Methods for Total Synthesis of Steroids. XVIII.[1] Δ^{14}-16-Keto Steroid Approach to Ring D. H.[2] Introduction of 17-Carboxy Group. Synthesis of 14α,17β and 14β,17α Isomers of *rac*-Estra-5(10),6,8-triene-17-carboxylic Acid

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Abstract: The 17-carboalkoxy group was introduced in high yield into the Δ^{14}-16-keto steroid system (as in **1**; rings AB aromatic in this paper) with dialkyl carbonate and sodium hydride. Of several methods described here for removing the 16-keto group, the best was Raney nickel hydrogenation (accompanied by ring A reduction) to the hydroxy ester **6**, followed by alkaline dehydration. Potassium hydroxide at 240° gave the 17β-carboxy-Δ^{14} isomer **9** which was hydrogenated to the 14α,17β-carboxy steroid with the natural configuration in rings CD, as in **11**, a three-step synthesis from **1**. At 150° potassium hydroxide gave the 14β-Δ^{16} isomer **8**, which was hydrogenated to the 14β,17α-carboxy isomer **10**. Other methods of reduction were explored, including direct hydrogenation–hydrogenolysis of the keto ester **4** to **11**, hydrogenolysis of the enol acetate **13**, and desulfuration of the 16-ethylene mercaptole **14**.

A three-step synthesis was developed by Wilds and Beck[1b] in 1944 for attaching ring D of the steroid nucleus to a tricyclic ketone. A major feature of this approach, in addition to brevity, was that it led to a Δ^{14}-16-keto steroid structure (*e.g.*, **1**), which permitted the facile introduction of a variety of 17-substituents, the main groups which differentiate the steroids. In earlier papers in this series were described the introduction of the 17-ketone and hydroxyl functions, and synthesis of the estriol analog in the desoxyequilenin series.[1b,1p] The present paper[4] is concerned with the introduction of the 17-carboxyl group, then removal of the 16-oxygen function and 14,15 double bond, with good control of stereochemistry in ring D. This method has been extended by us to the total synthesis of deoxycorticosterone,[1f] progesterone,[5] and other non-aromatic steroids *via* methyl 3-ketoetiocholanate.[1j,1m]

In the early work[1b] it was shown that methyl oxalate condensed in excellent yield at the 17 position of the unsaturated ketone **1** to give the glyoxylate **2**. Like some other glyoxylates derived from 5-ring ketones, however, this example eliminated carbon monoxide poorly (*ca.* 30% yield of **3**), even in the presence of soft-glass catalyst. A second method, from the intermediate tricyclic ester **5**, involved condensation with phenyl acetate and sodium triphenylmethide, then cyclization to **3** in *ca.* 35% over-all yield.[1e] Much lower yields in the related series with ring B reduced,[1e] however, made necessary a more general method.

Direct carboalkoxylation of the ketone **1** seemed attractive, by the excellent method of Wallingford and others.[6] In our initial work using diethyl carbonate and sodium amide in toluene, the 17-carboethoxy derivative **4** was obtained in 70–82% yields. Use of sodium hydride was less promising, until it was found that excess dimethyl carbonate as solvent promoted the reaction and the yields (90–95% of **3**).

As expected, these β-keto esters were mixtures of the C-17 epimers. The ratio of 17α to 17β epimer, however, depended upon the ester alkyl group and the treatment of the anion during work-up. The 17α-carboalkoxy isomer was the more stable and usually predominated, especially for the ethyl ester **4**. This aspect will be treated in part XX, with the configurational and conformational discussion of ring D and C-17.[7]

(1) For convenience in reference, we are now grouping the current papers and earlier ones in the series under the main heading Methods for Total Synthesis of Steroids, with subgroups where there are many papers (see footnote 2). Previous papers are assigned the following part numbers in the main series: (a) part I: A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943); (b) part II: A. L. Wilds and L. W. Beck, *ibid.*, **66**, 1688 (1944); (c) part III: A. L. Wilds, L. W. Beck, and T. L. Johnson, *ibid.*, **68**, 2161 (1946); (d) part IV: A. L. Wilds and W. J. Close, *ibid.*, **69**, 3079 (1947); (e) part V: A. L. Wilds and T. L. Johnson, *ibid.*, 70, 1166 (1948); (f) part VI: A. L. Wilds and C. H. Shunk, *ibid.*, 70, 2427 (1948); (g) part VII: C. H. Shunk and A. L. Wilds, *ibid.*, **71**, 3946 (1949); (h) part VIII: A. L. Wilds and C. H. Shunk, *ibid.*, **72**, 2388 (1950); (i) part IX: A. L. Wilds, J. A. Johnson, and R. E. Sutton, *ibid.*, 72, 5524 (1950); (j) part X: A. L. Wilds, J. W. Ralls, W. C. Wildman, and K. E. McCaleb, *ibid.*, **72**, 5794 (1950); (k) part XI: A. L. Wilds and R. G. Werth, *J. Org. Chem.*, **17**, 1149 (1952); (l) part XII: A. L. Wilds and R. G. Werth, *ibid.*, **17**, 1154 (1952); (m) part XIII: A. L. Wilds, J. W. Ralls, D. A. Tyner, R. Daniels, S. Kraychy, and M. Harnik, *J. Am. Chem. Soc.*, **75**, 4878 (1953); (n) part XIV: A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953); (o) part XV: A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); (p) part XVI: A. L. Wilds, R. H. Zeitschel, R. E. Sutton, and J. A. Johnson, *J. Org. Chem.*, **19**, 255 (1954); (q) part XVII: A. L. Wilds, C. H. Hoffman, and T. H. Pearson, *J. Am. Chem. Soc.*, 77, 647 (1955).

(2) Previous papers in the subgroup: Δ^{14}-16-Keto Steroid Approach to Ring D. Parts A–G correspond to parts II, III, IV, V, IX, XIII, and XVI, respectively, of Methods for the Total Synthesis of Steroids, as assigned in footnote 1.

(3) To whom inquiries should be directed.

