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The Anthrasteroid Rearrangement. VII. The Use of Selective Bromination in the Degradation of 5,7,9,14,22-Anthraergostapentaene to its 20-Keto Analog¹

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Bromination of 5,7,9,14,22-anthraergostapentaene (I) has been found to take place selectively with substitution at the 15-position. The monobromide IV upon further bromination underwent addition in the side chain yielding the tribromide VI. Physical and chemical evidence for structural assignments is given. In the absence of the 15-bromo substitution, the anthrasteroid was attacked by ozone faster at the Δ^{14} -bond than at the Δ^{22} -bond, but, when the 15-bromo derivative was ozonized, preferential cleavage in the side chain occurred. The resulting aldehyde VII was degraded *via* the enamine to the 15-bromo-20-ketone IX and then by reductive dehalogenation to 5,7,9,14-anthrapregnatetraene-20-one (XII). The spectroscopic properties of the new anthrasteroids are discussed.

In earlier reports of the anthrasteroid rearrangement, the possibility was raised that it might be of biochemical significance in the production of endogenous carcinogens.³⁻⁵ In order to test this hypothesis, we have begun a study of the biological transformations of unsaturated steroids and anthrasteroids. One of the compounds, *viz.*, 5,7,9,14-anthrapregnatetraene-20-one (XII), which we wished to investigate had been previously prepared³ from pregnenolone, but the necessity of introducing the $\Delta^{5,7}$ -system as a prelude to the $\Delta^{5,7,9(11)}$ -system required for rearrangement prompted us to examine its synthesis from 5,7,9,14,22-anthraergostapentaene (I) which is easily obtainable⁵ from 5,7,22-ergostatrien-3 β -ol (ergosterol).

Ozonization of I in the presence of pyridine was followed spectrophotometrically in a manner similar to that reported in a study of stigmaterol⁶; the strong band at 810 cm^{-1} characteristic of the styrene system in anthrasteroids disappeared more rapidly than did the strong absorption at 970 cm^{-1} for the *trans*-ethylenic double bond in the side chain, and we concluded that I was being degraded faster to the keto-aldehyde II than to the desired compound III. This was supported by the presence of a band for the conjugated ketone at 1665 cm^{-1} which increased with the disappearance of the band at 810 cm^{-1} .

The result of ozonization is in keeping with the greater susceptibility of the conjugated system (compared to the isolated double bond) toward electrophilic attack of ozone. This being so, we felt that electrophilic attack by bromine on the double bond conjugated to the benzenoid nucleus might also occur preferentially and might afford protection at C-14,15 during ozonization of the Δ^{22} -bond by a combination of steric hindrance and inductive withdrawal of electrons.

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(2) Recipient of National Science Foundation Summer Fellowship (1959) and Cooperative Graduate Fellowship (1960-1961); U. S. Public Health Service Trainee in the Training Program for Steroid Biochemistry under Grant No. 5001 of the National Institutes of Health (September, 1959-March, 1960).

(3) W. R. Nes, J. A. Steele and E. Mosettig, *J. Am. Chem. Soc.*, **80**, 5230 (1958).

(4) W. R. Nes and E. Mosettig, *ibid.*, **75**, 2787 (1953).

