Catalytic Hydrogenation of the Adduct.—Approximately 20 mg. of platinum oxide in tetrahydrofuran was prereduced in the usual manner. A solution of the adduct (0.4 g.) in 30 ml. of tetrahydrofuran was added. The adduct absorbed 95% of the theoretical amount of hydrogen (based on two double bonds) in 40 minutes. The hydrogenation was continued for a few hours during which time hydrogen was absorbed at a greatly reduced rate. The total hydrogen uptake was almost exactly 2 moles per mole of adduct. The product obtained by filtration and removal of the solvent under reduced pressure was a viscous, colorless liquid which could not be induced to crystallize. Sublimation of a portion of the product gave a tacky, viscous liquid which could not be crystallized. This material showed infrared maxima at 5.40, 5.60 and 5.84 μ and no high intensity absorption in the ultraviolet.

Preparation of the Bromolactone VI or VII.—The adduct (0.2 g.) was dissolved in 10 ml. of hot water, and the solution was cooled to 40°. Bromine (0.55 ml., 95% of the theoretical) was added dropwise with swirling. During the addition, the bromolactone precipitated. The mixture was chilled in ice, and the precipitate was collected and recrystallized from ethyl acetate giving 0.18 g. (63%) of crystalline bromolactone, m.p. 100.5–103°, $\lambda_{max}^{95\%\ EtOH}$ 227 mμ (5700); infrared maxima: 5.56, 5.78 and 5.92 μ. It was necessary to dry the bromolactone at 100° just prior to analysis to completely remove water from the sample.

Anal. Calcd. for $C_{12}H_{11}O_6Br$: C, 43.52; H, 3.35. Found: C, 43.62; H, 3.44.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS, AND FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Total Synthesis of *dl*-C-17 Oxygenated Anthrasteroids[1]

BY ALBERT W. BURGSTAHLER[2] AND ERICH MOSETTIG

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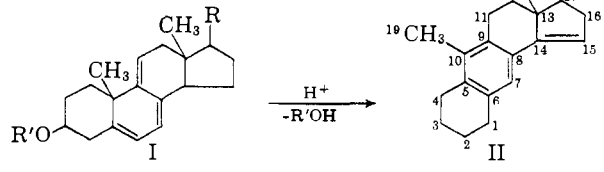
dl-17-Oxo- and 17β-hydroxyanthrasteroids (XV, R = CH_3 and II, R = OH, respectively) have been synthesized from the 4-oxo derivative (VI, R = CH_3) of 9-methyl-*s*-octahydroanthracene (V, R = CH_3) by application of the reaction sequence devised by Johnson, Petersen and Gutsche (ref. 8a) for the attachment of ring D in their total synthesis of equilenin.

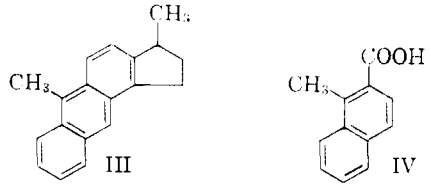
In the presence of an acid catalyst 3β-hydroxysteroidal-5,7,9(11)-trienes (I, R′ = H) and their esters (I, R′ = acyl or aroyl) undergo an interesting transformation involving dehydration, bond rearrangement and aromatization to yield unsaturated derivatives (II) of *s*-octahydroanthracene.[3]



I II

Because of its possible implications in any abnormal steroidal metabolism which might lead to the formation of active anthracenic carcinogens in the body,[4] the reaction has been the subject of considerable study from a chemical standpoint, especially by Nes and Mosettig and their co-workers,[3] and has been designated by them as the "anthrasteroid rearrangement." With the recent demonstration[5] of the detailed structure of these products as shown in II, rational efforts for the total synthesis of representative members of the group became feasible. Moreover, in view of various experimental difficulties involved in the preparation of certain anthrasteroids from natural sources, *e.g.*, II, when R = OH,[6] such a goal, if it held promise of having preparative utility, would not only be attractive for its own sake in providing final confirmation of the structure of anthrasteroids but would also be of considerable value for the practical purpose of making these substances and their derivatives more readily accessible for further biological examination.

While studies on the total synthesis of anthrasteroids have not been described as yet by other workers, the preparation of the parent dimethylcyclopentenoanthracene III by a multistage route from 1-methyl-2-naphthoic acid (IV) has been reported recently.[7] Conceivably, with appropriate modifications, this synthesis could be adapted



to the preparation of anthrasteroids; it would, however, necessarily be somewhat lengthy. In the present work, by employing a suitable preformed hydroanthracene unit, and by applying to it the elegant method of Johnson, Petersen and Gutsche[8] for the attachment of ring D, which was used with such outstanding success in their total synthesis of equilenin, we have realized a comparatively direct synthetic pathway to C-17 oxygenated anthrasteroids.

The starting material, 9-methyl-*s*-octahydroanthracene (V, R = CH_3), is easily obtained from an-

(1) Presented before the Division of Organic Chemistry at the 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) Visiting Scientist, U. S. Public Health Service, N.I.H., Summer, 1958.

(3) For nomenclature, numbering convention and references, *cf.* W. R. Nes, J. A. Steele and E. Mosettig, THIS JOURNAL, **80**, 5230 (1958); see also P. Bladon, *J. Chem. Soc.*, 2176 (1955).

