This material was cleaved with ozone in methylene chloride at −70° (same procedure as given later) or with osmium tetroxide-catalyzed hydroxylation followed by periodate cleavage (see ref. 1 for procedure), yielding in each instance the same noncrystalline product. Treatment of this material with refluxing methanolic potassium hydroxide failed to produce a pure material. None of the fractions from chromatographic analysis showed appreciable absorption at 240 mμ, indicating the absence of a conjugated cyclohexenone system.

18-Nor-17-methylandrost-13(17)-ene (**10**).—Androstan-17β-ol (**9**) was prepared by heating a stirred solution of 40 g. of 17β-hydroxyandrostan-3-one (**2**) in 0.4 l. of diethylene glycol containing 40 g. of potassium hydroxide and 50 ml. of 85% aqueous hydrazine in a slow stream of nitrogen at 140° for 30 min. and then at 190° for an additional hour. Dilution of the cooled solution with water, followed by filtration of the resulting crystalline mass and recrystallization of the product from methylene chloride–methanol, yielded 38.7 g. of material, m.p. 171–172°, identical in infrared absorption to an authentic sample.

Androstan-17β-ol (38 g.) and boric acid (20 g.) were mixed thoroughly and heated at 200° for 30 min. The mixture was then distilled at 400° and 10 mm. The distillate (18 g.) was dissolved in benzene and washed with aqueous potassium bicarbonate. A portion (3.1 g.) was purified from polar contaminants by chromatography over 150 g. of silica. Elution with petroleum ether gave 2.85 g. of a mobile oil, 18-nor-17-methyl-androst-13-(17)-ene (**10**); $[\alpha]_D$ −15°; $\Delta\nu$ 42 (C_{19}—CH_3), 95 ($C{=}CCH_3$) c.p.s.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.08; H, 11.72.

The distillation residue was dissolved in hot benzene and dilute aqueous potassium hydroxide. The washed and dried benzene solution was concentrated, affording 13 g. of semicrystalline material. Chromatography of 4.0 g. of this material on 50 g. of silica yielded 1.72 g. of the desired olefin **10**. Later eluates produced 1.95 g. of crystalline starting material (**9**), identified by melting point and infrared spectrum.

13,17-Secoandrostane-13,17-dione (**11**).—A solution of 10 g. of the olefin **10** in 100 ml. of methylene chloride and 2 ml. of pyridine were treated at −70° with a stream of oxygen containing ozone until the solution turned blue. Zinc dust, 10 g., and 10 ml. of acetic acid in 10 ml. of methylene chloride were added and the mixture was stirred in an ice bath for 30 min. The mixture was filtered and the filtrate was washed with water and aqueous potassium bicarbonate. Concentration of the dried extract afforded 12.5 g. of mobile oil, 4.0 g. of which was chromatographed on 150 g. of silica. The major portion was eluted with 2% ethyl acetate in benzene, yielding 1.98 g. of 13,17-secoandrostane-13,17-dione (**11**); $[\alpha]_D$ +3°; λ_{max} 5.82 μ; $\Delta\nu$ 44 (C_{10}–CH_3), 127 (–$COCH_3$) c.p.s. Despite a repeated chromatographic fractionation of this material and the use of a variety of solvents on the components, no crystalline material was obtained.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.73; H, 10.29.

18-Nor-D-homoandrost-13(17a)-en-17-one (**12**).—A solution of 0.80 g. of the diketone **11** (purified by chromatography) in 30 ml. of methanol containing 5 ml. of 15% aqueous potassium hydroxide was heated at reflux for 1 hr. The cooled solution was diluted with water, and the resulting precipitate was separated by filtration. The product was washed with water, air-dried, and dissolved in petroleum ether. The solution, after treatment with charcoal, was concentrated, yielding 0.30 g. of the pure unsaturated ketone **12**, m.p. 158–160°; $[\alpha]_D$ −39°; λ_{max} 5.98, 6.15 μ; λ_{max} 240 (16,800) mμ.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.62; H, 10.44.

Synthesis of 3-Methoxy-17-acetyl-18-norestra-1,3,5(10),16-tetraene

WILLIAM F. JOHNS

Division of Chemical Research, G. D. Searle and Company, Chicago 80, Illinois

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Conversion of the D-homo unsaturated ketone **5** to the title compound has been accomplished by a sequence of five reactions: reduction (to **2b**), Grignard addition (**11**), dehydration (**13**), ozonolysis (**18**), and cyclization (**20**). Formation of the dienedione **10**, a by-product of the reduction step, is also discussed.

The facile production of the unsaturated ketone **5** from estradiol 3-methyl ether in three steps[1] allowed continuation of a projected synthesis of 18-norestrone and 18,19-dinor steroids.[2] The potential physiological interest of such materials was clear from the enhanced activities of several 19-nor steroids as compared to their methylated analogs.[3]

Proper introduction of a single asymmetric center into the D-homo ketone **5** is necessary to produce a molecule having the desired, naturally occurring *trans–anti–trans* ring junctures of rings B, C, and D. None of the remaining reactions in the planned sequence would labilize these bridgehead carbon atoms; thus the stereochemistry of these centers would remain unchanged. Ample literature precedent exists for the reduction of systems such as $\Delta^{1(9)}$-decalone-2 to *trans*-2-decalone by means of metal–ammonia systems.[4] Application of this reaction to the planar molecule **5** was complicated only by the possible concommitant reduction of the A-ring. In practice this problem was circumvented by use of lithium–ammonia in the absence of alcohol[5] which allowed conversion in good yield of the unsaturated ketone **5** to the saturated ketone **2b**.

An alternate method was to use a metal–ammonia reaction in the presence of alcohol, effecting reduction of both the A-ring and the unsaturated ketone moieties to produce the enol ether **4a**. With this method of preparation the C-17 hydroxyl is expected to be in the more stable α-configuration.[4] Whereas Oppenauer oxidation of this compound afforded the corresponding C-17 ketone **4b**, pyridine–chromium trioxide caused oxidation of both the A-ring and the alcohol producing the ketone **2b**.

