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# Approaches to the Total Synthesis of Adrenal Steroids. XIII. Formation and Reaction of Racemic 16,20-Diketosteroids

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RECEIVED NOVEMBER 29, 1954

Intramolecular acylation of tricyclic acetonylacetic ester II derived from methallylacetic acid I provides the *dl*-11,16,20-triketopregnene III. Reaction of the latter compound with isopropyl iodide affords a 6:4 mixture of the 16- and 20-enol ethers V and VI. Each of these is convertible into 11,20-diketo-16-pregene VIII, the former by hydrogenolytic cleavage of the 16-enol ether with subsequent oxidation of the $\Delta^{16}$-20-alcohol and the latter by borohydride reduction of the 16-carbonyl group followed by acid hydrolysis and dehydration. Hydrogenolysis–hydrogenation of the 16-enol tosylate of III affords the 3-dioxolane of *dl*-11-ketoprogesterone. Two unnatural racemic 11-ketoprogesterones, isomeric with the natural steroids at $C_{13}$ and $C_{14}$, are prepared *via* the corresponding 11,16,20-triketones.

Previous papers in this series have described two methods for converting the key tricyclic intermediate 2$\beta$,4b-dimethyl-1$\beta$-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$-dodecahydrophenanthrene-4$\alpha$-ol (I)[1] into *dl*-11-ketoprogesterone[2,3] and thence cortisone.[4] A third method of closure of ring D involves an intramolecular acylation of the derived acetonyl ester II to form 11,16,20-triketone III. The practical success of this approach to adrenal steroids depends upon the specificity with which the oxygen atom at $C_{16}$ in triketone III can be removed. This paper is concerned with results obtained in the ring closure and a description of reactions directed toward removal of the $C_{16}$-oxygen.

The esterification of I was carried out more conveniently on a larger scale with methyl iodide and potassium carbonate in acetone than with diazomethane.[1] Oxidation of the methyl ester has been described previously[2]; both reactions occur in excellent yield. Conversion of the side-chain methylene group to the eventual $C_{20}$ carbonyl oxygen was effected as before in this series[5] by hydroxylation with osmium tetroxide followed by periodic acid cleavage of the resulting mixture of glycols. The yield of II over the four steps was about 75%.

With sodium methoxide in benzene, the acetonyl ester II cyclized nearly quantitatively. The product of this reaction had properties which would be anticipated for $\beta$-diketone III. Thus the compound was soluble in cold alkali from which it could be recovered by acidification. It gave an immediate violet color with ferric chloride and showed an ultraviolet absorption maximum at 285 m$\mu$.[6]

A 16,20-diketo steroid structure (5-pregnene-3$\beta$-ol-16,20-dione acetate) has been assigned to a degradation product of nologenin by Marker.[7] This substance is insufficiently characterized to allow comparison of its physical constants with those of our 16,20-diketone.[8] Recently, Inhoffen and coworkers[9] have assigned an enol form of the same

(1) G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, THIS JOURNAL, **76**, 1715 (1954).

(2) W. F. Johns, R. M. Lukes and L. H. Sarett, *ibid.*, **76**, 5026 (1954).

(3) G. I. Poos, W. F. Johns and L. H. Sarett, *ibid.*, **77**, 1026 (1955).

(4) G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, *ibid.*, **76**, 5031 (1954).

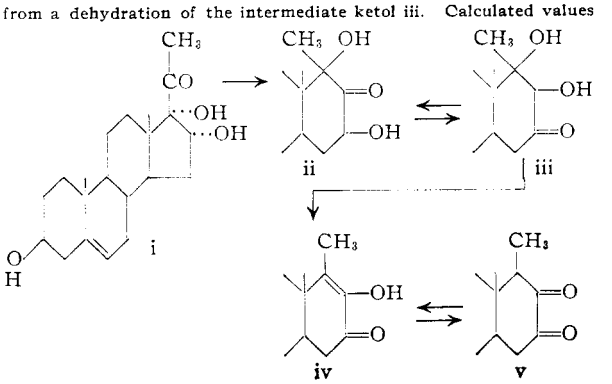
(5) L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, *ibid.*, **75**, 2112 (1953).

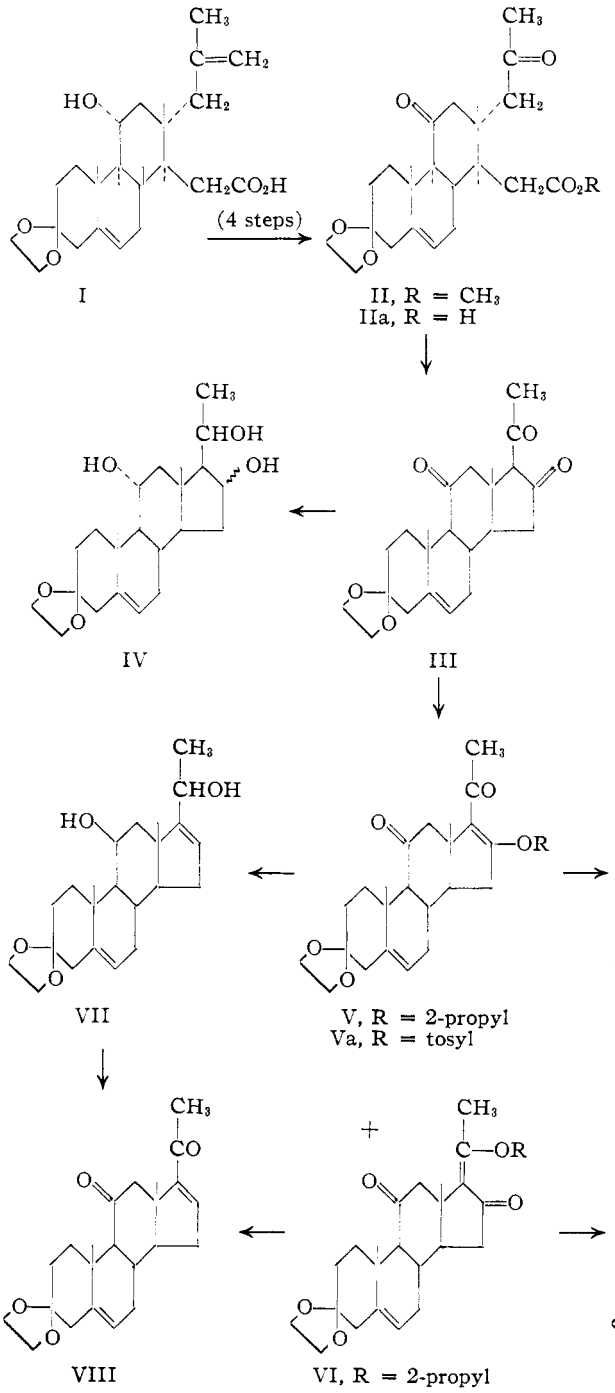
(6) The $C_{14}$- and $C_{13}$-epimers XII and XVII (see below) had the same maximum while $\epsilon_{mol}$ values varied from 5300 for III to 7900 for XII and 9100 for XVII, which indicated a variable degree of enolization for the three $\beta$-diketones. For XVII, the absorption maximum in aqueous methanol varied from 287 m$\mu$, $\epsilon_{mol}$ 9100 at *p*H 1 to 303 m$\mu$, $\epsilon_{mol}$ 19,500 at *p*H 13. See E. R. Blout, V. W. Eager and D. C. Silverman, THIS JOURNAL, **68**, 566 (1946).