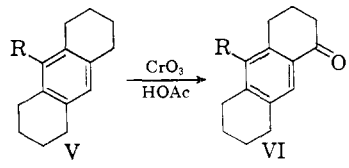
(4) For discussion and references, *cf.* ref. 3 and 6.

(5) A. W. Burgstahler, THIS JOURNAL, **79**, 6047 (1957).

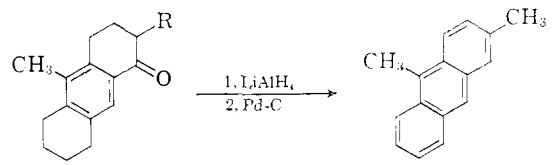
(6) W. R. Nes, J. A. Steele and E. Mosettig, *ibid.*, **80**, 5233 (1958).

(7) M. Nakazaki and S. Isoe, *Chemistry & Industry*, 43 (1958).

(8) (a) W. S. Johnson, J. W. Petersen and C. D. Gutsche, THIS JOURNAL, **69**, 2942 (1947); (b) *cf.* D. K. Bannerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *ibid.*, **78**, 3769 (1956). (c) For another application, see R. J. Collins and E. V. Brown, *ibid.*, **79**, 1103 (1957); also G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Chemisty & Industry*, 1319 (1957) and references cited therein.



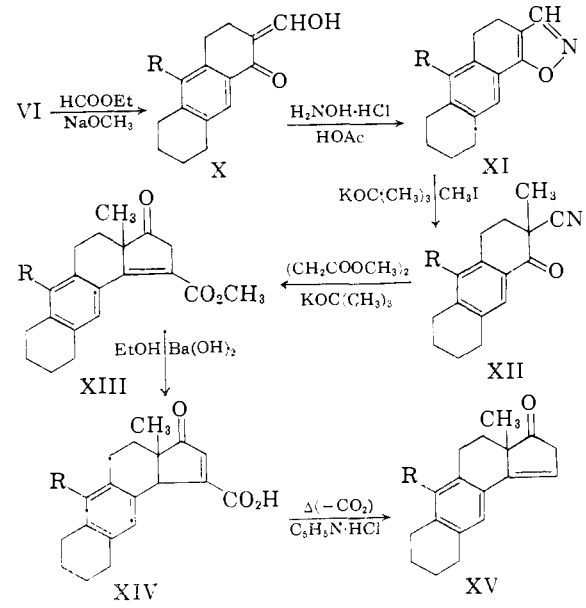
thracene by a known, three-step procedure consisting of partial hydrogenation of the latter to *s*-octahydroanthracene (V, R = H), followed by chloromethylation and hydrogenolysis.[9] In view of the previously observed steric hindrance associated with the methyl group in V (R = CH_3) during vigorous oxidation with nitric acid to form 1-methyl-2,3,5,6-tetracarboxybenzene,[10] it seemed likely that suitable conditions could be found for the selective introduction of oxygen into the C-4 position of V (R = CH_3) to provide the desired 4-oxo derivative VI (R = CH_3). In keeping with results in the analogous preparation of 1-oxo-*s*-octahydroanthracene (VI, R = H),[11] chromium trioxide in acetic acid at 15–20° served to produce, in fair yield, the ketone VI (R = CH_3), m.p. 76–77°, which was isolated and purified as the semicarbazone. To confirm the position of oxidation, this ketone was converted, *via* the Mannich base VII and also through the hydroxymethylene derivative X (R = CH_3, see below), to 4-oxo-3,9-dimethyl-*s*-octahydroanthracene (VIII), m.p. 87–89°, which had been obtained earlier in the anthrasteroid structure proof.[5] The further transformation of both VII and VIII to the known[12] 3,9-dimethylanthracene (IX) was also accomplished as indicated.[5,13]



VII, R = $CH_2N(CH_3)_2$; VIII, R = CH_3 IX

Since the reaction sequence developed by Johnson, Petersen and Gutsche[8a] for the attachment of ring D to a tricyclic ketone somewhat similar to VI led to an unambiguous structural result in their total synthesis of equilenin, as well as to the incorporation, at the penultimate stage, of a 14,15-double bond, which is also present in anthrasteroids, application of this same scheme to VI (R = CH_3) appeared to be ideally suited to the synthesis of the analogous C-17 oxygenated anthrasteroids (XV, R = CH_3 and II, R = OH).

By adhering closely to the procedures devised by the Johnson group,[8a] we found that the first stages, from VI to the methylated cyano ketone XII,



proceeded easily and in excellent yields, both in the model series (R = H) and in the methyl series (R = CH_3). However, as in the experience of Bannerjee and co-workers,[8b] and also Collins and Brown,[8c] we noted that, for optimum results, the succeeding Stobbe condensation step (XII → XIII) required lower temperatures than in the equilenin synthesis.[8a] Even so, the yields which we obtained at this stage were decidedly inferior to those achieved in the latter work. Hydrolysis of the Stobbe condensation product XIII with dilute alcoholic barium hydroxide under a nitrogen atmosphere afforded, in good yield, the keto acid XIV. In the formation of this product the shift of the double bond from the 14,15- to the 15,16-position, into conjugation with the 17-oxo group, parallels subsequent observations[14,8b] concerning the equilenin work and was confirmed here by the infrared and ultraviolet spectral differences between the keto ester XIII and the keto acid XIV and also by the fact that esterification of the latter with diazomethane did not revert it to XIII but led to an *isomeric* keto ester spectrally very similar to XIV. The final step, acid-catalyzed decarboxylation of XIV in refluxing aqueous pyridine hydrochloride, largely restored the double bond to the 14,15-position, as in the equilenin synthesis, and, in the series R = CH_3, furnished the desired 17-oxo anthrasteroid, *dl*-5,7,9,14-anthrastatetraen-17-one (XV, R = CH_3), m.p. 143–145°, in moderate yield. Although this particular anthrasteroid has not yet been prepared from natural sources, the infrared and ultraviolet absorption spectra of the synthetic product are in exact agreement with those of known authentic anthrasteroids.[3,6]