The enol ether **4a** was readily transformed into the unsaturated ketone **1a** and, in turn, into the diketone **1b**. If purification of the enol ether **4a** was omitted and instead the entire metal–ammonia reduction product was hydrolyzed, a new component was isolable. In addition to the major product, the unsaturated ketone **1a**, there was obtained 7% of a compound having an ultraviolet maximum at 242 mμ (ε 35,600) with twice the intensity of a steroidal cyclohexenone. All additional information about this material confirmed the fact that it had two unsaturated ketone groups. Only

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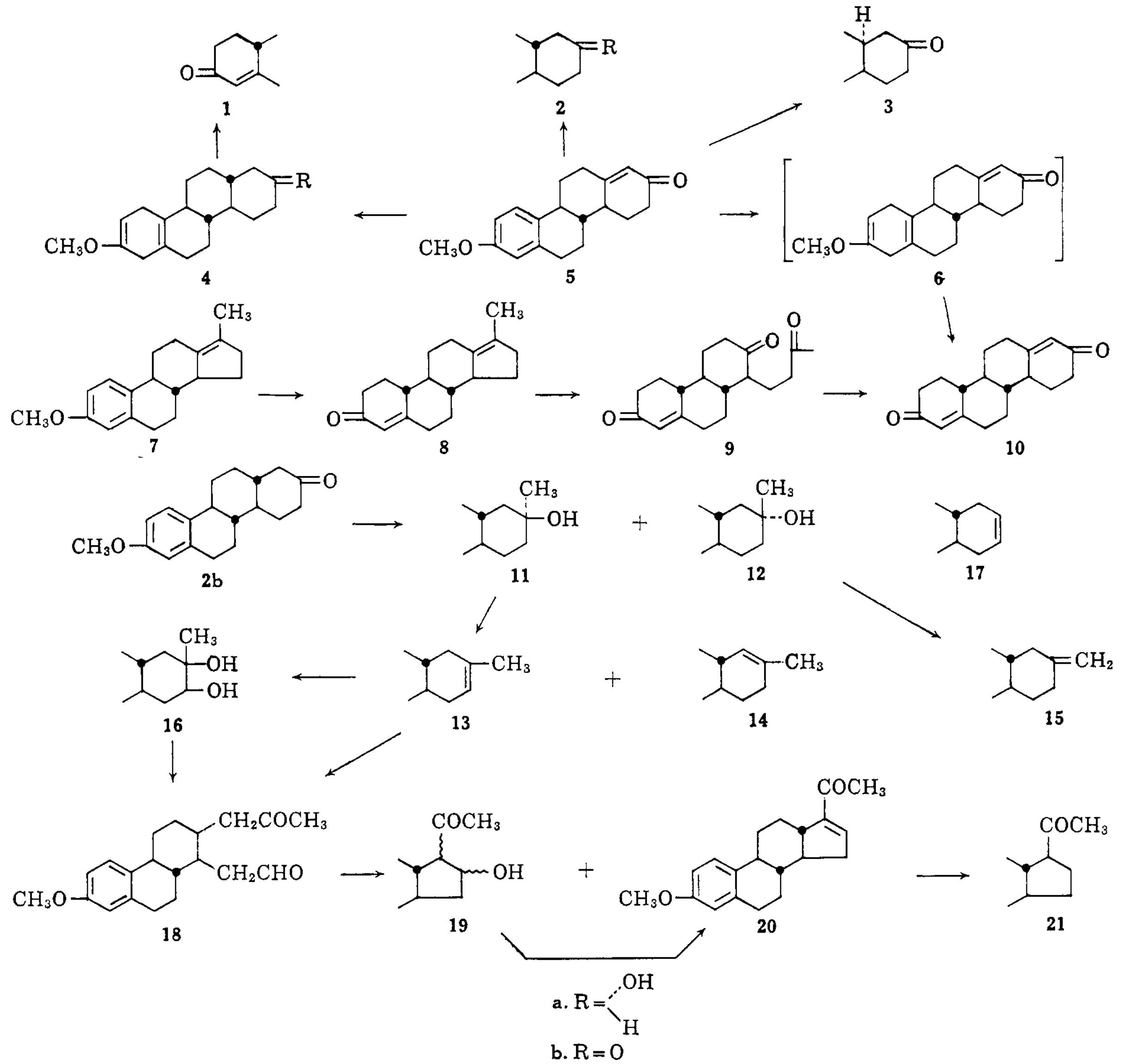
[1] W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

[2] W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).

[3] See, *e.g.*, H. P. Schedl, C. Delea, and F. C. Bartter, *J. Clin. Endocrinol. Metab.*, **19**, 921 (1959).

[4] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954); E. E. van Tamelen and W. C. Proost, Jr., *J. Am. Chem. Soc.*, **76**, 3632 (1954).

[5] F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *ibid.*, **74**, 2696 (1952); A. Bowers, H. J. Ringold, and E. Denot, *ibid.*, **80**, 6115 (1958).



one logical placement of these groups is possible, that shown in structure **10**.[6] An alternate synthesis of this material was accomplished from the readily available estratetraene **7** by reduction with lithium–ammonia, acid hydrolysis to the unsaturated ketone **8**, ozonolysis to the triketone **9**, and base-catalyzed cyclization to the same dienedione **10** previously obtained. The triketone **9** could also be produced by periodate cleavage of the corresponding 13,17 glycol.

Unsaturated ketones are known to be reduced readily with metal–ammonia systems, as is, for example, shown in the production of **2b** in this synthesis. Therefore, the formation of the dienedione **10** must be rationalized by hypothesizing removal of an intermediate such as **6** during the reaction, presumably by precipitation of an enolate salt.