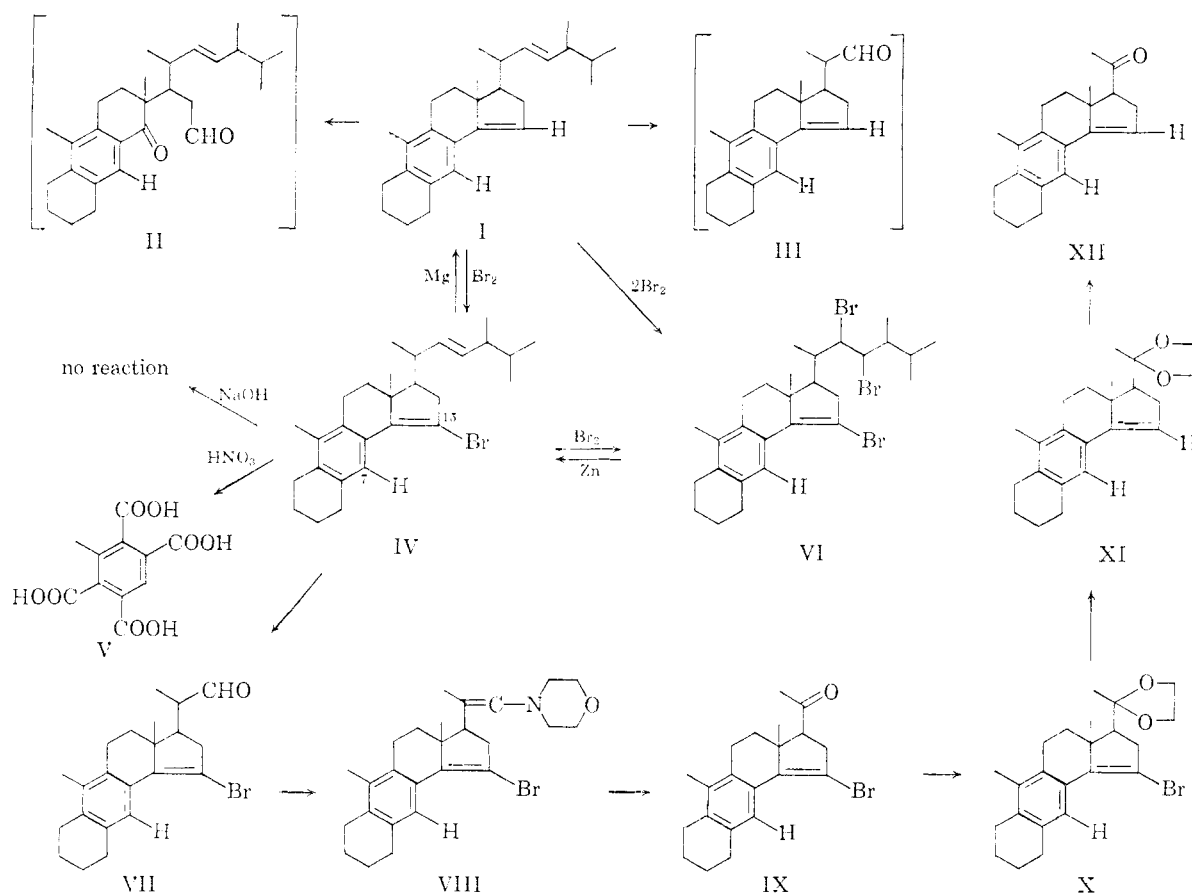
(5) W. R. Nes and E. Mosettig, *ibid.*, **76**, 3182 (1954).

(6) G. Slomp, Jr., and J. L. Johnson, *ibid.*, **80**, 915 (1958).

5,7,9,14,22-Anthraergostapentaene (I) was treated with a slight excess of 1 molar equivalent of bromine in ether at 0°. The product, isolated pure in nearly quantitative yield, was proved to be a monobromide by elemental analysis. Its ultraviolet spectrum (λ_{max} 222, 228, 270 and 306 $\text{m}\mu$) showed that the conjugated system was still present, and a bathochromic shift of 4 $\text{m}\mu$ in the band in the 260-270 $\text{m}\mu$ region (λ_{max} for I is 266 $\text{m}\mu$) indicated substitution on the chromophore. That allylic bromination had not occurred was ruled out further by treatment of the monobromide with refluxing ethanolic sodium hydroxide which failed to remove halogen. Only two positions (C-7 and C-15) are available for substitution on the chromophore; the latter is chosen as the correct one, since degradation of the compound to 1-methyl-2,3,5,6-tetracarboxybenzene (V, isolated as the tetramethyl ester) proved that substitution on the aromatic ring (at C-7) had not occurred. Monobromination was shown to be the only change in the molecule by reconvertng it to starting material through the Grignard complex with magnesium, and our monobromide must, therefore, be 15-bromo-5,7,9,14,22-anthraergostapentaene (IV).

The nuclear magnetic resonance spectrum⁷ of the monobromide (IV) independently confirmed the position of the halogen atom. A single sharp peak was observed at 1.820 (τ -value) and a triplet at 4.783 (τ -value). A singlet would be expected from the interaction of the proton at C-7 with the magnetic field, and the two protons on the Δ^{22} -bond should each give rise to a triplet; since each of the latter protons is in substantially the same environment, the two triplets should overlap, and actually only one triplet should be observed as was found experimentally. Had the bromine atom been at C-7, the singlet should not have been observed and a second triplet should have been found for the 15-H which has two adjacent protons at C-16. In order to be certain that these expectations were valid for the present type of compound, we studied the n.m.r. spectra (Table I) of the desbromide I, its 14,15,22,23-tetrahydro derivative (anthraergostatriene, prepared as previously described⁵ from I), and the 20-ketone XII. The desbromide I showed a triplet at essentially the

(7) The n.m.r. spectra were determined at the Worcester Foundation by Mr. Thomas Wittstruck under the direction of Dr. Neal McNiven, and we are indebted to them for their aid in interpreting the results.



