallization of this new product from methylene chloride–hexane gave 4-bromoestra-1,3,5(10)-triene-3,17β-diol diacetate (XIIa), the analytical specimen of which showed m.p. 171–173°; $[\alpha]_D$ +24°; ν_{max} 1770 and 1200 (phenolic acetate), 1735, and 1255 cm.$^{-1}$ (acetate); λ_{max} 268–270 (log ε 2.59) and 277 mμ (log ε 2.56); λ_{max} (for alkaline ethanol solution) 244 (log ε 3.86) and 304 mμ (log ε 3.87).

Anal. Calcd. for $C_{22}H_{27}BrO_4$: C, 60.68; H, 6.39; Br, 18.36; O, 14.70. Found: C, 60.31; H, 6.41; Br, 18.68; O, 14.60.

4-Bromoestra-1,3,5(10)-triene-3,17β-diol (XIIb).—Potassium carbonate (400 mg.) was added to a mixture of the above diacetate XIIa (160 mg.) and methanol (20 ml.), and the whole was maintained at reflux during 0.75 hr. before being neutralized with acetic acid. Concentration *in vacuo* to 3–4-ml. volume was followed by dilution with water (50 ml.). The resultant precipitate was collected and washed with water, giving 110 mg. of the diol XIIb, m.p. 160–190°. Chromatographic purification over alumina followed by one crystallization from methylene chloride–hexane afforded a crystalline solid (40 mg.), m.p. 203–215°, further purified by recrystallization to m.p. 209–212°; $[\alpha]_D$ +41° (in ethanol); ν_{max} 3580, 3300, 1615, 1565, and 1495 cm.$^{-1}$; λ_{max} 284 mμ (log ε 3.26); λ_{max} (for alkaline ethanol solution) 244 (log ε 3.88) and 314 mμ (log ε 3.51).

Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.53; H, 6.59; Br, 22.75; O, 9.10. Found: C, 61.52; H, 6.96; Br, 23.16; O, 9.36.

10β-Bromo-5α-fluoroestrane-3α,17β-diol (XIII).—A precooled (*ca.* −80°) suspension of estr-5(10)-ene-3α,17β-diol (IVa, 500 mg.) and N-bromoacetamide (270 mg.) in dry methylene dichloride (20 ml.) was added with stirring to a solution of anhydrous hydrogen fluoride (3.41 g.) in tetrahydrofuran (5.98 g.) at *ca.* −80° (acetone–Dry Ice). After stirring at −80° for 1 hr. and then at 0° for a further 16 hr., the reaction mixture was added to an excess of ice-cold sodium bicarbonate solution. Isolation with methylene dichloride and crystallization of the product from methanol afforded 10β-bromo-5α-fluoroestrane-3α,17β-diol (XIII, 330 mg.), m.p. 157–161° raised by several crystallizations from methanol to 169–171° dec., $[\alpha]_D$ 0°.

Anal. Calcd. for $C_{18}H_{28}BrFO_2$: C, 57.62; H, 7.55; Br, 21.29; F, 5.06. Found: C, 57.48; H, 7.48; Br, 22.28; F, 4.88.

Estra-4,9-diene-3,17-dione (XIV).—An excess of 8 *N* chromic acid (permanent orange coloration) was added to a solution of 10β-bromo-5α-fluoroestrane-3α,17β-diol (XIII, 500 mg.) in acetone (80-ml.) at 0°. After a further 2 min. at 0°, addition of water and isolation with methylene chloride afforded the crude oxidation product which was immediately heated under reflux for 3 hr. in methanol solution (150 ml.) containing sodium acetate (1.5 g.). Addition of ice–water and filtration gave a solid product which was adsorbed from hexane–benzene (1:1) onto alumina (25 g.). Elution with hexane–benzene (30:70, 500 ml.) and crystallization from acetone–hexane afforded estra-4,9-diene-3,17-dione (XIV, 120 mg.), m.p. 139–141° raised by crystallizations from the same solvent mixture to 141–143°, $[\alpha]_D$ −152°, λ_{max} 300–302 mμ (log ε 4.34), lit.[4] m.p. 130–131°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 80.24; H, 8.29; O, 11.61.