(7) R. E. Marker, *ibid.*, **69**, 2395 (1947).

(8) The chemical behavior of III proved to be markedly different from that reported by Marker for his compound (ref. 7). Thus hydrolysis (presumably alkaline) of the 3-acetate in Marker's product appeared to proceed without disturbing the remainder of the molecule while alkaline treatment of III opened the D ring and gave 90% of tricyclic acid IIa along with a trace of neutral steroid for which the *dl*-3-ethylenedioxy-5-androstene-11,16-dione structure was indicated by infrared analysis. An aluminum isopropylate reduction procedure reported by Marker to give 40% of 4,16-pregnadiene-3$\beta$,20$\beta$-diol gave, when applied to III, less than 20% of neutral material. (This result agrees with the reported failure of the Meerwein–Ponndorff method with other enolic substances. See H. Lund, *Ber.*, **70**, 1520 (1937); also a reference to unpublished results of H. Adkins and students by R. L. Frank and H. K. Hall, THIS JOURNAL, **72**, 1645 (1950)). With sodium in isopropyl alcohol, Marker observed the conversion of his 3$\beta$-ol to 5-pregnene-3$\beta$,20$\alpha$-diol in 80% yield while sodium alcohol reductions of III produced only mixtures of hydrogenolysis and hydrogenation products; the only pure product that could be isolated was a *dl*-3-ethylenedioxy-5-pregnene-11$\alpha$,16$\xi$,20$\xi$-triol (IV), obtained in less than 30% yield. Finally, catalytic hydrogenation of the Marker compound with platinum in alcohol was reported to reduce the 5,6-double bond while reduction with platinum in acetic acid followed by treatment with alkali gave allopregnane-3$\beta$,20$\beta$-diol in 80% yield. Catalytic hydrogenation of III proceeded readily to give a *non-enolic* mixture from which no single product was isolated either before or after treatment with base. These contrasts cast serious doubts on the structure of the Marker compound. Very recently K. Heusler and A. Wettstein, *Ber.*, **87**, 1301 (1954), have questioned the Marker nologenin formula (ref. 7) on the basis of their inability to convert a 16-acyloxy-17-hydroxy-20-ketone (the intermediate proposed by Marker) to a 16,20-diketone under the Marker conditions. Thus it would appear that the entire Marker interpretation is incorrect.

(9) H. H. Inhoffen, F. Blomeyer and K. Brüchner, *Ber.*, **87**, 593 (1954). The alkali stability, extraction from aqueous potassium hydroxide solution with chloroform, the lower position of the ultraviolet maximum and acetylation with acetic anhydride in pyridine to form a single product reported by Inhoffen for his compounds are difficult to rationalize with a 16,20-diketo structure in the light of the properties and behavior of III. The ease of rearrangement of 17-hydroxy-20-keto steroids under alkaline conditions (see R. B. Turner, THIS JOURNAL, **75**, 3484 (1953), and references therein) suggests the $\alpha$-diketone structure iv–v for the Inhoffen compound which could be expected from a dehydration of the intermediate ketol iii. Calculated values






structure to a product resulting from the action of alkali upon 5-pregnene-3$\beta$,16$\alpha$,17$\alpha$-triol-20-one.

Selective removal of the $C_{16}$-oxygen atom (*e.g.*, III → IX) in a practical yield requires either: (1) preferential reduction of the 16-keto group to an alcohol, dehydration and reduction of the resultant 16,17-double bond; or (2) preferential formation of a single enol derivative (*e.g.*, V or VI); or (3) formation of a readily separable mixture of the two enol derivatives and utilization of both isomers. Each of these approaches was investigated, with the following results.

Attempts at selective reduction were unsuccessful. Catalytic, sodium–alcohol and aluminum isopropylate reductions of III failed to give useful products.[8] Reductions with lithium aluminum hydride (inverse addition) and sodium borohydride also were investigated. In both cases only complex mixtures were obtained.

The triketone III could be converted readily to its enolic derivatives but in all cases mixtures of nearly equal amounts of 16- and 20-enols were obtained. Thus upon heating in acetone solution with potassium carbonate and isopropyl iodide, III was converted in excellent yield to a 6:4 mixture of the 16- and 20-isopropyl ethers (V and VI).[10,11] These isomers were readily separable by a combination of crystallization and chromatography. Lithium aluminum hydride reduction of 16-isopropyl ether V gave the hydrogenolysis product *dl*-3-ethylenedioxy-5,16-pregnadiene-11$\beta$,20$\xi$-diol (VII) in 40% yield. The structure of VII was assigned on the basis of its infrared spectrum and its oxidation with chromium trioxide–pyridine to the known[3] *dl*-3-ethylenedioxy-5,16-pregnadiene-11,20-dione (VIII). The 20-isopropyl ether VI also was converted to the $\Delta^{16}$-20-ketone VIII. Sodium borohydride reduction of VI provided a crystalline mixture which was treated with dilute sulfuric acid in tetrahydrofuran to selectively hydrolyze[1] the enol ether. Passage of the crude hydrolysis product over alkaline alumina afforded 60% of VIII. The reduction of VIII to *dl*-3-ethylenedioxy-5-pregnene-11,20-dione (IX)[2] has been described.[3] A more vigorous sodium borohydride treatment of VI served to reduce the 11-carbonyl group and afforded, after acid treatment and chromatography, 50% of *dl*-3-ethylenedioxy-5,16-pregnadiene-11$\beta$-ol-20-one (X).