(4) Because we have developed several approaches to the same structures, including the 17-carboxy steroids, and have used these in several series (rings AB or A aromatic, 3-methoxy or desoxy, and nonaromatic), and since in our current researches we have progressed beyond some of the stages being described, often combining a number of steps with an increase in over-all yields and decrease in labor, the reader interested in using the methods experimentally may wish more information than is in the current papers. To provide the most broadly useful procedures, we shall describe first the series in which the method and intermediates are most clearly defined. While in many cases it can be assumed that we have used the better methods for certain of the nonaromatic steroids, or are currently doing so, this is not the case for many of them. We have made arrangements to supply a copy of our current best procedure, in several of these series, to chemists interested in using them in research. In order to avoid unnecessary duplication of research, we welcome inquiries about our past and current researches, prior to appearance of the publications.

(5) B. Riegel and F. S. Prout, *J. Org. Chem.*, **13**, 933 (1948).

(6) (a) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, *J. Am. Chem. Soc.*, **63**, 2056, 2252 (1941); (b) E. Baumgarten, R. Levine, and C. R. Hauser, *ibid.*, **66**, 862, 1230, 1768 (1944).

(7) Certain of the theoretical discussions will be deferred to a later

With a good general method in hand for introducing the 17-carboalkoxyl group, we explored several ways to remove the 16-keto group and the 14,15 double bond. Since we had realized considerable stereoselectivity with the proper types of hydrogenation in our previous studies,[1c,1i,1p] we first investigated this method of reduction here.[7] Hydrogenation of the keto ester **4** with selective palladium catalysts or with platinum under ordinary conditions was not encouraging and gave variable results. Under the vigorous conditions for rearrangement and reduction of buried steroidal double bonds, however, with platinum oxide catalyst in acetic acid promoted with hydrochloric acid,[8] hydrogenation accomplished in one operation complete removal of the 16-oxygen, reduction of the 14,15 double bond, and also of ring A. This method was the first one used by us in the nonaromatic series, leading to methyl 3-ketoetiocholanate after oxidation at C-3.[1m] From the hydrogenation products of the ester **4** in the present aromatic series was isolated 10–20% of the ester of **11a**, shown to have the 14α,17β configuration of most natural steroids.[7] In the nonaromatic series, however, it was found that this crucial stereochemistry was controlled by the original configuration of the 17-carboxylic ester, and that the undesirable 17α configuration was the more stable;[7,9] this resulted in the 14β,17α isomer after hydrogenation when the keto ester was allowed to equilibrate, but in the natural 14α,17β isomer when the 17β-keto ester was formed from its anion under conditions of kinetic control.[9,10]

Seeking a reduction method with better chemical and steric control, we studied hydrogenation of the keto ester **4** with Raney nickel. Adkins and Billica[11] found that W-6 Raney nickel, selectively poisoned with triethylamine, would reduce double bonds at low pressure without hydrogenating a naphthalene ring. In several runs with the keto ester **4**, we obtained a mixture containing stereoisomers of the naphthalenic hydroxy ester **7**, but had difficulty in controlling the extent of reduction.[12] In one run the product evidently contained the ring D reduced keto ester, for after alkaline hydrolysis its cleavage product, the diacetic acid derivative **12**, was isolated.

More reproducible results were obtained by allowing hydrogenation with nickel to proceed to the hydroxy ester **6** with ring A reduced, obtained as a mixture of stereoisomers. Attempts to dehydrate with formic acid or with acetic anhydride led instead to the 16-formoxy or 16-acetoxy derivative of **6**. Phosphorus oxychloride in pyridine also was not promising.

Alkaline conditions proved to be dependable for dehydration of the hydroxy ester **6**. Treatment of the crude hydrogenation mixture with potassium hydroxide in ethylene glycol at 150° led to the Δ^{16}-unsaturated acid **8a** (54% from **4**). Subsequent work showed this acid to have rings C:D *cis*. When dehydration was carried out at 240° with potassium hydroxide in glycerol, the Δ^{16} double bond was shifted into conjugation with the aromatic ring, and the Δ^{14} acid was isolated (as the ester **9b**, 41% from **4**). The same product resulted (48%) when the Δ^{16} acid **8a** or ester was treated similarly. In the course of this change, the 17-carboxyl group was left in the more stable 17β configuration, as subsequent steps demonstrated. That this migration of the double bond is reversible was shown by treating the pure Δ^{14} ester **9b** similarly, resulting in a small amount of the Δ^{16} acid **8a**.[13]

Hydrogenation of the Δ^{14}-methyl ester **9b** with palladium gave a saturated ester, mp 114.5–115°, shown to have the 14α,17β configuration **11b**.[7,14]

Hydrogenation of the Δ^{16} ester **8b** gave a different reduced ester, mp 94.0–94.4°. From its method of preparation and the interconversions to be reported in the next paper, *via* a Δ^{14}-15,17-dicarboxy ring D derivative,[15] it is assigned the 14β,17α configuration **10b**.[7]

Johnson and McCloskey[16] synthesized by an independent method the 3-methoxy ring A aromatic derivative of **11a**. Barnes and Miller[14] independently synthesized the 3-deoxy analog, as well as **11a**. In each case evidence for the 14α,17β configuration was obtained.

Thus, by a proper choice of steps, the present sequence of reactions for introducing the 17-carboxyl group into the Δ^{14}-16-keto steroid system **1** allows a considerable amount of steric control, leading *via* **4** and **9** to the natural type of ring C:D and C-17 configuration as in **11**. The still shorter sequence from **5** to be reported in part XIX[15] allows equal steric control with higher yields. In a later paper will be described other successful routes from the keto ester **4** *via* the ring D dienic acid (as in **13**, lacking the 16-acetoxy group).[17]

In the preliminary phase of this study, other methods were explored for removing the 16-keto group. The work of Roll and Adams,[18] showing that enol acetates are readily hydrogenolyzed, led us to try the enol acetate **13**. On hydrogenation with platinum in acetic acid this gave a mixture from which both the 14α,17β isomer **11c** and the 14β,17α isomer **10c** were isolated.[19]

paper where the experimental basis will be clearer. Thus, the discussion of stereochemistry of catalytic hydrogenations, with its theoretical extensions, as well as the other stereochemical aspects of papers XVIII and XIX, will be given in paper XX.