Hydrogenation of the unsaturated ketone **5** over palladium catalyst gave a new saturated ketone (**3**) having a 13α-hydrogen. This compound was clearly different from **2b**. Optical rotatory dispersion measurements confirmed the assigned configurations at C-13 for both **2b** and **3**.[7]

Transformation of the cyclohexanone **2b** to an acetylcyclopentene derivative (such as **20**) followed the general methods outlined by Woodward[8] and by Stork.[9] Methylmagnesium bromide when added to the ketone **2b** produced a mixture of two methyl hydroxy compounds, **11** and **12**, partially separable by chromatography. The preponderant isomer (**11**) was eluted first, and on this basis its hydroxyl group could be assigned the axial configuration.[10] The dehydration products from each isomer provided more conclusive evidence to this point. Treatment of **11** with thionyl chloride in pyridine provided a mixture of two endocyclic olefins. The first olefin (**14**), $[\alpha]_D$ +80°, showed a single peak in its n.m.r. spectrum at 313 c.p.s. ($\Delta\nu$ from the tetramethylsilane signal at 60 Mc.), reasonably ascribed only to the 17a-proton on a 17(17a) double bond. The second compound, $[\alpha]_D$ −30°, exhibited a doublet at 321 and 326 c.p.s., clearly the C-16 isomer **13**. The proportion of these two olefins formed by this reaction could be estimated by integration of the n.m.r. spectrum of the mixture in the 300–330-c.p.s. region or from the rotation ($[\alpha]_D$ +15°), showing approximately 40% of the olefin **14** and 60% of the olefin **13** had been formed.

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(6) This compound has been prepared by total synthesis: A. J. Birch and H. Smith, *J. Chem. Soc.*, 1882 (1951).

(7) We wish to thank C. Djerassi for these measurements.

(8) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(9) G. Stork, H. J. E. Loewenthal, and P. C. Mukharji, *ibid.*, **78**, 501 (1956).

(10) S. Winstein and N. J. Holness, *ibid.*, **77**, 5564 (1955).

The second Grignard adduct (**12**) on dehydration gave preponderantly the exocyclic olefin **15**, easily identified from the n.m.r. signal at 278 c.p.s. (two protons). This is consistent with an equatorial hydroxyl group in the starting material, the favored *trans*-diaxial elimination being impossible except to the exocyclic position.[11]

In the direct reaction path, the mixture of Grignard adducts was dehydrated directly and the desired olefin **13** separated by crystallization. Additional olefin **13** was obtained by acid-catalyzed equilibration of the mixture to one ($[\alpha]_D$ $-14°$) containing approximately 70% of the desired olefin **13**.

Obtained as a by-product in the dehydration was a sulfite, transformed with perchloric–acetic acid to an acetate, and by pyrolysis to a new olefin. Both the sulfite and the acetate could be produced directly from the alcohol **2a**, showing the initial source of the sulfite to be from the alcohol **2a**, presumably a contaminant in ketone **2b** prior to the reaction with methyl magnesium bromide. The n.m.r. spectra of the crude olefin, besides showing the absence of the D-ring methyl group, also indicated that two isomers were present in a 2:1 ratio. The major component (**17**) was separable on recrystallization. The relative proportion of dehydration products of the secondary alcohol **2a** corresponds to that observed in the dehydration of C-3 hydroxyl groups of A/B *trans* steroids.[12]

Conversion of the olefin **13** to the ketoaldehyde **18** was effected either by ozonolysis or by hydroxylation with osmium tetroxide and subsequent cleavage with periodic acid. Cyclization of the ketoaldehyde **18** with aqueous potassium hydroxide[13] provided a mixture of unsaturated ketone **20** and the hydroxy ketone **19**. Further treatment of the latter with base afforded additional unsaturated ketone **20**.

In order to correlate the final products of this synthetic sequence to racemic compounds prepared by Nelson and Garland,[14] ketone **20** was hydrogenated to yield the saturated derivative **21**. Comparison of the infrared spectra showed the *d*- and *dl*-compounds to have identical structures.[15] Final proof of the stereochemistry of this series of compounds was arrived at through their eventual conversion to 18-norestrone methyl ether.[2]

Experimental[16,17]

3-Methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17-one (2b). A. By Direct Lithium–Ammonia Reduction of the Unsaturated Ketone 5.—A solution of 10.0 g. of the unsaturated ketone **5** in 50 ml. of dioxane and 50 ml. of ether was added over a 3-min. period to a solution of 0.5 l. of ammonia containing 1 g. of lithium wire. The solution was stirred for an additional 2 min. and 30 g. of ammonium chloride was added. The ammonia was distilled, and the remaining mixture was diluted with benzene and then with water. The organic layer was washed three times with water, dried, and concentrated *in vacuo*. The residue was recrystallized from acetone–petroleum ether yielding 4.0 g. of the pure saturated ketone **2b**, m.p. 190–192°; $[\alpha]_D$ $+31°$; λ_{max} 5.82 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.99; H, 8.65.

A second crop amounted to 3.8 g., m.p. 185–190°. The mother liquors showed in the infrared weak absorption at 5.99 μ indicating the reduction was not complete. That no significant reduction of the aromatic A-ring had occurred was seen by acid hydrolysis of the product; no increase was seen in the ultraviolet absorption in the 230–240-mμ region.

B. By Oxidation of the Dihydro Alcohol 4a.—A solution of 5.0 g. of the dihydro alcohol **4a** in 50 ml. of pyridine was added to 8.0 g. of chromium trioxide slurried in 80 ml. of pyridine. The solution was allowed to stand at room temperature overnight and was then diluted with water and extracted with ether. The extract was washed with water, dried, and concentrated to dryness. The residue was recrystallized from acetone–cyclohexane, yielding 3.65 g. of the crystalline ketone **2b**, m.p. 190–192°, identical in the infrared to an authentic sample.

C. By Oxidation of the Dihydro Ketone 4b.—The dihydro alcohol **4a** (1.8 g.) in 20 ml. of pyridine was added to a slurry of 2 g. of chromium trioxide in 20 ml. of pyridine. After 18 hr. the solution was diluted with water and extracted with ether. The ether extract was washed with water, dried, and concentrated to dryness. Chromatography of the residue on 35 g. of silica afforded the pure ketone **2b**, 0.65 g., m.p. 188–190°, identical with the previous product.