For the reduction of the above product to the corresponding carbinol, sodium borohydride was employed and yielded a single product, the 17β-hydroxy derivative,[15] *dl*-5,7,9,14-anthrastatetraen-

(9) G. M. Badger, W. Carruthers, J. W. Cook and R. Schoental, *J. Chem. Soc.*, 169 (1949); *cf.* ref. 10.

(10) W. R. Nes and E. Mosettig, THIS JOURNAL, **76**, 3186 (1954).

(11) G. Schroeter, *Ber.*, **57**, 2003 (1924).

(12) E. DeB. Barnett and N. F. Goodway, *J. Chem. Soc.*, 1754 (1929).

(13) Since 4,9-dimethylanthracene does not appear to have been described in the literature, the conventional method of proving the location of the carbonyl group in VI (R = CH_3), by dehydrogenation of the corresponding methyl carbinol, was not applicable. With this ketone now available, the preparation of various 4-substituted 9-methylanthracenes has been undertaken (A.W.B.).

(14) W. S. Johnson, C. D. Gutsche, R. Hirschmann and V. L. Stromberg, THIS JOURNAL, **73**, 322 (1951).

(15) For a discussion and examples of the closely related reduction of 17-oxo steroids, *cf.* L. F. Fieser, *Experientia*, **6**, 312 (1950); also ref. 8b.

17β-ol (II, R = OH), m.p. 129–130°, whose highly detailed infrared and ultraviolet spectra were identical in every respect to those of the corresponding optically active anthrasteroid (II, R = OH), which was prepared earlier from *d*-5,7,9(11)-androstatriene-3β, 17β-diol 17-benzoate (I, R′ = H, R = OBz).[6] Hence, although more direct comparison is precluded until the synthetic product is resolved and obtained as the appropriate enantiomer, the present results not only give strong support to the general formulation of anthrasteroids as II, in agreement with previous spectral and degradative evidence,[3,5] but also make attractive the total synthesis of other anthrasteroids and their derivatives by suitable extensions of the present scheme.

Finally, it remains to note that the infrared and ultraviolet spectra of a ketone isomeric with XV (R = CH_3), which was isolated earlier from acid treatment of 5,7,9(11)-androstatrien-3β-ol-17-one isocaproate (I, R′ = *i*-$C_6H_{11}O$; R = oxo),[16] differ markedly from the normal anthrasteroid spectral features of the synthetic *dl*-17-oxo anthrasteroid (XV, R = CH_3). Hence, an "abnormal" constitution must be ascribed to the former, and the question of its structure is reopened.[17] Further studies concerning the structure of this substance as well as biological tests with the present synthetic products and their derivatives are under way.

Experimental[18]

4-Oxo-9-methyl-*s*-octahydroanthracene (VI, R = CH_3).—The previously described[9,10] sequence for the preparation of 9-methyl-*s*-octahydroanthracene (V, R = CH_3) was followed except that the reductive dehalogenation of the 9-chloromethyl intermediate (V, R = CH_2Cl) was conducted in ethyl acetate under three atmospheres of hydrogen with a 10% palladium–charcoal catalyst. The yield of recrystallized V (R = CH_3), m.p. 51–51.5°, in this step was 86–90%.

To a well-stirred solution of 10 g. (0.05 mole) of V (R = CH_3) in 500 ml. of glacial acetic acid cooled to 15°, 40 ml. of an aqueous solution containing 7.0 g. (0.07 mole) of chromium trioxide (reagent grade) was added over a period of 1 hr. After being stirred overnight at 15–20°, the mixture was treated with 10 ml. of methanol to destroy residual oxidizing agent, and the bulk of the solvent was removed under reduced pressure on the steam-bath. When the mixture had been concentrated to a volume of 50 ml., it was diluted with 1 l. of water, acidified strongly with 100 ml. of 6 *N* sulfuric acid, digested for 5 min. on the steam-bath, cooled, and extracted with three 100-ml. portions of low boiling (30–40°) petroleum ether. The combined petroleum ether extracts were washed further with dilute acid and then with 100-ml. portions of 10% sodium hydroxide solution until the aqueous extracts remained colorless. After evaporation of the solvent on the steam-bath, the yellow, oily residue was treated with excess semicarbazide acetate in refluxing methanol for 0.5 hr. **The semicarbazone of VI** (R = CH_3) deposited slowly and was allowed to crystallize for several hours at 0°. When collected, washed and dried it weighed 5.5–6.0 g. (41–44% yield) and melted over the range 210–225° with decomposition. Recrystallized twice from acetic acid–ethanol or from dioxane–ethanol, it formed nearly colorless microscopic needles, m.p. 236–238° dec. (rapid heating) or 227–229° dec. (slow heating); yield 3.5–4.0 g. (26–30%).