(8) A. Windaus and G. Zühlsdorff, *Ann.*, **536**, 204 (1938).

(9) S. Kraychy, Ph.D. Thesis, University of Wisconsin, 1954, and other studies by him and Drs. Pasupati Sengupta and Suprabhat Chatterjee.

(10) The ketonization of enol anions, to give the less stable stereoisomer under kinetic control or the more stable isomer under equilibrium conditions, has been extensively studied and beautifully clarified by H. E. Zimmerman and co-workers, *J. Org. Chem.*, 20, 549 (1955); *J. Am. Chem. Soc.*, **81**, 3644 (1959), and the intervening papers of that series.

(11) H. Adkins and H. Billica, *ibid.*, **70**, 695 (1948).

(12) Better methods for preparing the 17-carboxylic acid derivatives retaining the naphthalenic ring system will be described in later papers of this series, proceeding from the keto ester **4** (Drs. P. Sengupta and S. Chatterjee), or *via* the Δ^{14}-15,17-dicarboxylic acid derivative.[15]

(13) Although this double-bond migration doubtless goes through the Δ^{15} isomer, none of this or the 17α isomer of the Δ^{14} acid was isolated in the present series. However, Dr. S. Chatterjee obtained the Δ^{15} acid (14β,17α isomer) in the ring AB aromatic series by another route and found it to isomerize as expected under the conditions used here. In any case, while the results indicate the Δ^{14}-17β isomer to be the stablest of the eight isomers all presumably in equilibrium, several retreatments of material in filtrates were necessary to get the best yields.

(14) R. A. Barnes and R. Miller, *J. Am. Chem. Soc.*, **82**, 4960 (1960).

(15) A. L. Wilds, N. A. Nelson, M. Harnik, E. M. Gross, H. W. Schnabel, and O. R. Rodig, part XIX, to be published.

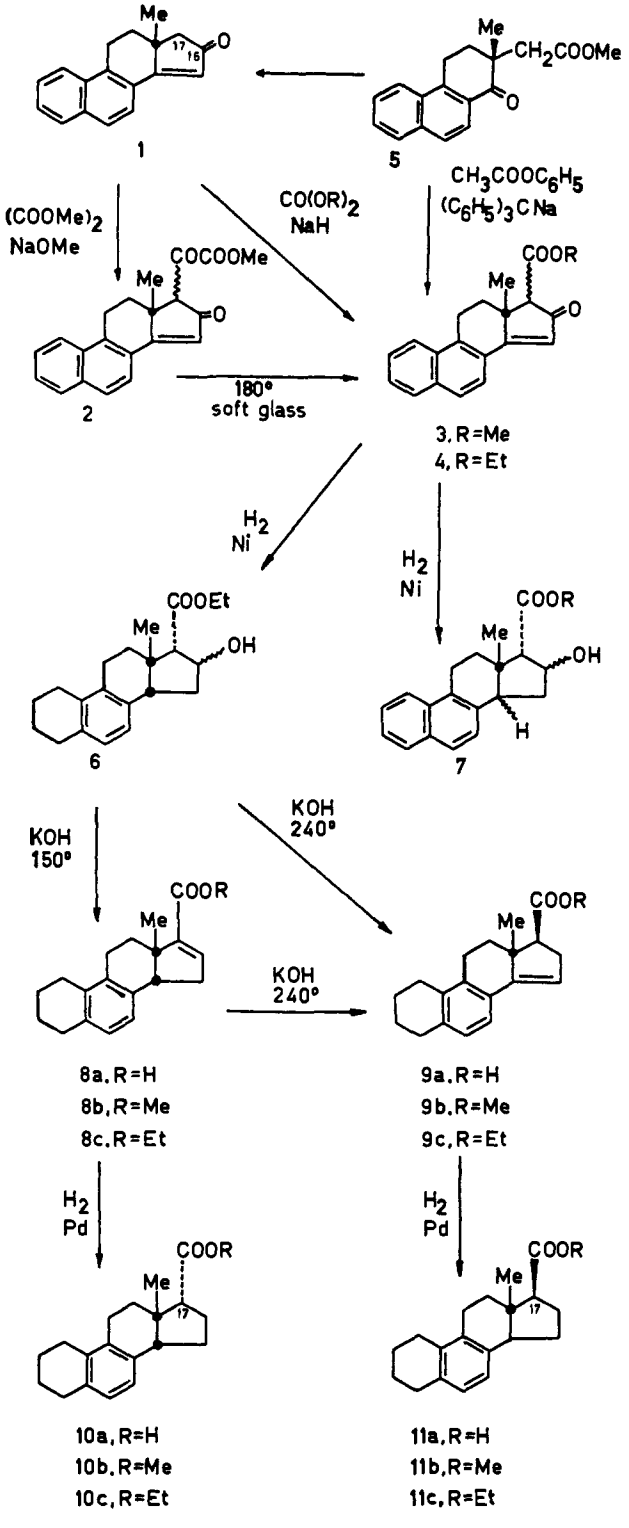
(16) A. L. McCloskey, Ph.D. Thesis, Univeristy of Wisconsin, 1951; see also D. K. Banerjee, *et al.*, *Tetrahedron Letters*, 76 (1961).

(17) A. L. Wilds, P. Sengupta, and S. Chatterjee; also similar studies with keto esters corresponding to **4** and **5** with a 3-methoxy group will be reported by A. L. Wilds, M. Harnik, T. Lies, G. Klinger, and M. Reinhart.

(18) L. J. Roll and R. Adams, *J. Am. Chem. Soc.*, **53**, 3469 (1931); see also H. H. Inhoffen, *et al.*, *Ann.*, **568**, 52 (1950).

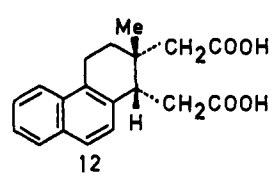
(19) This lack of specificity in reduction of **13** is not surprising when compared with hydrogenations of ring D diene esters in the nonaromatic steroid series; however, Dr. P. Sengupta found with the diene ester corresponding to **13** without the 16-acetoxy group that hydrogenation gave

In exploring the method for elimination of the 16-keto group *via* desulfuration, we obtained a mixture of stereoisomeric mercaptoles **14** from reaction of **4**



with ethanedithiol. Controlled desulfuration with Raney nickel gave the naphthalenic ester **15**. This approach was not continued when other methods proved more useful.[12,15]

largely the 14α,17β isomer. These and a number of pertinent examples from our researches will be discussed critically in later papers on the stereochemistry of catalytic hydrogenations.