same position as did the monobromide IV, but, in addition, Compound I exhibited a (poorly resolved) triplet at a lower τ -value of one-half the integrated intensity of the one at the higher τ -value. The triplets at lower and higher τ -values must, therefore, correspond, respectively, with the Δ^{14} - and Δ^{22} -bonds which possess one and two protons, respectively. This was corroborated by the spectrum of the 20-ketone XII which possessed the triplet only at the lower τ -value and by the spectrum of the reduced compound (anthraergostatriene) in which no triplet was present at all. Anthraergostatriene did give rise to a singlet in the spectral region under consideration, and the singlet can safely be assigned to the 7-H which lacks adjacent hydrogen atoms; it is interesting to observe, however, that the nuclear magnetic resonance of this proton is markedly influenced by changes in the conjugated system. As will be seen in Table I, the singlet is successively shifted toward lower τ -values by introduction of the Δ^{14} -bond and by a bromine atom. The nuclear magnetic resonance of a methylene group is known to be affected in much the same way by electronegative substituents.⁸

The preferential formation of the monobromide IV by substitution instead of a dibromide by addition is explicable on the basis of steric hindrance. Assuming the intermediacy of an α -bromonium ion, we would anticipate that subsequent β -attack

of a bromide ion at either C-14 or C-15 would be strongly inhibited by a 1,2- or 1,3-diaxial interaction with C-18. Such inhibition would result in dominance of proton-elimination with the re-establishment of the double bond. The importance of steric hindrance in controlling the course of the bromination is evident from the fact that styrene

TABLE I

Compound	N.M.R. SPECTRA OF ANTHRASTEROIDS ^a		
	Singlet	Triplets ^b	
5,7,9-Anthraergostatriene	3.383	None	None
XII	2.767	4.067	None
I	^c	4.042	4.758
IV	1.820	None	4.783

^a Data are recorded in τ -values: $\tau = 10,000 - \delta/\omega$ where δ = shift in c.p.s. from the peak of Me₄Si and ω = operating frequency in megacycles. ^b The value for the most intense peak of each triplet is given. ^c No singlet was observed. Presumably it was hidden beneath the strong peak at 2.762 of CHCl₃ which was present as an impurity in the solvent (CDCl₃).

and cinnamyl alcohol which are unhindered yield dibromides by addition⁹; furthermore, it is known that a proton in a 1,3-diaxial relationship to C-18 of D-homosteroids cannot be removed by heterocyclic bases, *e.g.*, collidine.¹⁰

When the monobromide IV was treated with one molecular equivalent of bromine, or when the starting material I was treated with two equivalents, the tribromide VI was obtained. Disap-

(8) For a discussion of this effect, see J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 26 and 26-30.

(9) M. P. DuQuenois, *Bull. soc. chim.*, [5] 4, 193 (1937).

(10) M. Uskokovic, M. Gut and R. I. Dorfman, *J. Am. Chem. Soc.*, 82, 958 (1960).

TABLE II
 SPECTROSCOPIC PROPERTIES OF ANTHRASTEROIDS^a

Compound	ν_{\max} , cm. ⁻¹		ν_{\max} , cm. ⁻¹	λ_{\max} , m μ (ϵ)	λ_{\max} , m μ (ϵ)	λ_{\max} , m μ (ϵ)	λ_{\max} , m μ (ϵ)	λ_{\max} , m μ (ϵ)	Origin ^b
I	1630	1600	1560	814	222 (26100)	227 (27100)	266 (18600)	296 (2760)	308 (2220)
XII	1632	1595	1560	823	221 (24600, 24600)	226 (25300, 25300)	266 (16300, 16400)	296 (2400, 2500)	308 (1900, 2000)
XI	1626	1599	1559	813	221 (25000)	226 (25850)	266 (16600)	296 (2400)	307 (1960)
IV	1616		1561	809	222 (22130)	228 (22100)	270 (19960)	sh.	306 (1700)
VI	1612		1560	809	222 (23650)	227 (23600)	270 (20200)	sh.	306 (1670)
VII	1613		1558	811	223 (20300)	228 (20700)	271 (19000)	sh.	307 (1470)
VIII	1612		1555	803	223 (28400)	228 (29000)	271 (20250)	sh.	306 (1610)
IX	1625		1560	805	223 (19850)	227 (20200)	271 (18400)	sh.	306 (1380)
X	1607		1560	803	222 (23700)	227 (23700)	270 (20000)	sh.	306 (1730)

^a Compounds above the line lack bromine; those below are 15-bromo derivatives. Ultraviolet data from this and previous studies incorporated in the table were obtained in isoctane solutions; infrared data were obtained from KBr pellets in this study and in solution in previous studies. As seen in the data for compounds XI and XII, this change in state has little effect. ^b Reference 5. ^c Reference 3. ^d This study.

pearance of the band at 970 cm.⁻¹ confirmed its structure. It was converted to the monobromide IV by treatment with zinc in the presence of acetic acid.