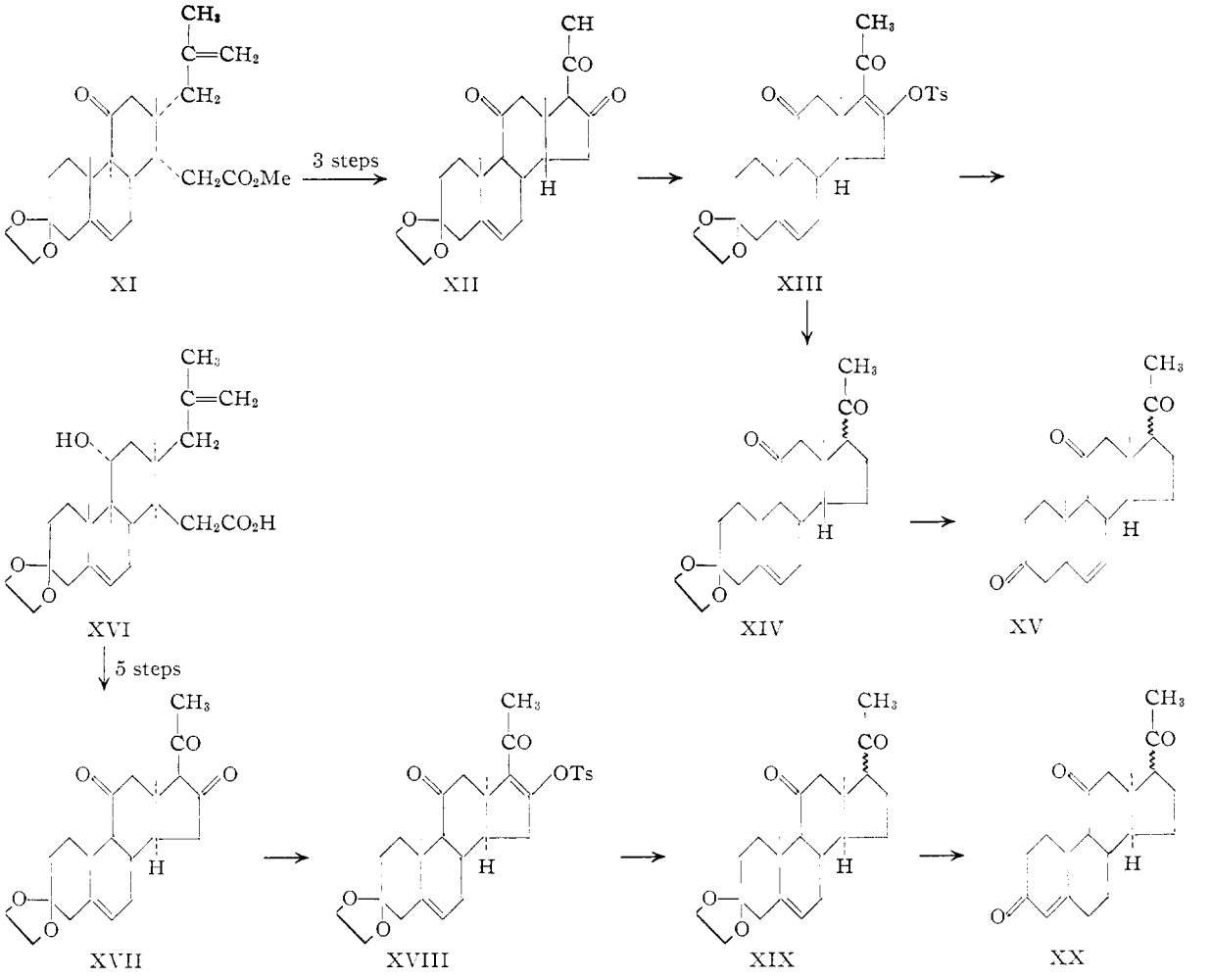
With *p*-toluenesulfonyl chloride in pyridine,[12]

for the positions of the ultraviolet absorption maxima for iv and its acetate are 278 and 245 m$\mu$, respectively (L. Dorfman, *Chem. Revs.*, **53**, 47 (1953)) while the values recorded by Inhoffen are 277 m$\mu$ for the free compound and 244 m$\mu$ for its diacetate. We have discussed this interpretation with Professor Inhoffen, who is in agreement with the D-homo-$\alpha$-diketone formulation and indicates that he plans further characterization of his product. The conversion of 5-pregnene-3$\beta$,16$\beta$,17$\alpha$-triol-20-one 3,16-diacetate to a non-enolic D-homo steroid under mild conditions has been described very recently by K. Heusler and A. Wettstein, *Ber.*, **87**, 1301 (1954).

(10) In the infrared, the 16-enol ether V had $\lambda_{max}$ 5.83 $\mu$ ($C_{11}$ C=O), 6.10 $\mu$ ($C_{20}$ C=O) and 6.32 $\mu$ ($C_{16}$ C=C) while the 20-enol ether VI showed $\lambda_{max}$ 5.81 $\mu$ ($C_{11}$ C=O), 5.90 $\mu$ ($C_{16}$ C=O) and 6.18 $\mu$ ($C_{17}$ C=C). The absorption of a conjugated steroid 20-ketone in the infrared is known to be at a higher wave length (*ca.* 6.00 $\mu$) than of a steroidal conjugated cyclopentenone (*ca.* 5.90 $\mu$); see R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, THIS JOURNAL, **70**, 2024 (1948).