3-Methoxy-18-nor-D-homoestra-2,5(10)-dien-17-α-ol (4a). A. Vigorous Birch Reduction of the Unsaturated Ketone 5.—A solution of 46.7 g. of the unsaturated ketone **5** in 700 ml. of tetrahydrofuran was added over a 60-min. period to 1.6 l. of ammonia and 700 ml. of *t*-butyl alcohol in a round-bottomed flask equipped with a Dry Ice condenser. Lithium wire was added in six 5-g. portions over this same period. Stirring was continued for 4 hr. at which time the solution had decolorized. The ammonia was distilled, water was cautiously added, and the solution was extracted with benzene. The extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated to dryness. The product, obtained from a chilled acetone solution, amounted to 28.6 g., m.p. 180–182°, and 9.9 g., m.p. 174–178°. Recrystallization of a portion of the first crop from acetone gave the analytically pure alcohol **4a**, m.p. 180–182°; λ_{max} 2.88, 5.83, 5.98 μ; no maxima in the ultraviolet.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.18; H, 9.64.

The corresponding 17-ketone (**4b**) was isolable in small amounts from a few runs by virtue of its lesser solubility in pyridine.

B. Birch Reduction of the Saturated Alcohol 2a.—The alcohol **2a** (1.3 g.) in 50 ml. of tetrahydrofuran was added to 200 ml. of ammonia and 50 ml. of *t*-butyl alcohol. To this solution was added 2.0 g. of lithium wire in four portions over a 30-min. period. The stirring was continued for 4 hr. at which time the color had discharged, the ammonia was distilled, and water was carefully added. A benzene extract was washed with water, dried, and concentrated to dryness, giving 0.52 g. of the alcohol **4a**, identical to that obtained previously.

18,19-Dinor-D-homo-17α-hydroxyandrost-4-en-3-one (1a).—The dihydroaromatic derivative **4a**, 0.40 g., was stirred in 25 ml. of methanol containing 5 ml. of water and 1.5 ml. of concentrated hydrochloric acid for 18 hr. The solution was diluted with water and filtered, yielding 0.34 g. of crystals. Recrystallization from acetone–petroleum ether gave the analytical sample, m.p. 189–191°; λ_{max} 2.92, 6.05, 6.21 μ; λ_{max} 240 mμ (ϵ 17,100).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.67; H, 9.35.

18,19-Dinor-D-homoandrost-4-ene-3,17-dione (1b).—Oxidation of the alcohol **1a** was effected by dissolving 1.0 g. in 40 ml. of pyridine containing 1.0 g. of chromium trioxide. After 90 min. the solution was diluted with water and extracted with ether. The extract was washed, dried, and concentrated to dryness. The residue was recrystallized twice from acetone–petroleum ether, yielding 0.30 g. of the pure diketone **1b**, m.p. 179–182°; $[\alpha]_D$ $-6°$; λ_{max} 5.82, 5.99, 6.15 μ; λ_{max} 240 mμ (ϵ 16,600).

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(11) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(12) J. Fajkos and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 3115 (1959).

(13) G. I. Poos, W. F. Johns, and L. H. Sarett, *J. Am. Chem. Soc.*, **77**, 1026 (1955).

(14) N. A. Nelson and R. B. Garland, *ibid.*, **79**, 6313 (1957).

(15) We wish to thank Dr. Nelson for affording us this comparison.

(16) We wish to thank E. G. Daskalakis and staff for the chromatography and R. T. Dillon for the analyses and spectra described here. We wish also to thank W. M. Selby and staff for the hydrogenations reported.

(17) Infrared spectra were determined in chloroform, ultraviolet spectra in methanol, and rotations in chloroform (1%). Petroleum ether refers to the fraction with b.p. 63–68°. Melting points are uncorrected. N.m.r. spectra were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., at 60 Mc., using tetramethylsilane as an internal standard.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.06; H, 8.93.

1β-(3-Ketobutyl)-1,2,3,4,4a,4aα,4bβ,5,6,7,9,10,10aβ-dodecahydrophenanthren-2,7-dione (9). **A. From the 13,17-Glycol of the Tetraene 7.**—The 13,17-glycol of the tetraene 7[1] (1.00 g.) in 50 ml. of tetrahydrofuran was added to a solution of 200 ml. of ammonia and 50 ml. of *t*-butyl alcohol. Lithium wire (2 g.) was added in six portions over a 30-min. period. After 3 hr. the solution was decolorized by addition of methanol, the ammonia was distilled, water, was added, and a benzene extraction was made. The washed and dried extract was concentrated, and the semicrystalline residue, 1.15 g., was dissolved in 40 ml. of methanol, 8 ml. of water, and 4 ml. of concentrated hydrochloric acid. After 1 hr. at room temperature the solution was treated with excess potassium bicarbonate, diluted with water, and extracted with 1:1 benzene–ethyl acetate. The extract was concentrated to dryness, and the resulting product (1.1 g.) was chromatographed on 30 g. of Florisil. Elution with 30% ethyl acetate in benzene afforded 0.86 g. of material, recrystallized from acetone–petroleum ether to yield 0.53 g. of the pure 13ξ,17ξ-dihydroxy-17-methyl-18,19-dinorandrost-4-en-3-one, m.p. 158–159°; $[\alpha]_D$ +58°; λ_{max}^{KBr} 2.87, 2.99, 5.97, 6.18 μ; λ_{max} 240 mμ (ε 17,800).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.49; H, 9.03. Found: C, 74.24; H, 8.70.

The previous glycol (0.15 g.) in 10 ml. of methanol and 0.4 ml. of pyridine was treated with a solution of 0.15 g. of periodic acid dihydrate in 1.5 ml. of water at room temperature for 1 hr. The solution was diluted with water and the product was isolated by benzene extraction. The residue was recrystallized from acetone–petroleum ether to yield 0.11 g. of the triketone **9**, m.p. 104–105°; λ_{max} 5.83, 6.00 μ; λ_{max} 238 mμ (ε 18,000).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.48.