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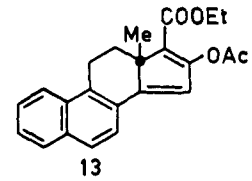

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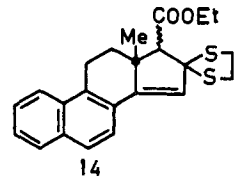

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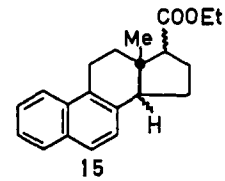

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Experimental Section[20]

Methyl *rac*-16-Keto-1,3,5(10),6,8,14-Estrahexaene-17-carboxylate (3). A mixture of 0.5 g of *rac*-1,3,5(10),6,8,14-estrahexaene-16-one (**1**, mp 148–149°, $\lambda_{max}^{CHCl_3}$ 5.92, 6.00 (double peak due to this conjugated CO system), 6.24 μ (conjugated C=C)),[1b] 10 ml of dimethyl carbonate, 0.25 g of sodium hydride (or an equivalent amount of the 48–55% dispersion in mineral oil), and 2 drops of methanol was refluxed for 5 hr under nitrogen with stirring, then was cooled, cautiously treated with cold methanol to decompose excess sodium hydride, and finally acidified with cold, dilute hydrochloric acid. Extraction with benzene–ether, washing with water, drying over sodium sulfate, and concentrating gave the keto ester in 93–95% yield, mp 145–151°. Recrystallization from methanol gave material with melting points varying from 149–153° to 156–158°, depending on the ratio of epimers, in over-all yields of 86–93%.[1b] Similar yields were obtained in runs ten times this scale[21] (λ_{max}^{EtOH} 219 mμ (ε 21,500), 238 (11,300), 268 (28,400), 278 (35,100), and 318 (24,400)).

Ethyl *rac*-16-Keto-1,3,5(10),6,8,14-estrahexaene-17α-carboxylate (4).[22] **A. Using Sodium Hydride.** A mixture of 3 g of the Δ^{14}-16-ketone **1**,[1b] 50 ml of redistilled diethyl carbonate, 1.2 g of sodium hydride (or an equivalent amount of the mineral oil dispersion), and a few drops of ethanol was allowed to react for 4 hr as described above for the methyl ester **3**, and the product was isolated similarly. Crystallization from ethanol gave a total of 2.42–2.55 g (63–66%) of keto ester with melting points ranging from 139–141° to 135–140°.

B. Using Sodium Amide.[23] Sodium amide was prepared from 0.2 g of sodium, 15 ml of liquid ammonia, and a trace of ferric nitrate. The ammonia was displaced by 10 ml of dry toluene, 1 g of the Δ^{14}-16-ketone[1b] added in 5 ml of toluene, heated at reflux under nitrogen with stirring for 0.5 hr; then 1 ml of diethyl carbonate was added and heating was continued for another 9 hr. The greenish black mixture was cooled, poured into ice and acetic acid, separated, and reextracted with benzene. From the organic layers the keto ester was isolated, in part *via* the insoluble potassium salt, using 10% potassium hydroxide and working at 0–5°. After acidification of the salt and alkaline extracts with cold hydrochloric acid, extraction with benzene, washing with bicarbonate solution, and drying, the keto ester **4** was crystallized from ethanol, giving 687 mg, mp 136–138.5°; 252 mg, mp 132–137.5°; and 123 mg, mp 126–135°; totalling 82%. In other runs the yields varied from 70 to

(20) Melting points are corrected, determined with a Hershberg apparatus, unless otherwise indicated; those marked vacuum were in Pyrex capillaries evacuated to at least 0.2 mm; micro melting points were taken with a calibrated microscope hot stage. Ultraviolet spectra were run in 95% ethanol on a Cary Model 11 spectrophotometer, and molecular extinction coefficients (ε) are reported. Infrared spectra were run in chloroform, unless otherwise indicated, using a Baird Model B instrument.

(21) These runs were made by Drs. Pasupati Sengupta and Suprabhat Chatterjee.

(22) In this compound the configurations at centers assigned are probably correct, but either (a) are not rigorously established, or (b) the isomer isolated was not fully separated from its epimer(s). Where followed by (?) the assignment represents our best assessment, but is not certain; where ξ is used, no assignment is made at present.

(23) Additional details and other related experiments are given in the Ph.D. Thesis of R. H. Zeitschel, University of Wisconsin, 1950.

80%. The purest sample of **ethyl ester** was obtained as prismatic needles from ethanol: mp 137.5–140°; λ_{max}^{EtOH} 219 mμ (ε 22,200), 238 (14,000), 268 (29,200), 278 (36,700), and 318 (25,200); $\lambda_{max}^{CHCl_3}$ 5.80 (ester CO), 5.96 (conjugated CO), and 6.25 μ (conjugated C=C). It gave a green color with alcoholic ferric chloride solution.

Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.7; H, 6.29. Found: C, 78.5; H, 6.37.

Raney Nickel Hydrogenation of Keto Ester 4 to Stereoisomeric Ethyl *rac*-16ξ-Hydroxy-14β-estra-5(10),6,8-triene-17α-carboxylates (6).[22] A suspension of 2.09 g of the keto ethyl ester **4** in 50 ml of 95% ethanol and 1 ml of triethylamine was treated with 1 teaspoonful of W-2 Raney nickel[24] and hydrogen at 25° and atmospheric pressure. Approximately 4 moles of hydrogen was absorbed in 15–20 hr, although for one run 3 days was required. Completeness of hydrogenation was checked by removing a small aliquot and looking for disappearance of the strong naphthalene peak at 230 mμ in the ultraviolet spectrum. Evaporation of the solvent gave 2.20 g of a colorless oil.