5α-Fluoro-10β-iodoestrane-3α,17β-diol (XV).—A precooled (*ca.* −80°) suspension of estr-5(10)-ene-3α,17β-diol (IVa, 500 mg.) and N-iodosuccinimide (384 mg.) in methylene chloride (50 ml.) was added to a solution of anhydrous hydrogen fluoride (10.0 g.) in tetrahydrofuran (17.6 g.) at *ca.* −80° (acetone–Dry Ice). After stirring at −80 for 1.5 hr. and then at 0° for a further 16 hr., the reaction mixture was added to an excess of ice-cold sodium bicarbonate solution. Isolation with methylene chloride and crystallization from methylene chloride–hexane afforded 5α-fluoro-10β-iodoestrane-3α,17β-diol (XV), m.p. 128–130° dec., unchanged after several crystallizations from the same solvent mixture.

Anal. Calcd. for $C_{18}H_{28}FIO_2$: C, 51.2; H, 6.68; F, 4.50; I, 30.05. Found: C, 51.23; H, 6.84; F, 4.78; I, 30.23.

The Photochemical Reaction of Nitrobenzene and Tolane

MONTE L. SCHEINBAUM[1]

The Converse Laboratories, Harvard University, Cambridge, Massachusetts

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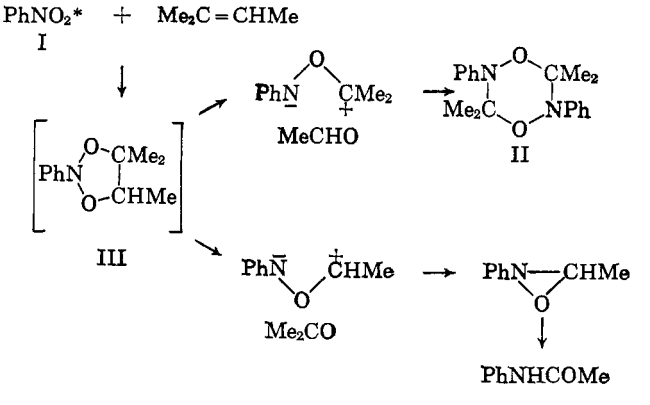
Products arising from the photochemical reaction of nitrobenzene and diphenylacetylene have been identified. Diphenylketene is postulated as an intermediate in the formation of benzophenone anil (V), carbon dioxide, and the β-lactam of β-anilinotetraphenylpropionic acid (VIII). Mechanistic pathways are discussed to account for the formation of dibenzanilide (VI) and other products. The photochemical rearrangements of N-phenylphenylbenzoyl nitrone (XVII) to dibenzanilide and of triphenyl nitrone to N,N-diphenylbenzamide are reported.

Büchi and Ayer[2] found that photochemically excited nitrobenzene (I) can effect cleavage of an olefinic double bond in a manner analogous to that of ozone. On irradiation of nitrobenzene with 2-methyl-2-butene, they obtained acetaldehyde, acetone, acetanilide, and a dimer (II). They postulated a 1,3,2-dioxazolidine intermediate (III), which is an analog of a primary ozonide.

The present paper is concerned with the action of photochemically excited nitrobenzene on tolane (IV). A petroleum ether (b.p. 38.7–57.9°) solution of tolane and nitrobenzene was irradiated for 3 days under an atmosphere of nitrogen with a mercury arc lamp (Hanovia Type A). A Pyrex filter was employed to remove the lower wave lengths capable of exciting to-



(1) Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zurich, Switzerland.

(2) G. Büchi and D. E. Ayer, *J. Am. Chem. Soc.*, **78**, 689 (1956).