B. From the Unsaturated Ketone 8.—A solution of 30 g. of the tetraene 7 in 300 ml. of tetrahydrofuran, 250 ml. of *t*-butyl alcohol, and 600 ml. of ammonia was treated with 12 g. of lithium wire in six portions over a 30-min. period. After 4 hr. the solution was decolorized with methanol, the ammonia was distilled, water was added, and a benzene extraction was made. The extract was washed with water, dried, and concentrated yielding 32 g. of a mobile oil. This oil was dissolved in 600 ml. of ethanol containing 30 ml. of hydrochloric acid. The solution was heated at reflux for 10 min. and then allowed to stand overnight at room temperature. After 18 hr. the solution was diluted with water and a poorly crystalline mixture was separated by filtration. This precipitate was dissolved in methylene chloride, and the resulting solution was washed with aqueous potassium bicarbonate, dried, and concentrated to dryness. Chromatography of the product (31 g.) on 1.7 kg. of silica gel yielded 24.2 g. of the crude unsaturated ketone by elution with 10% ethyl acetate in benzene. Recrystallization from petroleum ether gave 6.8 g. of pure **17-methyl-18,19-dinorandrost-4,13(17)-dien-3-one (8)**, m.p. 115–118°; $[\alpha]_D$ +51.5°; λ_{max} 5.97, 6.14 μ; λ_{max} 238 mμ (ε 17,000).

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.37; H, 9.31.

Ozonolysis of 2.9 g. of the olefin **8** in 250 ml. of methylene chloride and 1 ml. of pyridine was effected by passing a stream of oxygen containing 1.1 equivalents of ozone through the solution cooled to −70°. Zinc dust (5 g.) and 5 ml. of acetic acid in 5 ml. of methylene chloride were added and the mixture was stirred in an ice bath for 40 min. The solution was filtered and the filtrate was washed with aqueous potassium bicarbonate. The organic solvent was then removed and the resulting product crystallized from ether, yielding 0.70 g. of the triketone **9**, m.p. 104–105°. Chromatography of the mother liquors on 110 g. of silica gel yielded an additional 0.50 g. of the pure triketone **9** and 0.30 g. of starting material **8**.

1,2,3,5,6,6aα,6bβ,7,8,9,11,12,12aβ,12bα-Tetradecahydrochrysen-3,9-dione (10). **A. From the Triketone 9.**—A solution of 0.20 g. of the triketone **9** in 20 ml. of methanol and 2 ml. of 10% aqueous potassium hydroxide was heated at reflux. A precipitate formed quickly; after 10 min. the solution was cooled and filtered. The crystalline product was washed with water and air dried, yielding 0.17 g. of the dienedione **10**, m.p. 235–240°; λ_{max} 6.00, 6.17 μ; λ_{max} 242 mμ (ε 35,600).[6]

B. From the Hydrolysis of the Total Reduction Product of Ketone 5.[18]—A total of 42 g. of the crude alcohol **4a**, as obtained directly from the lithium–ammonia reduction described for the preparation of pure **4a**, was hydrolyzed with hydrochloric acid in methanol as described before. The product consisted mainly of the unsaturated ketone **1a**. Fractional crystallization of the mother liquors from acetone–petroleum ether yielded 3.9 g. of dienedione **10**, m.p. 238–240°, identical to the product preceding by comparison of the infrared spectra.

3-Methoxy-18-nor-D-homoestra-2,5(10)-dien-17-one (4b).—A solution of 1.22 g. of the alcohol **4a** in 7 ml. of redistilled cyclohexanone and 60 ml. of toluene was dried by distillation of 10 ml. of solvent. To this solution was added 1.6 g. of aluminum isopropoxide dissolved in 10 ml. of toluene over a 10-min. period. The reaction mixture was heated at reflux with stirring in a nitrogen atmosphere for a total of 35 min. The solution was cooled to 60° and 110 ml. of a saturated aqueous solution of Rochelle salts was added over a 10-min. period. The solution was then steam distilled rapidly for 90 min. A chloroform extract was made, washed with water, dried, and concentrated to dryness. Recrystallization of the residue from acetone–petroleum ether yielded 0.61 g. of product, m.p. 170–176°. Further recrystallization from acetone provided the pure ketone **4b**, m.p. 193–195°; $[\alpha]_D$ +83°; λ_{max} 5.81, 5.97 μ; no selective ultraviolet absorption.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.51; H, 8.96.

3-Methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17α-ol (2a).—The saturated ketone **2b** (1.8 g.) in 30 ml. of tetrahydrofuran was added to a stirred slurry of 0.5 g. of lithium aluminum hydride in 40 ml. of ether. After 30 min. at room temperature the solution was carefully treated with water followed by aqueous hydrochloric acid. A benzene extract was made and washed twice with water. The dried solution was concentrated, yielding 1.8 g. of crystalline residue. Recrystallization from acetone–petroleum ether afforded 1.35 g. of material, m.p. 159–162°. The pure alcohol **2a** was obtained from acetone, m.p. 162–163°; $[\alpha]_D$ +65°; λ_{max} 2.79 μ.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.79; H, 9.12.

Acetylation with acetic anhydride in pyridine at 100° for 2 min. followed by dilution with water, filtration, and recrystallization from acetone gave in quantitative yield **3-methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17α-ol acetate**, m.p. 153–154°; $[\alpha]_D$ +62°; λ_{max} 5.79 μ.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.80; H, 8.64.

3-Methoxy-18-nor-D-homo-13α-estra-1,3,5(10)-trien-17-one (3).—To 400 ml. of ethanol was added 5.65 g. of the ketone **5**, 1.0 g. of 5% palladium on charcoal, and 2 ml. of 10% aqueous potassium hydroxide. The mixture was shaken in an atmosphere of hydrogen. After 8 hr. the uptake of hydrogen ceased, the solution was filtered, acidified with a little acetic acid, and concentrated to dryness. The residue was chromatographed on 530 g. of silica. The eluates obtained with 2% ethyl acetate in benzene were combined and the resulting crystalline material (3.1 g., m.p. 134–138°) was recrystallized from petroleum ether (Darco) to yield the analytically pure ketone **3**, m.p. 140–141°; $[\alpha]_D$ +40°; λ_{max} 5.81 μ. The rotatory dispersion curve showed a positive Cotton effect with a maximum at 305 mμ ($[\alpha]_D$ +765°) at 0.101 g./100 ml. of methanol.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.99; H, 8.65.