The monobromide IV upon ozonization in the presence of pyridine followed by reduction with zinc smoothly yielded the 22-aldehyde VII with little or no attack at C-14,15. The aldehyde VII was degraded further by a sequence of steps analogous to that previously used in the conversion of stigmasterol to progesterone.^{8,11-12} Treatment of VII with morpholine in the presence of *p*-toluenesulfonic acid yielded the morpholinyl enamine VIII which, by either ozonization or oxidation with sodium dichromate, gave the 20-ketone IX. The protective halogen was then removed with magnesium followed by hydrolysis. During removal of the bromine atom, the carbonyl group was protected as the ethylene ketal; the keto function was regenerated by refluxing XI in a solution of acetic acid-ethanol-water which has been found to be a mild method of hydrolysis for other ketals.¹³ The final product, 5,7,9,14-anthrapregnatetraen-20-one (XII), was identical with an authentic specimen previously prepared from pregnenolone.³ The over-all yield from I was 10%.

The spectroscopic properties of various anthra-steroids prepared in this study are collected in Table II.¹⁴ Some interesting generalizations become evident. (a) When the conjugated system is extended by the bromine atom at C-15, a 4 m μ bathochromic shift occurs for the band in the 260-270 m μ region, but no significant shift occurs for the band in the 220-230 m μ region. (b) The intensity of the band in the 260-270 m μ region is increased slightly by the bromine atom, while the intensity of the band in the 220-230 m μ region is decreased. Thus, the desbromo compounds exhibit ϵ of *ca.* 17,000 (range 16,300-18,600) for the band at 266 m μ in contrast to an ϵ of *ca.* 19,000 (range 18,400-20,250) for the analogous band of the bromo compounds. Conversely, the desbromo compounds exhibit ϵ of *ca.* 25,000 (range 24,600-27,100) for the band at 222-227 m μ , while the corresponding band in the bromo compounds ex-

hibits ϵ of *ca.* 22,000 (range 19,850-23,700). The enamine VIII is an exception to the latter generalization owing to overlap with absorption from the C=C-N group; 1-piperidino-1-butene has a band at 228 m μ with an ϵ of 7,500.¹⁵ On this basis we would anticipate an ϵ of about 29,500 (22,000 plus 7,500) for VIII which is essentially what is observed. (c) The strong infrared band near 810 cm.⁻¹, which is due to an out-of-plane vibration of the benzenoid C-H when the aromatic system is extended by a Δ^{14} -bond,^{14,16} is shifted by *ca.* 10 cm.⁻¹ to smaller frequency by bromine substitution. (d) The stretching vibrations of the double bonds are altered by bromine substitution such that the doublet near 1,600 and 1,630 cm.⁻¹ appears only as a single band at 1,607-1,625 cm.⁻¹ with an increased intensity (relative to the band near 1,560 cm.⁻¹). (e) All of the anthra-steroids studied (Table II) possessed a band near 1,560 cm.⁻¹ (range 1,555-1,561 cm.⁻¹).

When compound XII was incubated with a bovine adrenal homogenate, it was rapidly metabolized. The details of the biochemical experiments will be published elsewhere.

Experimental¹⁷

Ozonolysis of 5,7,9,14,22-Anthraergostapentaene (I).—A procedure similar to the one recorded for the degradation of stigmasterol⁸ was used. In the present case, 202 mg. of I was dissolved in 13 ml. of methylene chloride containing 0.94% of pyridine, and the solution was cooled to -78°. A mixture of oxygen and ozone (0.4%) was passed into the solution; periodically, samples were removed and their infrared spectra determined directly without further treatment. The results are recorded in Table III.

15-Bromo-5,7,9,14,22-anthraergostapentaene (IV from I).—To a well stirred solution of 3.01 g. of 5,7,9,14,22-anthraergostapentaene (I) in 75 ml. of ether at 0° was added dropwise a solution of 0.495 ml. of bromine (1.20 molar equivalents) in 30 ml. of ether. Stirring was continued for 30 min.

(15) N. J. Leonard and D. M. Locke, *ibid.*, **77**, 437 (1955).

(16) It was not clear earlier (see ref. 14) whether this band arose from the 7-H or the 15-H. Since the data reported in the present paper prove that IV is a 15-bromide, the presence of a band near 810 cm.⁻¹ in the spectrum of IV proves that this absorption band is assignable to the 7-H. It is important to note, however, that this strong band is not found in compounds which lack the Δ^{14} -bond even though the 7-H is present which allows the strong band to be used diagnostically for the styrene-type of unsaturation in anthra-steroids.