Anal. Calcd. for $C_{16}H_{21}ON_3$ (271.35): C, 70.82; H, 7.80; N, 15.49. Found: C, 71.05; H, 7.86; N, 15.29.

In a typical experiment, liberation of the free ketone (VI, R = CH_3) was accomplished by decomposition of 1.5 g. (5.5 mmoles) of the twice recrystallized semicarbazone in a solution of 25 ml. of acetic acid and 10 ml. of 6 *N* sulfuric acid heated on the steam-bath for 1 hr. The mixture was diluted with water, and the product recovered by extraction with petroleum ether. The combined extracts were washed with 10% sodium hydroxide solution, dried over anhydrous magnesium sulfate, and treated with Darco to aid in the procurement of a colorless and more readily crystallized product. Filtration and removal of the solvent, followed by crystallization of the residue from 8 ml. of methanol at −30°, afforded 1.05 g. (88% yield) of VI (R = CH_3) as colorless needle clusters, m.p. 73–76°. Recrystallized from the same solvent these melted at 76–77.5° and had $\lambda_{max}^{CHCl_3}$ at 5.97(vs) and 6.28(s) μ and λ_{max}^{EtOH} at 220 (ε 28,900), 266 (13,000) and 306 mμ (1960). In addition, $\lambda_{max}^{isooctane}$ were measured at 221 (ε 33,150), 259 (14,520), 265 (13,150), 300 (1780) and 310 mμ (1640).

Anal. Calcd. for $C_{15}H_{18}O$ (214.29): C, 84.07; H, 8.47. Found: C, 84.23; H, 8.69.

The oxime of VI (R = CH_3) crystallized from ethanol as stubby prisms, m.p. 185–186.5° (soft. 182°). This derivative proved less satisfactory than did the semicarbazone for the isolation of the ketone from the oxidation reaction.

Anal. Calcd. for $C_{15}H_{19}ON$ (229.31): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.55; H, 8.38; N, 5.92.

The 2,4-dinitrophenylhydrazone of VI (R = CH_3) crystallized from chloroform–ethanol as small orange-red needles, m.p. 284–286° dec.

Anal. Calcd. for $C_{21}H_{22}O_4N_4$ (394.42): C, 63.94; H, 5.62; N, 14.21. Found: C, 63.68; H, 5.63; N, 14.41.

4-Oxo-3,9-dimethyl-*s*-octahydroanthracene (VIII).—Under the conditions described by Mosettig and May[19] 1.00 g. (4.65 mmoles) of the above ketone VI (R = CH_3), m.p. 74–76°, was allowed to react with 0.40 g. (4.9 mmoles) of recrystallized dimethylamine hydrochloride and 2 ml. of 37% formaldehyde in sufficient ethanol to provide a single phase. Although the basic, ether-soluble product failed to solidify, it readily deposited the crystalline hydrochloride, m.p. 196–198°, of **3-dimethylaminomethyl-4-oxo-9-methyl-*s*-octahydroanthracene** (VII) from ether–ethyl acetate when treated with anhydrous hydrogen chloride; yield 0.64 g (45%). This derivative was recrystallized from methanol–ethyl acetate as fine needle clusters, m.p. 197–198°, λ_{max}^{EtOH} at 218 (ε 27,400), 272 (14,250) and 308 mμ (2120).

Anal. Calcd. for $C_{18}H_{25}ON\cdot HCl$ (308.86): C, 69.99; H, 8.49; N, 4.54. Found: C, 69.95; H, 8.52; N, 4.42.

For further characterization, the free amino ketone VII (liberated from 350 mg. of the above hydrochloride by the addition of aqueous ammonia and recovery by extraction with ether) was treated with excess lithium aluminum hydride in ether solution at room temperature. The resulting amino alcohol, **3-dimethylaminomethyl-9-methyl-*s*-octahydro-4-anthrol** (220 mg.), crystallized readily from petroleum ether (60–70°) as prismatic plates, m.p. 108–109°, λ_{max} at 272 (ε 450) and 284 mμ (400).

Anal. Calcd. for $C_{18}H_{27}ON$ (273.40): C, 79.07; H, 9.95; N, 5.12. Found: C, 79.34; H, 10.09; N, 5.13.

(16) W. R. Nes, R. B. Kostic and E. Mosettig, THIS JOURNAL, **78**, 436 (1956); *cf.* ref. 6.

(17) On the assumption that ring B is aromatic in this isomeric product, the above spectral comparison now excludes the presence of the conjugated olefinic bond in the 5-membered ring containing the ketone grouping. In the event that aromatization occurred prior to the usual bond migration,[3,5] a ring A-unsaturated anthrasteroid arises as an alternative structure, but the ultraviolet absorption maximum at 279 mμ may be at too high a wave length to be entirely compatible with this suggestion, since, *e.g.*, $\Delta^{3,5,7,9}$ and $\Delta^{5,7,9,11}$ neoergostatetraene systems have their absorption maxima at the lower wave lengths of 265–270 mμ [*cf.* W. R. Nes and E. Mosettig, THIS JOURNAL, **76**, 3182 (1954), footnote 2]. Similarly, the absorption maximum of what would be a more nearly analogous chromophore, that of 3,9-dimethyl-1,2,5,6,7,8-hexahydroanthracene, has been found in the present work to occur at 269 mμ.