Heating 228 mg of the oil at reflux with 7 ml of 98% formic acid for 45 min gave a purple solution which became colorless on evaporation. The residue, which showed no evidence of dehydration in the ultraviolet or infrared spectrum, on trituration with ethyl acetate gave 49 mg of solid, mp 139–149°. Further recrystallization raised the melting point of the stereoisomeric mixture of **ethyl *rac*-16ξ-formoxy-14β-estra-5(10),6,8-triene-17α-carboxylate**[22] to 158.5–161.5°; $\lambda_{max}^{CHCl_3}$ broad 5.78–5.84 μ (two CO).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.1; H, 7.92. Found: C, 73.9; H, 7.81.

Heating 135 mg of the oily mixture of hydroxy esters for 1 hr in 3 ml of boiling acetic anhydride, similarly, gave an oily product which was crystallized from petroleum ether (bp 60–68°) to afford 51 mg of a mixture of acetates, mp 136–160°. Further recrystallization from ethyl acetate did not completely separate the mixture of stereoisomeric **ethyl rac-16ξ-acetoxy-14β-estra-5(10),6,8-triene-17α-carboxylates,**[22] mp 162.5–170.5°; $\lambda_{max}^{CHCl_3}$ broad 5.78–5.84 (two CO), 8.0 μ (acetate).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.6; H, 8.16. Found: C, 74.2; H, 8.04.

Hydrolysis of 1 g of the oily hydroxy ester mixture with 3 g of potassium hydroxide in 50 ml of methanol at room temperature for 3 days gave 0.91 g of acidic oil of which 0.35 g crystallized readily from benzene, mp 105–170°. After four recrystallizations from benzene–methanol, the melting point was 187–190° for the mixture of stereoisomeric ***rac*-16ξ-hydroxy-14β-estra-5(10),6,8-triene-17α-carboxylic acids.**[22] The spectrum showed only end absorption except for several ultraviolet maxima at 250–270 mμ with low ε value (*ca.* 600).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 76.0; H, 8.05. Found: C, 75.9; H, 8.33.

Stereoisomeric *rac*-16ξ-Hydroxy-14β-estra-1,3,5(10),6,8-pentaene-17α-carboxylic Acids (7, R = H).[22] In another run, in which 350 mg of the keto ester **4** was hydrogenated with 500 mg of W-6 Raney nickel catalyst[11] in 150 ml of ethanol containing 1 ml of triethylamine, the reaction was stopped after 2.1 moles of hydrogen was taken up in 2 hr. The ester was hydrolyzed with potassium hydroxide and the acid crystallized from benzene–cyclohexane to give 136 mg, mp 104–114°. Further recrystallization from cyclohexane-acetone gave 50 mg (15%) of acid, mp 182–185° (bath preheated to 150°). The ultraviolet spectrum showed the naphthalene ring system to be present, maxima at 230 mμ (69,700), 280 (4270), 321 (570), and minima at 245 (1510), 318 (265).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.80. Found: C, 77.1; H, 7.10.

In most runs it was difficult to stop at the naphthalenic stage. In another,[23] in which 200 mg of the keto ester **4** was hydrogenated with 200 mg of W-6 Raney nickel[11] in 75 ml of ethanol containing 0.5 ml of triethylamine, with uptake of 2 moles of hydrogen in 2 hr, hydrolysis with 5 ml of 45% potassium hydroxide and 5 ml of methanol for 2.75 hr at reflux gave 170 mg of acidic fraction from which 39 mg, mp 232–246°, was crystallized from petroleum ether–acetone. Further recrystallization raised the melting point to 261–263° (vacuum). Analysis and ultraviolet spectrum established it to be **2-methyl-1,2,3,4-tetrahydrophenanthrene-*cis*-(?)-1,2-diacetic acid (12),** λ_{max}^{EtOH} 229 mμ (ε 85,100), 280 (5510), 320 (530), and minima at 244 mμ (ε 1880) and 317 mμ (ε 355).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.1; H, 6.45. Found: C, 73.3; H, 6.03.

(24) R. Mozingo, "Organic Syntheses, Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

Alkaline Dehydration of Hydroxy Ester 6 to *rac*-14β-Estra-5(10),6,8,16-tetraene-17-carboxylic Acid (8a) and *rac*-5(10),6,8,14-Estratetraene-17β-carboxylic Acid (9a). A solution of 1.77 g of the oily hydroxy ester **6**, obtained by Raney nickel hydrogenation with uptake of 4 moles, was heated in 12 ml of redistilled ethylene glycol with 3 g of potassium hydroxide under nitrogen at 150° for 4 hr. After cooling, diluting, and acidifying, 1.4 g of colorless solid, mp 166–176°, was obtained, showing no indication of the Δ^{14} isomer **9a** in the ultraviolet spectrum. Recrystallization from methanol gave 0.55 g (37%) of the Δ^{16} acid **8a**, mp 198.5–204.5°.

The remaining material was retreated under nitrogen with 3 g o potassium hydroxide in 10 ml of ethylene glycol at 175–180° for 6 hr. The crude acid was esterified with diazomethane and chromatographed on 25 g of alumina (Fisher Scientific Co.). From the first 400 ml of eluate (20% benzene in petroleum ether) was obtained 362 mg, mp 68–84°, recrystallized from methanol to give 218 mg (14%) of the methyl ester of the Δ^{16} isomer, mp 81–83°. From the next 800 ml of eluate was obtained 167 mg of solid which on recrystallization from methanol afforded 77 mg (5%) of the methyl ester of the Δ^{14} isomer, mp 138.5–142°.

The remaining material in the filtrates and from the chromatogram was combined and treated with 1 g of potassium hydroxide in 5 ml of glycerol under nitrogen at 240° for 5 hr. The solid acid (516 mg) was reconverted to the methyl ester and chromatographed on 16 g of alumina. Material (65 mg) in the first 250 ml of eluate (20% benzene in petroleum ether) gave on recrystallization 51 mg of the Δ^{16} ester, mp 81–83°; that from the next 200 ml (165 mg) gave 138 mg (9%) of the Δ^{14} ester, mp 138–142°. Thus, a total of 54% of the Δ^{16} isomer **8a** and 14% of the Δ^{14} isomer **9a** was separated, based on the keto ester **4**.