(11) The ultraviolet spectra (V, $\lambda_{max}^{MeOH}$ 274 m$\mu$ $\epsilon$ 14,700; VI, $\lambda_{max}^{MeOH}$ 281 m$\mu$ $\epsilon$ 16,500) also served to distinguish the two ethers. The higher absorption maximum (281 m$\mu$) of VI can be attributed to the bathochromic effect of the exocyclic double bond. See L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), and references cited therein.

(12) L. Ruzicka, A. Plattner and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).




III was converted in good yield to a difficultly separable mixture of enol tosylates. Chromatography and repeated crystallization afforded a small amount of 16-enol tosylate Va (conjugated 20-carbonyl at 6.00 $\mu$ in the infrared).[10] A one-step hydrogenolysis–hydrogenation[12] with palladium–barium carbonate catalyst was used to convert both pure tosylate Va and the mixture of tosylates to *dl*-3-ethylenedioxy-11-ketoprogesterone (IX); in the latter case IX was accompanied by a compound that appeared by infrared analysis to be *dl*-3-ethylenedioxy-5-pregnene-11,16-dione.

The tricyclic intermediates isomeric at $C_1$ and $C_2$ with the natural series were converted to the corresponding 14-iso and 13-iso-11,16,20-triketopregnenes by the same reactions which provided III from I. From 2$\beta$,4b-dimethyl-1$\alpha$-carbomethoxy-2-methallyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,-10,10a$\beta$-dodecahydrophenanthrene-4-one (XI)[1] there was obtained *dl*-3-ethylenedioxy-14$\beta$-pregn-5-ene-11,16,20-trione (XII) in excellent yield over three steps. The latter gave principally the 16-enol tosylate XIII which was smoothly converted to *dl*-3-ethylenedioxy-11-keto-14$\beta$-progesterone (XIV)[13] by hydrogenolysis–hydrogenation. Acid hydrolysis of XIV afforded *dl*-11-keto-14$\beta$-progesterone (XV), readily distinguishable by infrared analysis from the corresponding C/D *trans* product.[2,14]

Application of the same sequence of reactions to 2$\alpha$,4b-dimethyl-1$\beta$-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$-dodecahydrophenanthrene-4a$\alpha$-ol (XVI)[1] was attended by equally satisfactory yields through 11,16,20-triketone XVII and 16-enol tosylate XVIII.[15]

(13) There was insufficient evidence available to assign configurations at $C_{13}$ in the abnormal C/D *cis*-pregnenes XIV and XIX.

(14) The infrared differences were principally in the "fingerprint" region of the spectra. C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, 3496 (1953), have noted a pronounced band at 9.50 $\mu$ in *trans* C/D $\Delta^8$-11-keto steroidal sapogenins which is absent in the corresponding *cis* C/D compounds. R. J. Highet (Ph.D. Thesis, University of Wisconsin, 1953) examined the infrared spectra of a number of *cis* and *trans* pairs of polycyclic angularly methylated compounds related to the steroids and found a rather consistent pattern in the 9.5–10.1 $\mu$ region of compounds with a carbonyl group adjacent to the angular site but no regular system of peaks in *cis–trans* pairs without an adjacent carbonyl function. The infra spectra of our *trans* C/D 11-ketoprogesterone (see ref. 2) and the two *cis* C/D isomers XV and XX as well as their corresponding 3-dioxolanes (IX, XIV and XIX) were featureless in the 9–10 $\mu$ region except for the marked C–O stretching vibration at 9.0–9.1 $\mu$ shown by IX, XIV and XIX.

(15) Results of enol tosylations of the three isomeric 11,16,20-triketones provide an interesting comparison. Both *cis* C/D triketones (XII and XVII) gave 16-enol tosylates (XIII and XVIII) as the only products while the natural *trans* C/D triketone III gave a mixture of 16- and 20-enolates (see above). The yields of 16-enol tosylates are roughly proportional to the extinction coefficients of the parent triketones (see footnote 6). That the *trans*-fused cyclopentane ring is less willing to accommodate a double bond than the *cis*-fused ring might be expected.

However, the hydrogenolysis–hydrogenation conditions so successfully used with Va and XIII gave very poor results with XVIII. From all of the reduction experiments with this compound, starting material, highly colored side products and only a small percentage of the desired 20-ketone XIX[13] were obtained. Since both of the isomeric compounds were reduced without difficulty, it is most probable that the unnatural $\alpha$-configuration of the $C_{13}$ angular methyl group in XVIII prevents the $\alpha$-side of the molecule from being adsorbed on the catalyst as in the reduction of a normal steroid.[16] Due to the low yield, XIX and sequentially XX were characterized only by their infrared spectra.

## Experimental[17]

**2$\beta$,4b-Dimethyl-1$\beta$-carbomethoxymethyl-2-acetonyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$-dodecahydrophenanthrene-4-one (II). A. Esterification of I.**—The esterification of I with diazomethane has been described.[1] A suspension of 9.00 g. of 2$\beta$,4b-dimethyl-1$\beta$-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$-dodecahydrophenanthrene-4$\alpha$-ol (I)[1] and 18 g. of anhydrous potassium carbonate in 100 ml. of acetone and 100 ml. of methanol (necessary in this case to prevent precipitation of the very insoluble potassium salt of I) was treated with 20 ml. of methyl iodide and stirred overnight at room temperature. Potassium iodide and excess potassium carbonate were removed by filtration and the filtrate was concentrated to low volume *in vacuo*. An ethereal solution of the residue was washed with water, dried and concentrated to afford a first crop of 7.05 g. (76%) of 2$\beta$,4b-dimethyl-1$\beta$-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$-dodecahydrophenanthrene-4$\alpha$-ol, m.p. 156–158°.[1] A second crop and recrystallized third crop amounted to 1.79 g., m.p. 154–157°, total yield 8.84 g. (95%).