(17) All melting points were determined on a Kofler hot-stage. Ultraviolet spectra were determined in isoctane either on a Cary or a Beckman recording spectrophotometer. Infrared data were obtained on a Perkin-Elmer, model 21, recording spectrophotometer. Rotations were measured in chloroform in approximately 1% concentrations at room temperature (20-25°). All solvents were commercial reagent grades. Alumina was the Activity Grade I of Woelm. Microanalyses are by Schwartzkopf Microanalytical Laboratories.

(11) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).

(12) F. W. Heyl and M. E. Herr, *ibid.*, **72**, 2617 (1950); M. E. Herr and F. W. Heyl, *ibid.*, **74**, 3627 (1952).

(13) W. S. Allen and S. Bernstein, *ibid.*, **77**, 1028 (1955).

(14) For additional spectroscopic data, cf. I. Scheer, W. R. Nes and P. Smeltzer, *ibid.*, **77**, 3300 (1955).

TABLE III

Time, min.	Molecular equivalents of O ₃ added	% Δ^{14} remaining ^a	% Δ^{22} remaining ^b
0	0	100	100
16	0.47	70	86
32	0.94	33	77
55	1.61	0	58
70	2.06	0	30

^a Values based on intensity of absorption at 810 cm.⁻¹.

^b Based on intensity of absorption at 970 cm.⁻¹.

after the addition was completed. The dark brown reaction mixture was evaporated to dryness under reduced pressure, and the residue was chromatographed on alumina in carbon tetrachloride. The product obtained in several early fractions was recrystallized from acetone and weighed 2.91 g., m.p. 105–107°. Concentration of the mother liquor gave an additional 0.20 g.; the total yield was 85% of theory. When the reaction was stopped 2 min. after addition of bromine, the yield was 96%. The analytical sample^{18,19} melted at 107–108°, $[\alpha]_D -30^\circ$, $[M]_D -137^\circ$, $\lambda_{max} 973$ cm.⁻¹.

Anal. Calcd. for C₂₃H₃₉Br (455.5): C, 73.83; H, 8.63; Br, 17.54. Found: C, 73.90; H, 8.70; Br, 17.91.

When the monobromide IV was refluxed in 5% ethanolic NaOH for 50 min., it was recovered unchanged.

Degradation of 15-Bromo-5,7,9,14,22-anthraergostapentaene (V from IV).—When 1.8 g. of IV was refluxed for 16 hr. in 40 ml. of 70% nitric acid, distilled to a volume of 1.5 ml. and cooled, 0.12 g. of crude 1-methyl-2,3,5,6-tetracarboxybenzene (V) was obtained. This was converted to the tetramethyl ester with diazomethane. The product, recrystallized from methanol, melted at 123–126° and weighed 70 mg. Chromatography on alumina and recrystallization raised the melting point to 125–126.5°. The compound failed to give a Beilstein test for halogen, did not depress the melting point of, but possessed an infrared spectrum identical with, an authentic sample.²⁰

Reductive Dehalogenation of 15-Bromo-5,7,9,14,22-anthraergostapentaene (I from IV).—The Grignard reagent was prepared essentially according to the method of Gilman, *et al.*²¹ A mixture of 102 mg. of IV, 15 mg. of magnesium turnings, 101 mg. of 70–80 mesh magnesium and 1 ml. of dry tetrahydrofuran was refluxed under nitrogen with stirring. The reaction appeared to take place after 5 min. of refluxing. After 40 min., a sample was withdrawn for ultraviolet analysis; a shift of the 270 m μ maximum to 266 m μ had occurred. After 55 minutes, 2 ml. of water was added slowly to the mixture and a vigorous reaction took place. The mixture was diluted with 5 ml. of water and extracted with 10 ml. of ether. The ether layer was washed 3 times with water and each extract was partitioned against another 10-ml. portion of ether. The combined solutions were dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The residue was crystallized from acetone and yielded 61 mg. of I, melting at 105–106.5°; when mixed with an authentic sample⁵ of I (m.p. 105–106°) the melting point was 105–106°.

15,22,23-Tribromo-5,7,9,14-anthraergostatetraene (VI from IV or I).—To a solution of 0.472 g. of IV in 6 ml. of ether at room temperature was added dropwise with magnetic stirring a solution of 0.08 ml. of Br₂ in 10 ml. of ether. The tribromide crystallized from the solution during a period of 30 min. following the addition of the bromine solution. After an additional 1 hr. at -20°, the solution was filtered and the crystals were washed with ether, yielding colorless needles which weighed 0.183 g. and melted at 233–234°; the mother liquor yielded 0.104 g. of needles which melted at 234–236°. The total yield was 45% of the theoretical value. After several recrystallizations from carbon tetrachloride, an analytical sample¹⁹ was obtained as fine colorless needles which melted at 240–240.5°, $[\alpha]_D +22^\circ$, $[M]_D +135^\circ$.