The purest sample of the Δ^{16} acid ***rac*-14β-estra-5(10),6,8,16-tetraene-17-carboxylic acid (8a)** was obtained by hydrolysis of the pure methyl ester using 5% potassium hydroxide in 2-methoxyethanol and refluxing under nitrogen for 2 hr. The acid was recrystallized from methanol as colorless leaflets, mp 208–209, $\lambda_{max}^{CHCl_3}$ 5.96 (CO) and 6.18 μ (conjugated C=C).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.8; H, 7.86. Found: C, 80.9; H, 8.04.

The **methyl ester (8b)** of the Δ^{16} acid, small colorless crystals from methanol, melted at 85.2–85.6°; $\lambda_{max}^{CHCl_3}$ broad 5.84–5.92 (CO) and 6.18 μ (conjugated C=C); the ultraviolet spectrum showed only end absorption except for low maxima at 250–270 mμ (ε *ca.* 600).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.0; H, 8.16. Found: C, 81.0; H, 8.26.

The purest sample of the Δ^{14} acid ***rac*-5(10),6,8,14-estratetraene-17β-carboxylic acid (9a)** also was obtained by hydrolyzing the pure ester. The colorless acid was recrystallized from methanol: mp 246.5–248°; λ_{max}^{EtOH} 217 mμ (ε 25,000), 223 (23,300), 230 (15,000), and 265 (19,400).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.8; H, 7.86. Found: C, 80.5; H, 7.88.

The **methyl ester (9b)** of the Δ^{14} acid crystallized as slender colorless needles from methanol: mp 142–143°; λ_{max}^{EtOH} 217.5 mμ (ε 24,600), 223 (23,200), 230 (15,600), and 265 (19,900); $\lambda_{max}^{CHCl_3}$ 5.82 (s, CO), 6.14, 6.26, 6.38 μ (all w).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.0; H, 8.16. Found: C, 81.0; H, 8.37.

Methyl *rac*-5(10),6,8,14-Estratetraene-17β-carboxylate (9b).

A. From the Δ^{16} Isomer (8b). Heating 200 mg of Δ^{16}-methyl ester (**8b**), mp 81–83°, with 1 g of potassium hydroxide in 4 ml of glycerol under nitrogen at 240° for 6 hr, using a takeoff condenser, followed by reesterification of the total acid with diazomethane and crystallization from methanol, gave 74 mg (37%) of the Δ^{14} ester, mp 137.5–141.5°. A second treatment at 240° for 5 hr gave an additional 21 mg, mp 138–142°, and a third treatment another 1 mg, mp 136–140°, after chromatography. The total corresponded to a 48% yield of the Δ^{14} ester (**9b**).

B. From the Crude Hydroxy Ester (6). The total hydroxy ester (**6**) obtained from hydrogenation of 582 mg of keto ester **4** with Raney nickel (4 moles uptake of hydrogen) was treated at 240° under nitrogen with 1 g of potassium hydroxide in 4 ml of glycerol for 1 hr, using a takeoff condenser to remove water and alcohol. After reconversion to the ester, 125 mg of the Δ^{14} methyl ester could be crystallized from methanol, mp 136–142°. A second treatment with potassium hydroxide gave 57 mg, mp 140–142°, and a third treatment followed by chromatography gave 35 mg, mp 138–142°, for a total of 41% of the Δ^{14} methyl ester (**9b**).

When the Δ^{14} methyl ester, mp 140–142°, was heated with potassium hydroxide in glycerol at 240° for 4 hr, reconverted to the methyl ester, and chromatographed, approximately 35% was

recovered, mp 138–142.5°, together with 4% of the Δ^{16} methyl ester (**8b**), mp 79–81.5°.

rac-**5(10),6,8-Estratriene-17β-carboxylic Acid (11a).** Hydrogenation of 274 mg of methyl *rac*-5(10),6,8,14-estratetraene-17β-carboxylate (**9b**), mp 140–142°, in 15 ml of methanol with 250 mg of 5% palladium-on-calcium carbonate catalyst[25] was complete in 0.5–3.0 hr (103% of theoretical uptake). Crystallization of the product from methanol gave 147 mg, mp 112–113.5°, and 59 mg, mp 110.5–113°, for a total of 74% yield. The pure **14α,17β methyl ester (11b)** crystallized as colorless prisms from methanol: mp 114.5–115°; $\lambda_{max}^{CHCl_3}$ 5.80 μ (CO); ultraviolet spectrum showed only end absorption except for several low maxima at 260–270 mμ (ε *ca.* 600).[14]

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.78. Found: C, 80.3; H, 8.84.

Hydrolysis of the methyl ester with 5% potassium hydroxide in 2-methoxyethanol at reflux for 3 hr (nitrogen) gave the **14α,17β acid (11a)** in 87% yield, mp 230.5–235.5°. Further recrystallization from chloroform–acetone gave the colorless acid, mp 235–236°.[14]

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.2; H, 8.51. Found: C, 80.6; H, 8.30.

Treatment of the acid with ethereal diazoethane gave the **14α,17β ethyl ester (11c)**, mp 120–120.8°. Further crystallization from ethanol gave colorless crystals, mp 121.0–121.2° (see below).

rac-**14β-Estra-5(10),6,8-triene-17α-carboxylic Acid (10a).** Hydrogenation of 156 mg of methyl *rac*-14β-estra-5(10),6,8,16-tetraene-17-carboxylate (**8b**), mp 81–83°, in 15 ml of methanol with 250 mg of 5% palladium-on-calcium carbonate catalyst[25] required 8 hr for absorption of 96% of the theoretical amount of hydrogen. Crystallization of the product from methanol gave 137 mg (88%) of the **14β,17α methyl ester (10b)**, mp 89–91°. Further recrystallization from methanol raised the melting point of the colorless plates to 94.0–94.4°, $\lambda_{max}^{CHCl_3}$ 5.80 μ (CO).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.78. Found: C, 80.1; H, 8.67.

By hydrolysis of the methyl ester **10b** as described above for **11b**, the **14β,17α acid (10a)** was obtained from methanol, mp 205–207°.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.2; H, 8.51. Found: C, 80.1; H, 8.64.