(18) Melting points were determined on a Kofler block calibrated against standard substances. Ultraviolet spectra were measured in ethanol (unless specified otherwise) on a Cary model 11 recording spectrophotometer by Mrs. Anne Wright. Infrared spectra were determined in chloroform or carbon disulfide solution, as indicated, on a Perkin–Elmer Infracord or model 21 double beam spectrophotometer with the assistance of Mr. H. K. Miller. Analytical samples were dried *in vacuo* at 80° or at temperatures 30° below their melting points, whichever was lower. Microanalyses were performed by the Analytical Service Laboratory at the National Institutes of Health under the direction of Dr. William C. Alford and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. J.

(19) E. Mosettig and E. L. May, *J. Org. Chem.*, **5**, 528 (1940).

Hydrogenation of 200 mg. of the amino ketone VII according to the procedure of Mosettig and May[19] led to a neutral ketonic product, which, by chromatography on alumina as described previously for the isolation of 4-oxo-3,9-dimethyl-*s*-octahydroanthracene (VIII),[5] furnished 48 mg. of crystalline material, m.p. 84–87°. Upon sublimation (90–100° (0.01 mm.)) this afforded 35 mg. (20% yield) of colorless, irregular prisms of purified **4-oxo-3,9-dimethyl-*s*-octahydroanthracene** (VIII), m.p. 87–89° (no depression on admixture with the earlier preparation).[5] Its infrared and ultraviolet spectra were also identical with those observed previously,[5] with $\lambda_{max}^{CHCl_3}$ at 5.97(vs) and 6.28(s) μ; λ_{max} at 221 (ϵ 29,400), 266 (14,700) and 305 mμ (2250); and λ_{min} at 235 (ϵ 1860) and 295 mμ (1980).

Anal. Calcd. for $C_{16}H_{20}O$ (228.32): C, 84.16; H, 8.83. Found: C, 84.29; H, 8.77.

By a modification of the procedure of Yanagita and Futaki,[20] this same ketone (VIII) was also obtained by hydrogenolysis of the hydroxymethylene derivative X (R = CH_3—see below) of VI (R = CH_3). The reduction of 242 mg. (1.0 mmole) of X (R = CH_3), m.p. 97–98°, in 30 ml. of 95% ethanol containing 2 ml. of added 12 *N* hydrochloric acid was conducted at 45–50° and required 3 hr. for completion. By chromatography,[5] 76 mg. (33% yield) of crystalline VIII, m.p. 85–88°, resulted.

The 2,4-dinitrophenylhydrazone of VIII crystallized from chloroform–ethanol as a mixture of orange-red microscopic needles and plates, m.p. 208–210° and 215–218°, respectively.

Anal. Calcd. for $C_{22}H_{24}O_4N_4$ (408.44): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.40; H, 5.94; N, 13.60.

Reduction of 95 mg. of the above ketone VIII, m.p. 85–87°, in the manner described previously,[5] afforded predominantly one isomer of **3,9-dimethyl-*s*-octahydro-4-anthrol**, which crystallized readily from benzene–petroleum ether (30–40°) in colorless matted needles, m.p. 142–143°, yield 67 mg. (71%).

Anal. Calcd. for $C_{16}H_{22}O$ (230.33): C, 83.43; H, 9.63. Found: C, 83.67; H, 9.39.

Dehydrogenation of 50 mg. of the above carbinol with 10% palladium–charcoal at 320° in a sealed tube and isolation of the product as described earlier[5] furnished 18 mg. of sublimed and recrystallized **3,9-dimethylanthracene** (IX), m.p. 84–85° (no depression on admixture with an authentic sample).[5,12] The maroon picrate, m.p. 126–127.5°,[5] likewise gave no depression of m.p. when mixed with an authentic sample. The infrared spectrum (CS_2) of 3,9-dimethylanthracene (IX) prepared in this manner was identical with that of an authentic specimen[5,12] and exhibited characteristic bands at 11.2(s), 11.95(m), 12.4(s), 12.95(w) and 13.5(vs) μ. This spectrum is clearly different from that of 2,9-dimethylanthracene[12,21] [$\lambda_{max}^{CS_2}$ 11.35(s), 11.55(m), 11.9(m), 12.55(w), 12.9(m) and 13.5(vs) μ], which would have resulted if the original ketone had the alternative 1-oxo-9-methyl structure. The ultraviolet spectrum of IX has already been recorded.[5]

Dehydrogenation of 100 mg. of the amino alcohol (m.p. 108–109°), derived from the Mannich base VII (see above), similarly afforded 8 mg. of purified 3,9-dimethylanthracene, m.p. and mixed m.p. 84–85°; picrate, m.p. 126–127.5°.

Treatment of 5 mg. of 3,9-dimethyl-*s*-octahydro-4-anthrol (m.p. 141–143°) with 0.5 ml. of phosphorus oxychloride in 5 ml. of pyridine for 10 min. at 50° furnished *ca.* 3 mg. of evaporatively distilled **3,9-dimethyl-1,2,5,6,7,8-hexahydroanthracene**, λ_{max} 269 mμ (ϵ 14,000). λ_{min} 244 mμ (ϵ 5500). Further characterization of this material was deferred.