(18) See Table I for n.m.r. spectral data.

(19) See Table II for spectroscopic characteristics.

(20) W. R. Nes and E. Mosettig, *J. Am. Chem. Soc.*, **76**, 3186 (1954).

(21) H. Gilman, E. A. Zoellner, W. M. Selby and C. Boatner, *Rec. trav. chim.*, **54**, 584 (1935).

Anal. Calcd. for C₂₃H₃₉Br₃ (615.3): C, 54.65; H, 6.39; Br, 38.96. Found: C, 54.72; H, 6.38; Br, 38.04.

When the procedure was carried out with I in place of IV, the product was identical to that described above.

15-Bromo-5,7,9,14,22-anthraergostapentaene from 15,22,23-Tribromo-5,7,9,14-anthraergostatetraene (IV from VI).—To a solution of 10.1 g. of tribromide VI in 140 ml. of boiling tetrahydrofuran was added 40 ml. of glacial acetic acid and 8 g. of zinc dust. This mixture was refluxed with magnetic stirring for 1 hr. at which time the mixture was filtered to remove excess zinc and then diluted with water. The mixture was extracted with 200 ml. of diethyl ether. The ether phase was washed successively once each with 100-ml. portions of water and 10% aq. NaOH and then 3 times with water. The organic phase was dried over anhydrous Na₂SO₄ and evaporated to dryness. The residue after crystallization from acetone gave 5.70 g. of IV melting at 105–107°; the mother liquor yielded 0.93 g. of IV melting at 98–107°. The total yield (6.63 g.) was 88% of the theoretical value. The infrared spectrum of the material so obtained was identical with that of a sample prepared by direct monobromination, and there was no depression of their melting points upon admixture.

15-Bromo-5,7,9,14-anthraergostatetraene-22-al (VII from IV).—A solution of 8.00 g. of the monobromide IV in 200 ml. of methylene chloride containing 0.94% of pyridine was cooled to -77° and 1.1 moles of ozone per mole of anthraeroid was passed into the reaction flask over a period of 4.6 hr. at a concentration of about 1.87% in oxygen. At the end of this time, the cold mixture was poured into a flask containing 30 g. of zinc dust and 60 ml. of glacial acetic acid. The magnetically stirred mixture was brought quickly to 20° and stirred for 2 hr. at this temperature. The mixture was filtered, diluted with 200 ml. of methylene chloride and extracted 5 times with 200-ml. portions of water. Each water wash was re-extracted with the same 200-ml. portion of methylene chloride. The methylene chloride layers were combined, dried over Na₂SO₄, and evaporated to dryness under reduced pressure at a temperature below 35°. The crude product (7.4 g.) was chromatographed in benzene on 309 g. of magnesium trisilicate (previously dried for 24 hr. at 160°) which yielded 2.61 g. of starting material IV. Benzene-ether 1:1 (by volume) eluted the aldehyde VII. With a correction for the starting material recovered, the 3.47 g. of aldehyde represents 75% of the theoretical yield. For the synthesis of the enamine VIII all of the fractions containing aldehyde were found to be usable. The analytical sample¹⁹ was crystallized from ethyl acetate-isopropyl alcohol and formed colorless flat prisms melting at 107–109°, $[\alpha]_D +14^\circ$, $[M]_D +54^\circ$. The infrared spectrum showed the characteristic aldehyde C-H stretch at 2,680 cm.⁻¹ and the aldehyde carbonyl absorption at 1,715 cm.⁻¹.

Anal. Calcd. for C₂₂H₂₇BrO (387.36): C, 68.21; H, 7.03. Found: C, 68.38; H, 7.14.

While the aldehyde was stable on magnesium trisilicate, it was converted on alumina to hydroxylic materials (ν_{max} 3,650 cm.⁻¹) with less carbonyl absorption in the infrared presumably as a result of aldol condensation.