Esterification of the acid with ethereal diazoethane, or refluxing the methyl ester for 4 hr with sodium ethoxide prepared from 50 mg of sodium in 5 ml of absolute ethanol, gave the same **14β,17α ethyl ester (10c)**, as colorless crystals from ethanol, mp 113.2–114.0° (see below).

Hydrogenation of the Keto Ester (4) with Platinum. A solution of 400 mg of the keto ethyl ester (**4**), mp 139–140°, in 20 ml of acetic acid containing 4 drops of concentrated hydrochloric acid and 200 mg of platinum oxide catalyst (American Platinum Works) was hydrogenated overnight at 25° and atmospheric pressure. The oily product was hydrolyzed with 6% potassium hydroxide in ethanol at 25° for 3 days. The acidic fraction was crystallized from methanol, yielding 40 mg, mp 218–224°. This acid mixture, with diazomethane, gave the methyl ester of *rac*-estra-5(10),6,8-triene-17β-carboxylic acid (**11b**), mp 112–113.5°, mmp 112–114.5°.

Ethyl *rac*-**16-Acetoxy-1,3,5(10),6,8,14,16-estraheptaene-17-carboxylate (13).** A solution of 797 mg of the keto ethyl ester **4**, mp 137.5–140°, in 3.2 ml of dry pyridine was treated slowly and with cooling with 1.6 ml of acetyl chloride. After 5 days at 25°, the brown mixture was washed in benzene solution with cold 10% potassium hydroxide solution, dilute acid, and water, and dried to give 1.18 g of dark oil. The portion soluble in cyclohexane was crystallized from methanol, giving 482 mg (54%) of enol acetate **13**, mp 99–105.5°. Further recrystallization gave colorless material: mp 105.5–107°; ultraviolet λ_{max} 235 mμ (ε 39,800), 283 (16,600), 294 (17,800), 350 (20,000), and λ_{min} 219 mμ (ε 21,900), 262 (5890), 288 (12,900), and 305 (5250).

Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.2; H, 6.12. Found: C, 76.2; H, 6.29.

Hydrogenation of the Enol Acetate 13. To 50 mg of prereduced platinum oxide catalyst in 8 ml of acetic acid was added 139 mg of the enol acetate, mp 102.5–105°, in 14 ml of acetic acid, and hydrogenation at 25° was continued for 15 hr (5.0 moles uptake). Evaporation of the solvent gave an oil which was hydrolyzed by refluxing with 2 ml of 45% potassium hydroxide and 2 ml of methanol for 70 min. Repeated recrystallization of the acidic oil (80 mg) from ethanol gave 20 mg (18%) of *rac*-**5(10),6,8-estratriene-17β-carboxylic acid (11a)**, mp 239–242°.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.2; H, 8.51. Found: C, 80.0; H, 8.55.

Conversion to the methyl ester **11b** gave material melting at 111–112.2°, and undepressed when mixed with the authentic methyl ester of the 14α,17β acid.

In another run 250 mg of the enol acetate was reduced with uptake of 5 moles of hydrogen in 4 hr. The oily ethyl ester was crystallized from ethanol to give 63 mg (29%), mp 96–101°, and 20 mg, mp 105–139°. Recrystallization of the first crop gave 32 mg of material which partially melted at 105–106°, resolidified, and remelted at 112–113.5°, indicating polymorphic forms. A mixture with the authentic **ethyl** *rac*-**14β-estra-5(10),6,8-triene-17α-carboxylate (10c)** (see above) melted at 112–114°; the two ester samples gave essentially superimposable infrared spectra (CS_2); ultraviolet λ_{max} 269 mμ (ε 389), 278 (302), and λ_{min} at 245 mμ (ε 93), 276 mμ (ε 282).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.7; H, 9.03. Found: C, 80.8; H, 9.15.

When the filtrate was heated at reflux for 95 min with 2 ml of 45% potassium hydroxide and 2 ml of methanol, only 20 mg of acidic material was formed. From the neutral fraction (100 mg) 32 mg (15%) crystallized from methanol. Further recrystallization gave 20 mg (9%) of **ethyl** *rac*-**5(10),6,8-estratriene-17β-carboxylate (11c)**, mp 120.8–121.0°. The mixture melting point with an authentic 14α,17β sample (see above) was not depressed, while a mixture with the 14β,17α ester melted at 89–93°. The two 14α,17β ester samples also gave essentially superimposable infrared spectra (CS_2), which differed significantly from those of the 14β,17α ester samples; ultraviolet λ_{max} 269 mμ (ε 380), 278 (288), and λ_{min} at 245 mμ (ε 135), 276 mμ (ε 282).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.7; H, 9.03. Found: C, 80.4; H, 9.21.

Ethyl *rac*-**16-Ethylenedithio-1,3,5(10),6,8,14-estrahexaene-17ξ-carboxylate (14).**[22] A stream of dry hydrogen chloride was passed for 2 hr at 20–25° through a solution of 200 mg of the keto ethyl ester (**4**), mp 138–141°, in 4 ml of dry benzene containing 0.7 ml of ethanedithiol and 100 mg of sodium sulfate. The red solution was poured into cold 20% potassium hydroxide solution and extracted well with benzene, washing with cold 5% alkali and water. The crude mercaptole mixture (235 mg, micro mp 130–150°) was recrystallized from cyclohexane giving 136 mg, mp 134–139°, and 54 mg, mp 110–133°. After repeated recrystallizations of the stereoisomeric mixture from cyclohexane a sample of one isomer melting at 205.5–206.5° (vacuum) was obtained (dried for 8 hr at 80° and (0.1 mm)).

Anal. Calcd for $C_{23}H_{24}O_2S_2$: C, 69.7; H, 6.10. Found: C, 70.1; H, 6.51.

The once recrystallized mercaptole gave a negative ferric chloride test. One such sample prepared in ether solution (mp 142–147°, clear at 163°) showed absorption maxima at 260 mμ (ε 36,300), 270 (32,400), 298 (24,000), 310 (22,900), and minima at 266 mμ (ε 30,900), 281 (16,200), 305 (17,400).