**B. Oxidation.**—The product of this reaction has been described but no details of its preparation were given (footnote 12, ref. 2). A solution of 8.84 g. of the methyl ester of I in 85 ml. of pyridine was added to the complex prepared by the addition of 8.5 g. of chromium trioxide to 85 ml. of pyridine. After 20 hours at room temperature, 170 ml. of water was added to the reaction mixture. Extraction with three 400-ml. portions of ether followed by washing with water, drying and concentration afforded a crystalline residue. Recrystallization from ether gave a first crop of 6.88 g., m.p. 140–142°.[2] The second crop and recrystallized third crop amounted to 1.52 g., m.p. 137–140°, total yield 8.40 g. (95%).

**C. Hydroxylation.**—To a solution of 8.39 g. of 2$\beta$,4b-dimethyl-1$\beta$-carbomethoxymethyl-2-methallyl-7-ethylenedioxy - 1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$ - dodecahydrophenanthrene-4-one in 15 ml. of benzene and 70 ml. of ether was added 5.62 g. of osmium tetroxide. The osmate ester rapidly precipitated and after 12 minutes 340 ml. of ethanol was added. After dissolution of the osmate ester, a solution of 34 g. of sodium sulfite in 225 ml. of water was added and the reaction mixture was agitated vigorously until hydrolysis was complete (15 minutes). The precipitated inorganic material was separated by filtration and washed thoroughly with ethanol. Concentration of the filtrate under vacuum provided an oil which was extracted into ether, washed with water, dried and concentrated to provide 7.62 g. of crystalline residue. Acidification of the aqueous wash and chloroform extraction gave a small amount of the glycol acid (m.p. 190–200°) which was converted to the glycol ester with potassium carbonate–ethyl iodide in acetone. Alumina chromatography of the combined ester separated 2.26 g. (27%) of unchanged methallyl ester and provided 5.55 g. (84% based on starting material consumed) of the mixture of glycols, 2$\beta$,4b-dimethyl-1$\beta$-carbomethoxymethyl-2-(2-methyl-2,3-dihydroxypropyl)-7-ethylenedioxy - 1,2,3,4,4a$\alpha$,5,6,7,8,10,10a$\beta$ - dodecahydrophenanthrene-4-one melting at 141–155°. A sample recrystallized several times from ether for analysis melted at 146–150°.

*Anal.* Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.46; H, 8.39.

**D. Cleavage.**—The glycol ester above, 5.44 g., in 40 ml. of ethanol and 14 ml. of pyridine was treated with a solution of 5.50 g. of paraperiodic acid in 28 ml. of water. After 15 minutes at room temperature the reaction mixture was diluted with water and the ethanol was distilled under vacuum. The resulting crystals were separated by filtration, washed thoroughly with water and air-dried; 4.91 g. (97%), m.p. 128–132°. Recrystallization from ether gave a sample of 2$\beta$,4b-dimethyl-1$\beta$-carbomethoxymethyl-2-acetonyl-7-ethylenedioxy-1,2,3,4,4a$\alpha$,4b,5,6,7,8,10,10a$\beta$-dodecahydrophenanthrene-4-one (II) which melted at 132–134°; $\lambda_{max}$ 5.79, 5.83 $\mu$.

*Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.00; H, 7.90.

***dl*-3-Ethylenedioxy-5-pregnene-11,16,20-trione (III).**—To the solid sodium methoxide prepared by baking (150°, 0.1 mm., 30 minutes) the residue obtained by the evaporation of 11.5 ml. of 1 *N* methanolic sodium methoxide solution was added a solution of 4.70 g. of II in 40 ml. of dry benzene. The reaction flask was sealed to exclude air and the mixture was stirred at room temperature overnight. The pale yellow mixture initially became homogeneous and then slowly precipitated sodium salt. Ice-water and ether were added to the resultant thick suspension and the mixture was shaken vigorously, allowed to separate and the aqueous layer immediately acidified with excess sodium dihydrogen phosphate. The ethereal solution was extracted with several portions of cold water which were added to the acidified part. The product which had precipitated was collected by filtration, washed with water and dried; 4.35 g. (100%), m.p. 150–157°. Recrystallization from ethyl acetate–ether afforded 4.18 g. (96%) of III, m.p. 156–159°. A sample recrystallized from ethanol melted at 154–156°, gave a violet color with alcoholic ferric chloride and had $\lambda_{max}$ 285 m$\mu$, $\epsilon$ 5,300; $\lambda_{max}$ 3.0–3.2, 5.70 (weak), 5.88, 6.01, 6.19 $\mu$.

*Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.47; H, 7.82. Found: C, 71.64; H, 7.68.

**Catalytic Reduction of III.**—A solution of 105 mg. of III in 30 ml. of ethanol containing 100 mg. of prereduced platinic oxide absorbed 8.5 ml. of hydrogen (1.2 equivalents) at atmospheric pressure and room temperature in 35 minutes whereupon hydrogen uptake virtually ceased. Filtration of the catalyst and concentration of the ethanol afforded a crystalline residue which gave no color with alcoholic ferric chloride. Recrystallization from various solvents gave mixtures which melted between 175 and 200°. All of the material was dissolved in 7 ml. of benzene and treated with 100 mg. of potassium *t*-butoxide at 100° for ten minutes. Recovery of the material and alumina chromatography gave mixtures which melted between 155 and 185°, eluted with ether–petroleum ether.

**Sodium–Alcohol Reduction of III.**—One gram of sodium was added to 200 mg. of III in 15 ml. of boiling *n*-butyl alcohol. After the sodium had dissolved, the solution was cooled, diluted with water and extracted with chloroform. The chloroform solution was washed, dried and concentrated to give a crystalline residue which was chromatographed over 6 g. of acid-washed alumina. Crystalline mixtures melting between 180 and 225° were eluted with ether, ether–chloroform, chloroform and ethyl acetate. With methanol there was eluted 65 mg. of crystalline product which melted at 215–237°. Recrystallization from acetone, ethyl acetate–methanol and acetone–methanol gave 33 mg. of a *dl*-3-ethylenedioxy-5-pregnene-11a,16$\xi$,20$\xi$-triol (IV), m.p. 241–242°; $\lambda_{max}$ 3.02, 9.0 $\mu$.

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.79; H, 9.07.