22-(Morpholinyl-N)-15-bromo- $\Delta^{5,7,9,14,20(22)}$ -anthraergostatetraene (VIII from VII).—A sample of 3.28 g. of crude aldehyde VII obtained by chromatography on magnesium trisilicate was dissolved in 30 ml. of toluene containing 0.90 ml. of morpholine and 9 mg. of *p*-toluenesulfonic acid. This mixture was refluxed for 3.5 hr. under an atmosphere of nitrogen while the water from the reaction was collected in a Bidwell-Sterling trap. At the end of the reaction time, the solvent was removed on a steam-bath under reduced pressure, and the crude product was stored for 3 days in a vacuum desiccator over phosphorus pentoxide. The pale yellow residue crystallized during this time. Recrystallization from acetone yielded 2.89 g. of colorless flat prisms melting at 130–136°; an additional 0.22 g. of colorless product was obtained from the mother liquors. The total yield of 3.12 g. was 81% of the theoretical value. Several recrystallizations of the enamine from petroleum ether (b.p. 65–70°) raised the melting point of the analytical sample¹⁹ to 135–136°, $[\alpha]_D -97^\circ$, $[M]_D -443^\circ$.

Anal. Calcd. for C₂₈H₃₄BrNO (456.46): C, 68.41; H, 7.51; N, 3.07. Found: C, 68.35; H, 7.80; N, 3.24.

The infrared spectrum of VIII showed no carbonyl absorption, but a band at $1,652\text{ cm}^{-1}$ (probably due to the stretching of the $\text{C}=\text{C}-\text{N}$ grouping) was present together with a very strong band at $1,118\text{ cm}^{-1}$ due to the $\text{C}-\text{O}-\text{C}$ stretching of the morpholino portion of the molecule.

15-Bromo- $\Delta^{5,7,9,14}$ -anthrapregnatetraen-20-one (IX).—(a) A solution of 1.00 g. of enamine VIII in 30 ml. of 0.94% pyridine in methylene chloride was cooled to -78° and *ca.* 1.6 moles of O_3 per mole of enamine was bubbled in through a gas dispersion tube in the form of 1.0% O_3 in O_2 . The excess of 60% avoided the problem of separation of starting material from product. At the end of the reaction time, the mixture was poured into a flask containing 3.75 g. of Zn and 7.5 ml. of glacial acetic acid. The mixture was stirred rapidly for 2 hr. at 20° , filtered, the residue rinsed with 30 ml. of methylene chloride, and the organic phase extracted successively with 25-ml. portions of the following: water twice, cold 5% aq. NaOH, water twice, cold 10% HCl, and finally water three times. Each wash was re-extracted with the same portion of methylene chloride. The organic layers were dried over the anhydrous Na_2SO_4 , combined, and evaporated to dryness under reduced pressure. The crude residue of 0.67 g. was placed on a 20-g. magnesium trisilicate column and eluted successively with CCl_4 , CCl_4 -ether (1:1) and ether. The first fraction eluted by the CCl_4 -ether (1:1) yielded, when crystallized from isopropyl alcohol, 191 mg. of long colorless needles melting at $137-139^\circ$. This was recrystallized from isopropyl alcohol to give an analytical sample¹⁹ melting at $137.5-139^\circ$ which after drying under high vacuum at 100° for 1 hr. melted at $137.5-138.5^\circ$, $[\alpha]_D -36^\circ$, $[\text{M}]_D -134^\circ$. The infrared spectrum showed a strong carbonyl stretching absorption band at $1,702\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{BrO}$ (373.3): C, 67.56; H, 6.75; Br, 21.41. Found: C, 67.75; H, 6.71.

(b) An alternative method of oxidation of the enamine which gave a better yield than the ozonolysis described above was by treatment with $\text{Na}_2\text{Cr}_2\text{O}_7$ plus acetic acid.¹¹ To a solution of 1.74 g. of $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$ in 8.8 ml. of glacial acetic acid was added 5.9 ml. of thiophene-free benzene and the mixture was cooled in an ice-acetone-bath to -8° . Then 1.33 g. of the enamine VIII dissolved in 8.8 ml. of thiophene-free benzene was added dropwise over a period of 15 min. to the cold magnetically stirred solution. Stirring was continued for 2 hr., and then 2.9 ml. of methanol was added; stirring was continued 30 min. longer at 0 to -8° . The final mixture was diluted with 35 ml. of water. Most of the dark brown color went into the aqueous phase which was re-extracted with benzene; the two benzene layers were combined and extracted successively with 5-ml. portions of water, ice-cold 10% NaOH twice, water, cold 10% HCl twice, and water four times. Each wash was re-extracted with the same 15 ml. of benzene. The pale yellow benzene layers were dried over Na_2SO_4 , combined, and evaporated to dryness. The crude yellow residue (1.02 g.) was dissolved in benzene and chromatographed on 85 g. of magnesium trisilicate by elution with benzene, benzene-ether (1:1), and ether. The benzene-ether fractions yielded 340 mg. of colorless needles from ethanol-water melting at $138.5-140^\circ$ and 101 mg. melting at $135-140^\circ$. The total yield was 42% of the theoretical value.