Sequence from VI to the *dl*-17-Oxo Anthrasteroid (XV).—In the following steps, the standardized procedures of Johnson, Petersen and Gutsche[8a] were employed essentially without change, and hence, for the most part, detailed experimental descriptions are omitted. At each stage the results obtained in the model series (R = H) starting from the ketone VI are recorded first.

A. The Hydroxymethylene Ketone X.—From 3.50 g. (17.3 mmoles) of 1-oxo-*s*-octahydroanthracene (VI, R = H), m.p. 47–48° [prepared according to the directions of Schroeter[11] and purified *via* the semicarbazone, m.p. 260–262° dec.[11]], there was obtained (warm sodium methoxide-in-benzene)[8] 3.73 g. (95% yield) of **1-oxo-2-hydroxymethylene-*s*-octahydroanthracene** (X, R = H), which crystallized from petroleum ether (30–40°) as fine, jagged clusters of canary-yellow prisms, m.p. 54–56°; λ_{max} 250 (ϵ 3750), 276 (7130), 332 (9260) and 342 mμ (9040); λ_{infl} 306 mμ (ϵ 8240).

Anal. Calcd. for $C_{15}H_{16}O_2$ (228.28): C, 78.92; H, 7.06. Found: C, 78.88; H, 7.27.

From 3.10 g. (14.5 mmoles) of 4-oxo-9-methyl-*s*-octahydroanthracene (VI, R = CH_3), m.p. 74–76° (see above), there was obtained 3.45 g. (98% yield) of **3-hydroxymethylene-4-oxo-9-methyl-*s*-octahydroanthracene** (X, R = CH_3), which deposited from petroleum ether (60–70°) in large, light yellow needle clusters, m.p. 97.5–98.5°; λ_{max} 248 (ϵ 4000), 308 (11,000) and 340 mμ (9900); λ_{infl} 280 (ϵ 7500) and 328 mμ (10,100).

Anal. Calcd. for $C_{16}H_{18}O_2$ (242.30): C, 79.31; H, 7.49. Found: C, 79.37; H, 7.29.

B. The Isoxazole XI.—With a 5-minute reflux period in glacial acetic acid,[8] 1.5 g. (22 mmoles) of hydroxylamine hydrochloride served to convert 2.30 g. (10.1 mmoles) of X (R = H), m.p. 54–56°, to 2.10 g. (94% yield) of purified **5,6,7,8,10,11-hexahydroanthra[2,1-d]isoxazole** (XI, R = H), which crystallized from methanol as large, colorless, flat plates, m.p. 99–99.5°; λ_{max} 228 (ϵ 14,640), 234 (12,700), 273 (14,060), 287 (15,290), 305 (10,720) and 314 mμ (10,740).

Anal. Calcd. for $C_{15}H_{13}ON$ (225.28): C, 79.97; H, 6.71; N, 6.22. Found: C, 79.86; H, 6.83; N, 6.16.

In the same manner, 2.05 g. (8.45 mmoles) of X (R = CH_3), m.p. 97–98°, was converted by means of 1.0 g. (14.5 mmoles) of hydroxylamine hydrochloride to 1.89 g. (93% yield) of purified **9-methyl-5,6,7,8,10,11-hexahydroanthra-[2,1-d]isoxazole** (XI, R = CH_3), which crystallized from petroleum ether (60–70°) in nearly colorless, irregular prisms, m.p. also 99–99.5°; λ_{max} 230 (ϵ 16,150), 236 (13,610), 278 (15,460), 290 (16,770), 300 (9620) and 314 mμ (8620).

Anal. Calcd. for $C_{16}H_{17}ON$ (239.30): C, 80.30; H, 7.16; N, 5.85. Found: C, 80.41; H, 7.03; N, 5.68.

C. The Methylated Cyano Ketone XII.—The methylation of 2.0 g. (8.9 mmoles) of the isoxazole XI (R = H), m.p. 98–99°, by the direct procedure with potassium *t*-butoxide and methyl iodide[8] furnished 1.75 g. (82% yield) of purified **1-oxo-2-cyano-2-methyl-*s*-octahydroanthracene** (XII, R = H), which crystallized from benzene-petroleum ether (60–70°) as small, irregular prisms, m.p. 109–110°; λ_{max} 217 (ϵ 22,480), 268 (15,690) and 305 mμ (2770); $\lambda_{max}^{CHCl_3}$ 4.5(w) and 5.96(s) μ.

Anal. Calcd. for $C_{16}H_{17}ON$ (239.30): C, 80.30; H, 7.16; N, 5.85. Found: C, 80.45; H, 7.30; N, 5.82.

Similarly, from 1.79 g. (7.5 mmoles) of the isoxazole XI (R = CH_3), m.p. 98–99°, there was obtained 1.50 g. (79% yield) of purified **4-oxo-3-cyano-3,9-dimethyl-*s*-octahydroanthracene** (XII, R = CH_3), which crystallized from benzene–petroleum ether (60–70°) as colorless, fine clusters, m.p. 123–124° (soft. 121°); λ_{max} 220 (ϵ 23,480) and 273 mμ (13,900); λ_{infl} 307 mμ (ϵ 2390); $\lambda_{max}^{CHCl_3}$ 4.5(w) and 5.96(s) μ.

Anal. Calcd. for $C_{17}H_{19}ON$ (253.33): C, 80.57; H, 7.56; N, 5.53. Found: C, 80.66; H, 7.56; N, 5.45.