This material was homogeneous by paper chromatography, running slightly ahead of its C-13 epimer.

Semicrystalline material, 0.65 g., was obtained by elution with 20% ethyl acetate in benzene and was recrystallized from petroleum ether–ether to give 0.30 g., m.p. 144–148°. The analytical sample was obtained from ether; λ_{max} 2.89, 5.86 μ; Δν 137 c.p.s. ($-COCH_3$).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.57; H, 8.12.

This material, stable to base-catalyzed dehydration, was not investigated further.

3-Methoxy-17α-methyl-18-nor-D-homoestra-1,3,5(10)-trien-17-ol (11).—The saturated ketone **2b**, 4.6 g., in 100 ml. of benzene was added over a 30-min. period to a solution of 250 ml. of ether containing 40 ml. of 3 *M* methylmagnesium bromide in *n*-butyl ether (Arapahoe Chemicals, Inc.). The solution was then boiled for 18 hr., cooled, and treated carefully with water

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(18) We wish to thank R. Dahm for his assistance with these experiments.

and sufficient dilute hydrochloric acid to dissolve the precipitated salts. The solution was extracted with benzene and the extract was washed with aqueous potassium bicarbonate solution. The dried and concentrated extract yielded 4.4 g. of semicrystalline material which was chromatographed on 300 g. of silica. Elution with 1% ethyl acetate in benzene yielded fractions weighing 2.9 g. which were crystallized from acetone to yield 1.80 g. of the pure alcohol **11**, m.p. 169–170°; $[\alpha]_D$ +53°; λ_{max} 2.75 μ; $\Delta\nu$ 73 c.p.s. (17α-CH_3).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.67; H, 9.32.

Further elution of the column with 1% ethyl acetate in benzene afforded first a mixture of compound **11** and then fractions weighing 0.61 g., recrystallized from acetone to afford 0.20 g., of **3-methoxy-17β-methyl-18-nor-D-homoestra-1,3,5(10)-trien-17-ol (12)**, m.p. 160–162°; $[\alpha]_D$ +59°; λ_{max} 2.74 μ; $\Delta\nu$ 74 c.p.s. (17β-CH_3).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.93; H, 9.21.

This material was clearly different in its infrared spectrum from its epimer.

3-Methoxy-17-methyl-18-nor-D-homoestra-1,3,5(10),16-tetraene (13) and 3-Methoxy-17-methyl-18-nor-D-homoestra-1,3,5-(10),17(17a)-tetraene (14).—A solution of 15 ml. of thionyl chloride in 40 ml. of pyridine at 5° was added to 38 g. of the total Grignard adduct (**11**,**12**) in 200 ml. of pyridine over a 20-min. period. After a total of 1 hr. the solution was diluted with water and then with aqueous potassium bicarbonate. The mixture was extracted with chloroform and the extract was washed with water and with aqueous bicarbonate solution. A portion (5 g.) of the residue (34 g.), obtained by concentration of the extract, was chromatographed on 150 g. of silica. The first component, 0.7 g., was obtained by elution with 5% benzene in petroleum ether and was recrystallized from methanol and then from petroleum ether to yield 0.26 g. of the pure 17(17a)-olefin **14**, m.p. 112–113°; $[\alpha]_D$ +80°; $\Delta\nu$ 313 c.p.s. (C_{17a}–H).

Anal. Calcd. for $C_{19}H_{26}O$: C, 85.05; H, 9.28. Found: C, 85.07; H, 9.19.

The rotation of subsequent fractions decreased indicating an increase in the proportion of the second isomer (**13**). Later fractions, 0.90 g., were recrystallized from petroleum ether, methanol, and ethanol, yielding 0.36 g. of the pure Δ^{16}-olefin **13**, m.p. 126–128°; $[\alpha]_D$ −30°; $\Delta\nu$ 321, 326 c.p.s. (C_{16}–H).

Anal. Found: C, 84.84; H, 9.27.

In another run starting with the pure isomer **11**, m.p. 169–170°, essentially the same procedure as before afforded 0.93 g. of product from 1.0 g. of starting material. This material was chromatographed over 70 g. of silica to effect separation of the olefins. Elution with 10% benzene in petroleum ether gave 0.80 g. of the olefin (**13** and **14**) mixture, $[\alpha]_D$ +15°; integration of the expanded n.m.r. peaks and rotational data indicated the presence of approximately 40% of isomer **14** and 60% of isomer **13**.

3-Methoxy-17-methylene-18-nor-D-homoestra-1,3,5(10)-triene (15).—A stirred solution of 0.30 g. of the equatorial isomer **12** in 20 ml. of pyridine at −5° was treated with 0.50 ml. of thionyl chloride. After 1 hr. the solution was poured into aqueous potassium bicarbonate solution and extracted with benzene. The extract yielded 0.27 g. of crystalline material which was purified on 25 g. of silica. The olefin, 0.18 g., obtained by elution with benzene, was recrystallized from aqueous methanol to yield 0.12 g. of the tetraene **15**, m.p. 112–114°; $\Delta\nu$ 278 c.p.s. ($C_{17}{=}CH_2$).

Anal. Calcd. for $C_{20}H_{26}O \cdot 1/4\ H_2O$: C, 83.72; H, 9.31. Found: C, 83.52, 83.37, 83.52; H, 8.99, 8.92, 10.01.

This compound, homogeneous by paper chromatography, sublimed to an oil on drying.

The mother liquors contained olefins **13** and **14**, as indicated by n.m.r.