**Alkaline Cleavage of III.**—Eight milliliters of 1 *N* potassium hydroxide and 16 ml. of ethanol containing 505 mg. of III was heated under reflux overnight. Ethanol was distilled and the aqueous residue was extracted with chloroform. Evaporation of the chloroform afforded 23 mg. (5%) of neutral product which after recrystallization from benzene–ether melted at 215–222° and showed $\lambda_{max}$ 5.75, 5.90 $\mu$.

(16) L. Fieser and M. Fieser in "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 655.

(17) Melting points were determined on a Kofler micro hotstage. Infrared spectra are of the solids in Nujol and ultraviolet spectra are of methanolic solutions unless otherwise noted.

The spectrum is consistent with the expected *dl*-3-ethylenedioxy-5-androstene-11,16-dione structure.

Acidification of the potassium hydroxide solution with sodium dihydrogen phosphate liberated 510 mg. of crystalline acid. Recrystallization from ethyl acetate provided 476 mg. (90%) of 2β,4b-dimethyl-1β-carboxymethyl-2-acetonyl-7 - ethylenedioxy - 1,2,3,4,4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4-one (IIa), m.p. 178–182°. The analytical sample melted at 180–182° after recrystallization from ethyl acetate and benzene–ether.

*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.26; H, 7.72.

**Isopropyl Ethers of III. *dl*-3-Ethylenedioxy-16-isopropoxy-5,16-pregnadiene-11,20-dione (V) and *dl*-3-Ethylenedioxy-20-isopropoxy-5,17-pregnadiene-11,16-dione (VI).**—One gram of the triketone III, 2 g. of anhydrous potassium carbonate and 2 ml. of isopropyl iodide in 20 ml. of acetone was heated overnight under reflux. The mixture was concentrated to a thick paste under vacuum, water and benzene were added and the aqueous part was extracted with benzene. The washed and dried benzene extract yielded 1.12 g. of crystalline residue upon concentration. Recrystallization from benzene afforded 564 mg. (51%) of 16-enol ether V with m.p. 236–239°. A sample recrystallized from ethanol and benzene had m.p. 237–239°; $\lambda_{max}$ 274 mμ, ε 14,400; $\lambda_{max}$ 5.83, 6.10, 6.32 μ.

*Anal.* Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.76; H, 8.33.

The benzene mother liquors from the separation of V were chromatographed on 20 g. of alkaline alumina. Ether–petroleum ether eluted 465 mg. (42%) of the 20-enol ether VI which melted at 173–184°. Ether recrystallization raised the melting point to 184–186°; $\lambda_{max}$ 281 mμ, ε 16,600; $\lambda_{max}$ 5.81, 5.90, 6.18 μ.

*Anal.* Found: C, 72.88; H, 8.49.

Elution with chloroform provided an additional 78 mg. (7%) of 16-enol ether V of m.p. 235–239°, total yield 642 mg. (58%).

***dl*-3-Ethylenedioxy-5,16-pregnadiene-11β,20ξ-diol (VII).**—To a solution of 500 mg. of lithium aluminum hydride in 10 ml. of tetrahydrofuran was added 388 mg. of 16-enol ether V in 10 ml. of the same solvent. After the mixture had been stirred 1.5 hours at room temperature, sufficient water was added dropwise to destroy excess hydride and hydrolyze organic complexes. The mixture was filtered and the inorganic filter cake was washed thoroughly with tetrahydrofuran. Evaporation of the filtrate to dryness provided a non-crystalline residue which was dissolved in benzene and adsorbed on 15 g. of alkaline alumina. Early ether–petroleum ether eluates gave 175 mg. of partially crystalline mixtures. Ether and chloroform eluted 220 mg. of crude *dl*-3-ethylenedioxy-5,16-pregnadiene-11β,-20ξ-diol (VII), m.p. 170–185°. Benzene recrystallization provided 138 mg. (41%) of pure VII, m.p. 186–187°; $\lambda_{max}$ 2.96, 6.0–6.15 μ (weak).

*Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.60; H, 9.43.

***dl*-3-Ethylenedioxy-5,16-pregnadiene-11,20-dione (VIII).**

**A. From VII.**—Eighty milligrams of the diol VII was oxidized with 80 mg. of chromium trioxide in 1.8 ml. of pyridine at room temperature overnight and worked up as described previously. The 78 mg. of crude crystalline product provided 55 mg. (69%) of pure VIII by ether recrystallization, m.p. and mixed m.p. 194–196°.[3]

**B. From VI.**—A solution of 115 mg. of 20-enol ether VI in 5 ml. of 93% ethanol was treated with 70 mg. of sodium borohydride and kept at room temperature overnight. Dilution with water followed by chloroform extraction gave 112 mg. of a crystalline mixture, m.p. 140–200°; $\lambda_{max}$ 2.85, 5.87, (weak 6.00, 6.24 μ). To a portion (90 mg.) of this mixture in 8 ml. of tetrahydrofuran was added 0.5 ml. of 10% sulfuric acid. After 3.5 hours at room temperature, dilute sodium bicarbonate solution was added, the tetrahydrofuran was removed *in vacuo* and the product extracted with chloroform. An ether solution of the residue was passed over 3 g. of alkaline alumina. Evaporation of the ether provided 60 mg. of crude VIII, m.p. 178–189°. Ether recrystallization gave a sample of VIII with m.p. and mixed m.p. 194–197°.[3]

***dl*-3-Ethylenedioxy-5,16-pregnadiene-11β-ol-20-one (X).**—A solution of 104 mg. of 20-enol ether VI in 5 ml. of 95% ethanol containing 110 mg. of sodium borohydride was kept at room temperature overnight and then treated with an additional 100 mg. of borohydride and heated under reflux for four hours. The work-up described in the previous section gave 102 mg. of a gum which provided some crystals, m.p. 134–143°, $\lambda_{max}$ 2.80, 2.90, 5.97 μ (weak), from ether. Treatment of the entire reaction product with sulfuric acid in tetrahydrofuran as described above followed by chromatography over 3 g. of alkaline alumina afforded 45 mg. (50%) of X, m.p. 202–210°, eluted with ether–petroleum ether. Two recrystallizations from methanol gave 34 mg. of pure X, m.p. 214–216°; $\lambda_{max}$ 2.83, 5.99, 6.25 μ.

*Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.91; H, 8.75.

**Enol Tosylation of III. *dl*-3-Ethylenedioxy-16-tosyloxy-5,16-pregnadiene-11,20-dione (Va).**—The trione III (295 mg.) in 3.7 ml. of pyridine was treated with 370 mg. of *p*-toluenesulfonyl chloride and left at room temperature for 22 hours. The cooled reaction mixture was treated dropwise with 2.3 ml. of saturated sodium bicarbonate solution and allowed to stand until neutralization was complete (15 minutes). Benzene was added and the organic part was washed with a limited amount of dilute hydrochloric acid and then with water and sodium bicarbonate solution. Drying and concentration yielded 375 mg. (91%) of crystalline tosylate mixture, m.p. 132–145°. Rapid alumina chromatography was accompanied by considerable loss but gave crystalline tosylate mixtures from the ether–petroleum ether eluates with m.p. 175–190°. Repeated benzene–ether recrystallization of this material afforded 20 mg. of pure 16-enol tosylate Va, m.p. 199–201° dec.; $\lambda_{max}$ 5.83, 6.00, 6.16, 6.22 μ.

*Anal.* Calcd. for $C_{30}H_{36}O_7S$: C, 66.64; H, 6.71. Found: C, 66.50; H, 6.55.

***dl*-3-Ethylenedioxy-5-pregnene-11,20-dione (IX).**—To a solution of 52 mg. of 16-enol tosylate Va in 10 ml. of benzene was added 2 g. of 5% palladium-on-barium carbonate and the mixture was shaken with hydrogen at a pressure of about 40 p.s.i. An additional 0.8 g. of catalyst was added after two hours and again after four hours. The hydrogenation was continued overnight; catalyst was then removed by filtration and the benzene was evaporated. The crystalline residue was recrystallized from ether–petroleum ether and gave 28 mg. (76%) of the 3-dioxolane of *dl*-11-ketoprogesterone (IX), m.p. 175–178°, which was not depressed when mixed with a sample prepared by a different method.[2]

**Hydrogenolysis–Hydrogenation of Tosylate Mixture.**—A sample of the crude tosylate mixture described under the preparation of Va was recrystallized from benzene–ether (218 mg., m.p. 152–157°) and submitted to reduction under the conditions described above. The crude product amounted to 181 mg. It was adsorbed on 5.4 g. of acid-washed alumina. Early 2:8 ether–petroleum ether eluates provided 65 mg. of crystals which melted at 125–145°. Several ether–petroleum ether recrystallizations gave 17 mg. with m.p. 142–145° and $\lambda_{max}$ 5.76, 5.88 μ. The spectrum was consistent with the *dl*-3-ethylenedioxy-5-pregnene-11,16-dione structure. Further elution with ether–petroleum ether gave mixtures and then 62 mg. of crude IX, m.p. 150–175°. Repeated recrystallization from ether, methanol and ether–petroleum ether served to separate 38 mg. of IX, m.p. and mixed m.p. 175–178°.

**Enol Acetylation of III.**—To the slurry obtained by adding 0.5 ml. of acetyl chloride to 5 ml. of cold pyridine was added 200 mg. of III. The mixture was stirred an hour at room temperature, ether and ice were added and the separated ether layer was washed with limited dilute hydrochloric acid and then water and sodium bicarbonate solution. The organic phase was dried and concentrated affording a crystalline residue. One recrystallization from ether gave 160 mg., m.p. 165–195°. Successive recrystallization from ether, ethanol, ethyl acetate, ethanol and ether separated 21 mg. of *dl*-3-ethylenedioxy-20-acetoxy-5,17-pregnadiene-11,16-dione, m.p. 214–220°; $\lambda_{max}$ 246 mμ, ε 14,000; $\lambda_{max}$ 5.68, 5.80, 5.92, 6.08 μ.[18]

(18) The 5.92 μ infrared conjugate carbonyl band indicated the 20-enol acetate structure (see ref. 10) while the ultraviolet maximum at 246 mμ compares with that of an analogous compound, 17-pregnene-3α,12α,20-triol-16-one triacetate with $\lambda_{max}$ 249 mμ, ε 11,200; prepared by C. W. Marshall and T. F. Gallagher, THIS JOURNAL, 71, 2325 (1949).

*Anal.* Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.29; H, 7.23.

***dl*-3-Ethylenedioxy-14β-pregn-5-ene-11,16,20-trione (XII).**—Hydroxylation of 2β,4b-dimethyl-1α-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one[1] (XI, 1.45 g.) with osmium tetroxide by the procedure described for I provided 600 mg. of glycol ester, m.p. 143–155°, along with 720 mg. of crystalline glycol acid. Cleavage of the glycol ester with periodic acid gave 579 mg. of 2β,4b-dimethyl-1α-carbomethoxymethyl-2-acetonyl-7-ethylenedioxy-1,2,3,4,4aα,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one, m.p. 139–142°. Recrystallization from benzene–petroleum ether raised the melting point to 144°.

*Anal.* Found: C, 68.87; H, 8.08.

The Claisen ring closure procedure used with II converted 540 mg. of the above 1α-carbomethoxymethyl isomer to 400 mg. (80%, first crop from ethyl acetate–ether) of *dl*-3-ethylenedioxy-14β-pregn-5-ene-11,16,20-trione (XII) melting at 210–214°. A sample recrystallized from ethanol had m.p. 213.5–215°, $\lambda_{max}$ 286 mμ, $\epsilon_{mol}$ 7,900, and gave a violet color with alcoholic ferric chloride.

*Anal.* Found: C, 71.74; H, 8.12.

***dl*-3-Ethylenedioxy-14β-pregn-5-ene-11,20-dione (XIV) and *dl*-11-Keto-14β-progesterone (XV).**—Procedures essentially identical to those employed in the natural series were used.