D. The Unsaturated Tetracyclic Δ^{14}-Keto Ester XIII and Δ^{15}-Keto Acid XIV.—The potassium *t*-butoxide-catalyzed[8] (sodium hydride[22] was completely ineffective) condensation of dimethyl succinate with the methylated cyano ketone XII did not proceed satisfactorily at a temperature of 50–55° as in the equilenin synthesis.[8a] When the reaction was conducted in dry benzene-*t*-butyl alcohol (1:1) at 10–20° over a period of 8 to 10 hours (longer time[8b] led to diminished yields of product), 1.00 g. (4.18 mmoles) of the model cyano ketone XII (R = H), m.p. 108–110°, afforded 0.52 g. (40% yield) of crude ***dl*-19-nor-5,7,9,14-anthrastatetraene-15-carbomethoxy-17-one** (XIII, R = H), m.p. 83–87°. Recrystallized from petroleum ether (60–70°), this substance was obtained as nearly colorless, irregular prism clusters, m.p. 91–92°, λ_{max} 220 (ϵ 15,000) and 294 mμ (10,850); $\lambda_{max}^{CHCl_3}$ 5.74(vs) (isolated 5-membered ring ketone carbonyl) and 5.88(s) μ (cinnamic acid type ester carbonyl).

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(21) D. D. Phillips and J. Cason, THIS JOURNAL, **74**, 2934 (1952).

(22) *Cf.* G. H. Daub and W. S. Johnson, *ibid.*, **72**, 501 (1950).

Anal. Calcd. for $C_{20}H_{22}O_3$ (310.38): C, 77.39; H, 7.14. Found: C, 77.12; H, 7.23.

Saponification of 300 mg. (0.97 mmole) of the above keto ester with 350 mg. (1.11 mmoles) of barium hydroxide octahydrate in 20 ml. of dilute ethanol under nitrogen[8] furnished, by extraction of the acidic product with chloroform, 270 mg. (94% yield) of once-crystallized ***dl*-19-nor-5,7,9,15-anthrastatetraene-15-carboxy-17-one** (XIV, R = H), m.p. 185–190° dec. When recrystallized from benzene–petroleum ether (60–70°) this material was obtained as very light yellow granules, m.p. 188–193° dec. (soft. 184°); λ_{max} (broad) 221 mμ (ε 17,600), weak end-absorption to 350 mμ, $\lambda_{max}^{CHCl_3}$ 5.88(vs) μ (superimposed conjugated 5-membered ring ketone and carboxyl carbonyls).

Anal. Calcd. for $C_{19}H_{20}O_3$ (296.35): C, 77.00; H, 6.80. Found: C, 76.77; H, 6.90.

The methyl ester of XIV (R = H) was prepared in *ca.* 80% yield by brief contact of the acid with excess diazomethane in ether.[14] It crystallized from petroleum ether (30–40°) as elongated prisms, m.p. 93–95°; λ_{max} (broad) 224 (ε 18,500) and 303 mμ (520); $\lambda_{max}^{CHCl_3}$ 5.88(vs) μ (superimposed conjugated 5-membered ring ketone and ester carbonyls). A mixed m.p. of this substance with the original Stobbe condensation product (XIII, R = H) was depressed to 68–83°.

Anal. Calcd. for $C_{20}H_{22}O_3$ (310.38): C, 77.39; H, 7.14. Found: C, 77.49; H, 7.31.

When applied to the methyl series, the above modified conditions in the Stobbe condensation led to the conversion of 1.00 g. (3.95 mmoles) of the cyano ketone XII (R = CH_3), m.p. 121–124°, to 0.95 g. of a light yellow, neutral oil which, although it solidified to a glass on cooling, could not be induced to crystallize. However, it appeared to consist largely of the desired ***dl*-5,7,9,14-anthrastatetraene-15-carbomethoxy-17-one** (XIII, R = CH_3), since its ultraviolet and infrared spectra very closely resembled those of the crystalline counterpart in the model series (XIII, R = H), with intense λ_{max} at *ca.* 220 and 295 mμ and $\lambda_{max}^{CHCl_3}$ at 5.74(vs) and 5.88(s) μ, also containing an appreciable shoulder at 5.78 μ, due probably to residual dimethyl succinate.

Saponification of all of the above product with 2.5 g. (8.0 mmoles) of barium hydroxide octahydrate (allowing an excess for the dimethyl succinate suspected not to have been completely removed from the keto ester in its isolation —see infrared data above) provided 650 mg. of once-crystallized ***dl*-5,7,9,15-anthrastatetraene-15-carboxy-17-one** (XIV, R = CH_3), m.p. 195–200° dec. (soft. 185°). This represents an over-all yield of 53% from the cyano ketone XII (R = CH_3). Recrystallization from benzene containing a few drops of ethanol furnished 560 mg. of light yellow, diamond-shaped crystals, m.p. 197–201° dec. (soft. 185°); λ_{max} (broad) 221 mμ (ε 16,880), weak end-absorption extending to 350 mμ, $\lambda_{max}^{CHCl_3}$ 5.88(vs) μ (superimposed conjugated 5-membered ring ketone and carboxyl carbonyls).

Anal. Calcd. for $C_{20}H_{22}O_3$ (310.38): C, 77.39; H, 7.14. Found: C, 77.54; H, 7.13.