Acid-Catalyzed Isomerization of the Olefin Mixture (13 and 14).—The olefin mixture (0.65 g., $[\alpha]_D$ +26°) was dissolved in 50 ml. of benzene containing 0.10 g. of *p*-toluenesulfonic acid. The stirred solution was distilled slowly, portions being withdrawn at intervals. The rotation was seen to drop rapidly to −14° within 1 hr. and then remained unchanged. The product was isolated by washing the benzene solution with aqueous potassium bicarbonate, drying over anhydrous magnesium sulfate, and concentrating to dryness under reduced pressure. One portion, 0.36 g., on recrystallization from ether–methanol gave 0.20 g. of the olefin **13**, m.p. 126–128°; $[\alpha]_D$ −26°; n.m.r. showed a small amount of the isomer **14** as contaminant.

3-Methoxy-18-nor-D-homoestra-1,3,5(10)-trien-17α-ol Sulfite (2a Sulfite).—The alcohol **2a** (1.5 g.) dissolved in 20 ml. of pyridine was cooled to −15° and to this stirred solution was added 1.0 ml. of thionyl chloride in 10 ml. of pyridine over a 2-min. period. After 30 min. the solution was poured onto an iced aqueous potassium bicarbonate solution. The resulting precipitate, 0.75 g., m.p. 215–218°, on recrystallization from methylene chloride–methanol showed no change in melting point; λ_{max} 7.39, 8.32 μ (sulfite bands).

Anal. Calcd. for $C_{38}H_{50}O_5S$: C, 73.75; H, 8.14; S, 5.18. Found: C, 73.92; H, 8.43; S, 5.31.

An additional 0.30 g. of sulfite, m.p. 213–216°, was obtained from the mother liquors. Incompleteness of reaction was evidenced by appearance of a hydroxyl band (starting material) in the infrared spectrum of the mother liquors.

The sulfite was stable to boiling pyridine for 20 hr. and to boiling in 1% potassium hydroxide in aqueous dioxane for 24 hr.

Treatment of 0.30 g. of the sulfite in 3 ml. of acetic acid and 0.1 ml. of 70% perchloric acid at 100° for 25 min., yielded, after dilution with water and ether extraction, 0.25 g. of a crystalline solid. Recrystallization from methanol gave 0.12 g. of the C-17 acetate of alcohol **2a**, m.p. 152–153°, identical in the infrared to an authentic sample.

3-Methoxy-18-nor-D-homoestra-1,3,5(10),16-tetraene (17).—The sulfite (0.7 g.) was distilled at 1 mm., 230–260°, yielding 0.60 g. of a crystalline product which was chromatographed on 20 g. of silica. Elution with 50% benzene–petroleum ether gave 0.32 g. of a mixture of two olefins; the n.m.r. spectra of this material showed it to consist of one-third of the 17(17a)-olefin (333 c.p.s.) and two-thirds of the C-16 olefin **17** (340, 343 c.p.s.). Recrystallization from methanol afforded 0.18 g. of the tetraene **17**, m.p. 114–117°; $[\alpha]_D$ −10°; $\Delta\nu$ 340, 343 c.p.s.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 85.26; H, 9.13.

Eluted after 100% benzene was a second crystalline material (0.30 g.), recrystallized from acetone–petroleum ether to provide 0.20 g. of the alcohol **2a**, m.p. 157–159° (identical by infrared).

3-Methoxy-17-methyl-18-nor-D-homoestra-1,3,5(10)-trien-16ξ,17ξ-diol (16).—To a solution of 0.30 g. of the olefin **13**, ($[\alpha]_D$ −30°) in 20 ml. of ether was added 0.27 g. of osmium tetroxide. After 2 hr. at room temperature the solution was diluted with 30 ml. of ethanol and a solution of 2 g. of sodium sulfite in 4 ml. of water. The mixture was then heated at reflux for 1 hr. The mixture was filtered, washing the filter cake generously with hot ethanol. The combined filtrates were concentrated to a small volume, diluted with water, and extracted with chloroform. The extract, washed with water and dried over anhydrous magnesium sulfate, was concentrated to dryness yielding 0.30 g. of a crystalline mixture. Recrystallization from acetone–petroleum ether yielded the pure glycol **16**, solvated with a half mole of acetone, m.p. 170–173°; λ_{max}^{KBr} 2.90 μ.

Anal. Calcd. for $C_{20}H_{28}O_3 \cdot 1/2C_3H_6O$: C, 74.74; H, 9.04. Found: C, 74.99; H, 8.90.

1β-Formylmethyl-2α-acetonyl-1,2,3,4,4aα,9,10,10aβ-octahydrophenanthren-7-ol 7-methyl Ether (18). A. By Cleavage of the Diol 16.—A solution of 8.30 g. of periodic acid dihydrate in 40 ml. of water and 9.85 g. of glycol **16** in 300 ml. of methanol and 40 ml. of pyridine were mixed at 5°. The mixture was then removed from the cooling bath and allowed to stand at room temperature for 1 hr. The solution was diluted with 100 ml. of water and the resulting product filtered, yielding 5.10 g. of ketoaldehyde **18**, m.p. 136–139°, and 3.25 g., m.p. 127–133°. Recrystallization from benzene–petroleum ether gave the analytically pure ketoaldehyde **18**, m.p. 143–143.5°; λ_{max} 3.67, 5.83 μ.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.61; H, 8.27.

B. By Ozonolysis of the Olefin 13.—A solution of 0.56 g. of the olefin **13** in 50 ml. of methylene chloride and 50 ml. of methanol at −70° was treated with a stream of oxygen containing ozone. When the effluent gases showed a sharp increase in ozone concentration (after absorption of roughly 1 equivalent), the solution was removed from the stream of ozone, and treated with 5 g. of zinc dust and 5 ml. of acetic acid in 5 ml. of methylene chloride. The mixture was stirred at 0° for 20 min., was filtered, and was diluted with water. The layers were separated, the organic layer being washed again with water and with aqueous sodium bicarbonate. The dried extract was concentrated to dryness leaving a crystalline residue. Recrystallization from benzene–petroleum ether afforded 0.36 g. of the ketoaldehyde **18**, m.p. 135–139°, identical to the compound obtained previously by comparison of infrared spectra.