From 289 mg. of XII there was obtained 353 mg. (88%) of the 16-enol tosylate XIII melting at 155–175°. Recrystallizations from chloroform–methanol and benzene gave m.p. 198–200°; $\lambda_{max}$ 5.86, 5.97, 6.05, 6.22 μ.

*Anal.* Found: C, 67.04; H, 6.61.

Hydrogenolysis–hydrogenation of 180 mg. of the tosylate XIII afforded 86 mg. (69%, first crop from methanol) of *dl*-3-ethylenedioxy-14β-pregn-5-ene-11,20-dione (XIV) which melted at 166–170°. The analytical sample melted at 171–172.5° after recrystallization from ethyl acetate; $\lambda_{max}$ 5.86, 9.05 μ. The infrared solution spectrum ($CHCl_3$) was different from that of compound IX beyond 6 μ.

*Anal.* Found: C, 74.07; H, 8.78.

Hydrolysis of 55 mg. of XIV was carried out in 1 ml. of tetrahydrofuran with 0.5 ml. of 3 *N* perchloric acid at room temperature for 3.5 hours. Crystallization of the product from benzene–petroleum ether afforded 41 mg. of *dl*-11-keto-14β-progesterone (XV), m.p. 151–153°. After recrystallization from ethyl acetate and ether–petroleum ether, XV had m.p. 153° and 168°; $\lambda_{max}^{CHCl_3}$ 5.86, 6.0, 6.17 μ.

*Anal.* Found: C, 76.85; H, 8.40.

***dl*-3-Ethylenedioxy-13α-pregn-5-ene-11,16,20-trione (XVII).**—The experimental procedures used for the conversion of I to III were used.

**A. Esterification.**—Potassium carbonate–methyl iodide was used to esterify 2α,4b-dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XVI)[1] in acetone. The product was recrystallized from ethyl acetate–ether petroleum ether and melted at 138–139°; $\lambda_{max}$ 2.93, 5.82, 6.05 μ.

**B. Oxidation.**—Chromic anhydride–pyridine converted the above 4α-hydroxy methyl ester to 2α,4b-dimethyl-1β-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,-4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one, m.p. 125–126°; $\lambda_{max}$ 5.76, 5.87, 6.05 μ.

*Anal.* Found: C, 72.28; H, 8.48.

**C. Hydroxylation.**—Reaction of the above keto methyl ester with osmium tetroxide afforded the mixture of glycols, 2α,4b-dimethyl-1β-carbomethoxymethyl-2-(2-methyl-2,3-dihydroxypropyl)-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,-10aβ-dodecahydrophenanthrene-4-one. A portion recrystallized from ethyl acetate had m.p. 172–174°; $\lambda_{max}$ 2.95, 5.76, 5.88 μ.

*Anal.* Found: C, 66.63; H, 8.97.

**D. Cleavage.**—Periodate cleavage of the crude glycol mixture gave 2α,4b-dimethyl-1β-carbomethoxymethyl-2-acetonyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one, m.p. 108–109°; $\lambda_{max}$ 5.78, 5.82 μ.

*Anal.* Found: C, 68.74; H, 8.23.

**E. Ring Closure.**—The above acetonylacetic ester was cyclized in the presence of sodium methoxide. The product, *dl*-3-ethylenedioxy-13α-pregn-5-ene-11,16,20-trione (XVII), was recrystallized from ethyl acetate and melted at 226–229°; $\lambda_{max}$ 285 mμ, ε 9,100; $\lambda_{max}^{pH\ 1}$ 287 mμ, ε 9,100; $\lambda_{max}^{pH\ 13}$ 303 mμ, ε 19,500; $\lambda_{max}$ 5.85, 6.07, 6.17 μ.

*Anal.* Found: C, 71.21; H, 7.53.

***dl*-3-Ethylenedioxy-13α-pregn-5-ene-11,20-dione (XIX) and *dl*-11-Keto-13α-progesterone (XX).**—Reaction of XVII with *p*-toluenesulfonyl chloride in pyridine proceeded to give 16-enol tosylate XVIII. After recrystallization from ethyl acetate, XVIII had m.p. 189–190°; $\lambda_{max}$ 5.82, 5.97, 6.09, 6.22 μ.

*Anal.* Found: C, 66.44; H, 6.69.

Palladium–barium carbonate hydrogenation of XVIII gave a mixture which consisted of starting material, colored side products and, by chromatography, about 5% of *dl*-3-ethylenedioxy-13α-pregn-5-ene-11,20-dione (XIX), m.p. 142–145°; $\lambda_{max}$ 5.87, 9.0 μ.

Acid hydrolysis of XIX gave *dl*-11-keto-13α-progesterone, m.p. 153–158°; $\lambda_{max}$ 5.88, 5.97, 6.17 μ.

RAHWAY, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ALBERTA]

# Derivatives of Indole, 6-Amino-3-indoleacetic Acid[1]

BY R. K. BROWN AND R. A. GARRISON

RECEIVED JANUARY 25, 1955

6-Nitrogramine methiodide reacts more readily than does 6-nitrogramine itself with aqueous potassium cyanide in a buffered solution to produce 6-nitro-3-indoleacetonitrile. Removal of the nitrile from the aqueous phase by an organic phase as soon as it is formed increases the yield of the product. Hydrolysis of the nitrile to the carboxylic acid required concentrated hydrochloric acid. Raney nickel and hydrogen converted both 6-nitro-3-indoleacetonitrile and 6-nitro-3-indoleacetic acid to the corresponding amines.

The well known plant growth stimulating property of 3-indoleacetic acid along with the obvious structural similarity between 6-aminoindole[2] and the carcinogens 2-aminofluorene[3] and 3-aminodibenzothiophene[4] prompted interest in the preparation of 6-amino-3-indoleacetic acid. Although 3-indoleacetic acid itself fails to induce tumor growth,[5] the incorporation of the amino moiety in the aromatic ring may well yield a compound possessing interesting physiological properties.

(1) Taken in part from a thesis submitted by R. A. Garrison in partial fulfillment of the requirements for the M.Sc. degree, Department of Chemistry, University of Alberta.

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(5) M. J. Shear and J. Leiter, *J. Natl. Cancer Inst.*, **2**, 241 (1941).