As in the model series, the 15,16-position of the double bond in this acid was confirmed chemically by the preparation of the methyl ester of XIV (R = CH_3) in *ca.* 75% yield by brief contact of the acid with excess diazomethane in ether. After sublimation at 0.005 mm. (bath 150–160°) and crystallization from petroleum ether (30–40°), this derivative was obtained as colorless, jagged prisms, m.p. 102–104°; λ_{max} (broad) 224 mμ (ε 19,000) and 305 mμ (520), $\lambda_{max}^{CHCl_3}$ 5.88(vs) μ (superimposed conjugated 5-membered ring ketone and ester carbonyls). This material failed to "seed" the crystallization of the Stobbe condensation product XIII (R = CH_3).

Anal. Calcd. for $C_{21}H_{24}O_3$ (324.40): C, 77.75; H, 7.46. Found: C, 77.81; H, 7.56.

E. The *dl*-17-Oxo Anthrasteroid (XV).—Decarboxylation of the above Δ^{15}-keto acids (XIV, R = H and CH_3) in aqueous pyridine hydrochloride[8a] at the reflux temperature (bath 150°) proceeded without coloration and appeared to be complete in 0.5 hr. From 200 mg. (0.675 mmole) of XIV (R = H), m.p. 188–193° dec., there was obtained, after one crystallization from dilute methanol, 40 mg. (23% yield) of crude ***dl*-19-nor-5,7,9,14-anthrastatetraen-17-one** (XV, R = H), m.p. 120–123°. After sublimation at 0.001 mm. (bath temp. 75–80°) and several recrystallizations from petroleum ether (30–40°) this substance was obtained as colorless needle clusters, m.p. 131–132° (soft. and change of form at 124–126°), λ_{max} 219 (ε 28,500), 261 (16,100), 297 (3560) and 307 mμ (3000); λ_{min} 239 mμ (ε 6150); $\lambda_{max}^{CS_2}$ 5.74(s) and 12.35(s) μ.

Anal. Calcd. for $C_{18}H_{20}O$ (252.34): C, 85.67; H, 7.99. Found: C, 85.65; H, 8.26.

The oily, neutral mother-liquor concentrates from the decarboxylation appeared to consist mostly of the conjugated Δ^{15}-ketone, since the infrared carbonyl stretching occurred largely at 5.88 μ ($CHCl_3$). Preliminary efforts to obtain this material crystalline were unsuccessful (but see below).

From 500 mg. (1.60 mmoles) of XIV (R = CH_3), m.p. 197–201°, there resulted 140 mg. (33% yield) of nearly pure ***dl*-5,7,9,14-anthrastatetraen-17-one** (XV, R = CH_3), which was obtained as almost colorless, jagged prisms, m.p. 134–137°, by crystallization from benzene–petroleum ether (30–40°). Recrystallization from the same solvent mixture furnished 105 mg. (25%) of product, melting at 143–145° (soft. 140°); λ_{max} 219 (ε 28,700), 223.5 (29,000), 263 (16,270), 293 (1720) and 303 mμ (1340); λ_{min} 239 mμ (ε 5050); $\lambda_{max}^{CS_2}$ 5.74(s) and 12.4(s) μ.

Anal. Calcd. for $C_{19}H_{22}O$ (266.37): C, 85.67; H, 8.33. Found: C, 85.50; H, 8.13.

The mother-liquor concentrates gradually deposited an additional crystalline product, m.p. 65–70°, whose infrared spectrum [$\lambda_{max}^{CHCl_3}$ 5.74(w) and 5.88(s) μ] indicated that it was probably the isomeric Δ^{15}-ketone, containing a small amount of XV (R = CH_3). Isolation of this lower melting product in pure form by crystallization was apparently severely handicapped by the presence of the less soluble Δ^{14}-ketone (XV, R = CH_3), and further attempts were deferred for the present until larger scale preparation of these materials is completed.

***dl*-5,7,9,14-Anthrastatetraen-17β-ol** (II, **R = OH**).—A solution of 75 mg. (0.28 mmole) of the above *dl*-17-oxo anthrasteroid (XV, R = CH_3), m.p. 143–145°, in 10 ml. of ether was added, at room temperature (23°), to 15 ml. of a methanol solution of an excess of sodium borohydride (150 mg., 4.0 mmoles). After having stood for 45 min. at room temperature, the clear reaction mixture was warmed on the steam-bath and the surplus borohydride decomposed by the addition of a few drops of acetic acid. Water (50 ml.) was then added and the product recovered by extraction with two 50-ml. portions of ether. The combined ether extracts were washed with 5% sodium carbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether and crystallization of the residue from benzene–petroleum ether (30–40°) afforded 60 mg. (79% yield) of the desired carbinol (II, R = OH) as colorless plates, m.p. 129–130°; λ_{max} 221 (ε 24,500), 227 (25,300), 266.5 (16,340), 297 (2330) and 308 mμ (1950); λ_{min} 242 mμ (ε 4930); λ_{infl} 233 mμ (ε 15,500); $\lambda_{max}^{CS_2}$ 12.30(s) μ.

Anal. Calcd. for $C_{19}H_{24}O$ (268.38): C, 85.02; H, 9.01. Found: C, 85.03; H, 9.10.

The above absorption features (including the complete infrared spectrum) are, by direct comparison, identical with those of the corresponding product (II, R = OH) obtained previously by means of the anthrasteroid rearrangement of material derived from natural sources.[6]

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