The 20-keto compound IX prepared by the sodium dichromate/acetic acid technique showed the same infrared spectrum and the same ultraviolet spectrum and had the same melting point as the sample prepared by ozonolysis; no melting point depression occurred when the two samples were mixed.

5,7,9,14-Anthrapregnatetraen-20-one (XII from IX).—To a solution of 500 mg. of IX in 90 ml. of toluene, 5.5 ml. of ethylene glycol was added. The solution was refluxed with

a water trap for 2 hours to remove any moisture in the solvents, and then 35 mg. of *p*-toluenesulfonic acid was added. Refluxing in the presence of the trap was continued for 21 hr. The cooled mixture was extracted with 30 ml. of 1 *N* aq. NaHCO_3 and then three times with water. After the organic phase was dried over Na_2SO_4 , the solvent was removed under reduced pressure. The resulting oily ketal X weighed 580 mg. and was used for further reactions below. In a similar experiment, the product (15-bromo-20,20-ethylenedioxy- $\Delta^{5,7,9,14}$ -anthrapregnatetraene, X) was chromatographed on magnesium trisilicate by elution with benzene-ether (1:1). Crystallization from acetone gave colorless needles melting at $93-99^\circ$. Recrystallization from acetone and ethanol-water gave an analytical sample¹⁹ melting at $102-104^\circ$, $[\alpha]_D 0^\circ$. There were four new absorption bands at 1,058, 1,093, 1,100 and $1,141\text{ cm}^{-1}$ indicating the presence of the ketal moiety²² in X.

Anal. Calcd. for $\text{C}_{23}\text{H}_{29}\text{O}_2\text{Br}$ (417.4): C, 66.18; H, 7.00. Found: C, 66.27; H, 7.15.

The crude ketal X (500 mg.) was dissolved in 4 ml. of tetrahydrofuran (distilled from LiAlH_4) and 190 mg. of a mixture of magnesium turnings and powder (70-80 mesh) was added. The reaction was initiated with *ca.* 0.1 ml. of methyl iodide and allowed to proceed under reflux with stirring in an atmosphere of nitrogen. The conversion to XI was followed by removing samples periodically and observing the extent of the shift in the absorption band in the 260-270 $\text{m}\mu$ region. After 8 min., the band was at the expected 266 $\text{m}\mu$, and refluxing was continued for a few more minutes to ensure complete reaction. Water (3.0 ml.) was then added and, after the resulting vigorous reaction had subsided, the mixture was extracted with 30 ml. of ether. The washed (H_2O) and dried (Na_2SO_4) organic phase was evaporated to dryness under reduced pressure and yielded 408 mg. of debrominated ketal XI which was used for further reaction described below. In a similar run, the crude ketal (20,20-ethylenedioxy- $\Delta^{5,7,9,14}$ -anthrapregnatetraene, XI) was chromatographed on magnesium trisilicate by elution with benzene-ether (1:1). Crystallization of the eluted material from acetone yielded colorless prisms melting $104-108^\circ$. By recrystallizations from acetone and from ethanol, an analytical sample¹⁹ was obtained melting $107.5-108.5^\circ$, $[\alpha]_D -52^\circ$, $[\text{M}]_D -175^\circ$. The infrared spectrum exhibited the typical 4 bands for a ketal²² at 1,054, 1,079, 1,095 and $1,133\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{23}\text{H}_{30}\text{O}_2$ (338.5): C, 81.61; H, 8.93. Found: C, 81.84; H, 9.16.

Cleavage of the ketal was carried out in a manner similar to the method of Allen and Bernstein.¹⁹ The crude debrominated ketal XI (408 mg.) was dissolved in 25 ml. of ethanol and to the solution was added 12.5 ml. of 50% aq. acetic acid. The mixture was refluxed for 2 hr., cooled, neutralized with NaHCO_3 , and concentrated to a small volume under reduced pressure. The remaining mixture was extracted with chloroform (210 ml.) from which 324 mg. of semi-crystalline XII was obtained after the solvent was removed. The crude product was chromatographed on 15 g. of basic alumina in CCl_4 -ether (1:1) and yielded, after crystallization from ethanol- H_2O , 132 mg. of colorless crystals, m.p. $128-133^\circ$. An additional 24 mg. was recovered from the mother liquor. The total yield was 40% of the theoretical value calculated on the basis of conversion from IX. The melting point was raised to $137-139^\circ$ by two recrystallizations from ethanol- H_2O . The final product did not depress the melting point of a sample⁸ (m.p. $138-139^\circ$) prepared from pregnenolone, and the infrared spectra of the two samples were identical. The ultraviolet spectrum of XII prepared from I was in excellent agreement with the values reported for XII prepared from pregnenolone.^{18,19}

(22) F. D. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 161 (1952).