3-Methoxy-17-acetyl-18-norestra-1,3,5(10),16-tetraene (20). **A. From the Ketoaldehyde 18.**—Potassium hydroxide (15.6 g.) and the ketoaldehyde **18** (26.0 g.) were added to 780 ml. of water. The flask was then evacuated and about 30 ml. of water was distilled. The mixture was then heated at reflux in a nitrogen atmosphere with stirring for a total of 5 hr. The material in the flask quickly changed to an oil and then slowly began to crystallize. The solution was cooled, was treated with excess acetic acid, and was filtered with a generous water wash. The air-dried material, 24.0 g., was chromatographed on 450 g. of acid-washed alumina. A total of 13.4 g. of material, eluted with 50% benzene–petroleum ether, was recrystallized from methanol to yield 7.6 g. of product, m.p. 166–169°, and 4.55 g., m.p. 163–168°. Recrystallization of a portion of this material led to a pure sample of **20**, m.p. 168–169°; $[\alpha]_D$ +112°; λ_{max} 5.99 μ; λ_{max} 231 mμ (ϵ 13,900).

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 81.04; H, 8.16. Found: C, 81.08; H, 8.31.

Following elution of 5.8 g. of semicrystalline mixture with 10% ethyl acetate in benzene there was obtained 3.7 g. of crystalline material by washing the column with ethyl acetate. Recrystallization from acetone–petroleum ether provided 1.45 g. of material, m.p. 169–173°. Pure **3-methoxy-17ξ-acetyl-18-nor-estra-1,3,5(10)-trien-16ξ-ol (19)** was obtained by recrystallization from acetone–ether, m.p. 172–174°; $[\alpha]_D$ +64°; λ_{max}^{KBr} 2.90, 5.98 μ.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.39; H, 8.11.

B. From the Hydroxy Ketone 19.—A solution of 0.10 g. of the hydroxy ketone **19** and 30 ml. of dioxane containing 5 ml. of 10% aqueous potassium hydroxide was heated at reflux under nitrogen for 20 hr. The solution was cooled and diluted with water yielding 90 mg. of crystals. These were dissolved in benzene and chromatographed on 10 g. of silica. Crystalline material (80 mg.), eluted at 5% ethyl acetate in benzene, was recrystallized from methanol to give 40 mg. of the unsaturated ketone **20**, m.p. 161–164°, identical in the infrared to the previously obtained material.

This dehydration was also effected by heating at reflux for 7 hr. a solution of 0.31 g. of the hydroxy ketone **19**, 1 g. of benzoic acid, and 0.875 ml. of triethylamine. Isolation of the product by ether extraction and chromatography yielded 0.11 g. of the unsaturated ketone **20** and 0.15 g. of starting material **19**. Partial dehydration could also be effected by sublimation.

3-Methoxy-17-acetyl-18-norestra-1,3,5(10)-trien-20-one (21). A solution of 0.175 g. of the unsaturated ketone **20** in 30 ml. of ethanol containing 0.40 g. of 5% palladium on charcoal was stirred in an atmosphere of hydrogen. One equivalent of hydrogen was taken up in 15 min. The catalyst was filtered and the solution was concentrated to dryness. The product was recrystallized from petroleum ether, yielding 55 mg. of pure saturated ketone **21**, m.p. 125–126°; λ_{max} 5.86 μ.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.47; H, 8.81.

This material was identical in the infrared to a sample of the *dl*-material.[14,15]

Condensed Cyclobutane Aromatic Compounds. XXV. The Thermal Decomposition of 1,2,5,6-Tetrabromo-3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene

M. P. CAVA, R. POHLKE, AND M. J. MITCHELL

Evans Chemical Laboratory, The Ohio State University, Columbus 10, Ohio

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The thermal decomposition of 1,2,5,6-tetrabromo-3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene (I) yields not 5,10-dibromobenzo[*b*]biphenylene (II), as previously believed, but rather 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI). The proof of structure of VI is described, and the mechanism of its formation from I is discussed. Spectral evidence confirming the structure of I is presented.

The reaction of excess potassium *t*-butoxide with $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene has been reported to give a mixture of the colorless 1,2,5,6-tetrabromo-3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene (I, m.p. 214°) and the yellow 5,10-dibromobenzo[*b*]biphenylene (II, m.p. 222–223°). Structure I was assigned to the colorless tetrabromide on the basis of two reactions: (1) catalytic reduction of I gave 1,2,5,6-dibenzocyclooctadiene (III) in high yield, and (2) dibromide II was formed in 35.8% yield when tetrabromide I was refluxed in ethanolic sodium iodide solution for two weeks.[1] More recently, the direct thermal conversion of I into II by refluxing a solution of I in *o*-dichlorobenzene for four hours has been claimed.[2] The product from this reaction was described as orange-brown needles, m.p. 222–223°.

Since it has been found that the hydrocarbon 3,4,7,8-dibenzotricyclo[4.2.0.0^{2,5}]octadiene (IV) forms an adduct (V) with *N*-phenylmaleimide at moderate temperatures,[3,4] we investigated the reaction of this dienophile with tetrabromide I in nitrobenzene at 200°. No Diels–Alder adduct was obtained, but a brown crystalline substance, $C_{16}H_8Br_2$, m.p. 222–225°, was isolated in 64% yield. This compound was not identical with yellow dibromide II by the criteria of mixture melting point and infrared comparison; we have assigned to it the structure of 5,10-dibromo-7*H*-indeno[2,1-*a*]indene (VI). The same brown dibromide VI, in impure form, was the only product isolable by us from attempts to reproduce the reported conversions of I into biphenylene II[1,2]; however, when a little phenol was added to scavenge the elemental bromine which was otherwise present, the pyrolysis of I in *o*-dichlorobenzene proceeded very cleanly, giving pure VI in 92% yield.

As expected on the basis of the assigned structure, dibromide VI shows a marked similarity to the known dichloro analog (VII)[5,6] in both its infrared and ultraviolet absorbtion spectra (see Experimental section). Furthermore, like VII, VI was reduced catalytically by palladium on charcoal in the presence of triethylamine to give 4*b*,5,9*b*,10-tetrahydro-7*H*-indeno[2,1-*a*]indene (VIII)[7] in high yield. Finally, dibromide VI

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