Desulfuration of the 17-Carbethoxy Mercaptole (14). The crude solid mercaptole (240 mg, mp 130–153°) prepared from 200 mg of the keto ethyl ester (**4**) was dissolved in 15 ml of purified dioxane and 0.3 ml of water, then refluxed and stirred with about 0.8 g of aged W-2 Raney nickel catalyst (2.5 months old).[24] After 2.5 hr the test for sulfur in the solution was negative (following evaporation of an aliquot and sodium fusion). The filtered solution was evaporated and the oily solid was chromatographed on 5 g of alumina (Alcoa). The first 180 ml of petroleum ether (bp 60–68°) provided 119 mg of solid melting in the range 79–110°. After one recrystallization 61 mg (32%) of solid, mp 109.5–114.5°, was obtained. The melting point of this isomer of **ethyl** *rac*-**14ξ-1,3,5(10),6,8-estrapentaene-17ξ-carboxylate (15)**[22] was 116.4–117.2°, after further recrystallization from the same solvent. The ultraviolet absorption spectrum showed the unconjugated naphthalene ring to be present, maxima at 231 mμ (ε 95,500), 275 (5250), 286 (5750), 308 (1180), 313 (690), 321 (795), and minima at 245 mμ (ε 1410), 306 (1150), 311 (645), and 317 (355), although the compound was not fully pure.

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.8; H, 7.84. Found: C, 80.9; H, 7.95.

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(25) This catalyst was prepared by alkaline formaldehyde reduction of a solution of palladium chloride in hydrochloric acid, stirred with a suspension of calcium carbonate, following the standard procedures for this type of catalyst, then was washed well and dried *in vacuo*, finally at 80°.

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The Mitomycin Antibiotics. Synthetic Studies. XII.[1] Indoloquinone Analogs with Variations at Positions 5 and 6

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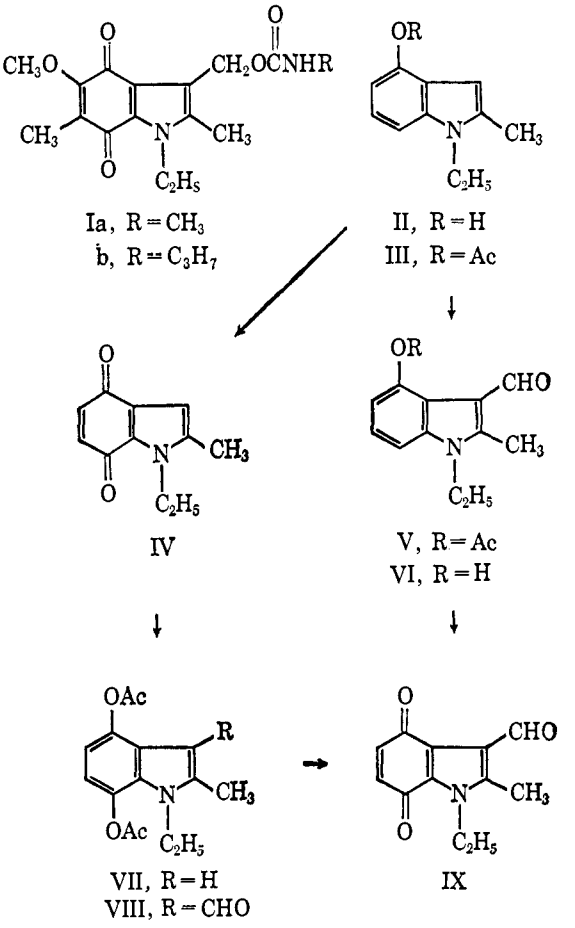
Contribution from the Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. *Received October 7, 1965*

Abstract: A synthesis of 1-ethyl-3-formyl-2-methyl-4,7-indoloquinone (IX) was devised. Substitution into the quinone ring of IX was effected by use of bromine and of *p*-toluenethiol. The dibromo derivative XI was converted to isomeric bromomethoxyindoloquinones. Treatment of these (separated) isomers with sodium borohydride afforded in each case 3-hydroxymethylindoloquinones that had lost bromine, in addition to the anticipated bromo compounds. The nature of this bromine loss is discussed. When bromomethoxyindoloquinone carbamates were treated with ammonia, the methoxy group was lost in preference to the bromine. Participation of the bromine in accelerating the displacement of methoxy by ammonia is described. Structures of the indoloquinone carbamates derived from the isomeric bromomethoxy compounds and from isomeric *p*-toluenethioindoloquinones were defined by unequivocal synthesis of 1-ethyl-3-hydroxymethyl-6-methoxy-2-methyl-4,7-indoloquinone *n*-propylcarbamate (XVIIb), a compound prepared in each of these series, by a route involving Hooker oxidation of a corresponding 5-hydroxy-6-methylindoloquinone.

Following the demonstration of antibacterial activity for indoloquinone analogs (I)[2a] of the mitomycins,[2b] a comprehensive program of structural variation on these lead compounds was undertaken. In this paper we describe the preparation of analogs of I having a variety of substituents at positions 5 and 6 of the quinone ring, with the remainder of the molecule unchanged. Our approach to these analogs was based on the synthesis of a key indoloquinone (*e.g.*, IX) unsubstituted in the quinone ring, but having the requisite alkyl groups at positions 1 and 2, and at position 3 a formyl group that could be transformed into a hydroxymethylcarbamate[2a] after appropriate substitution into the quinone ring.

The preparation of formylquinone IX from 1-ethyl-4-hydroxy-2-methylindole (II)[3] required two critical operations: (1) introduction of a 3-formyl group and (2) oxidation of a 4-hydroxyindole to the corresponding *p*-quinone. Our first attempt was to deal with these operations in the enumerated order. Direct Vilsmeier–Haack formylation[4] of hydroxyindole II afforded only a very low yield of 3-formyl-4-hydroxyindole VI, with much tar formation. However, by converting II to an acetate, formylating, and deacetyling (II → III → V → VI), an acceptable over-all yield (24%) of VI was obtained. Oxidation of VI to formylquinone IX proved somewhat disappointing. Fremy's salt (potassium nitrosodisulfonate),[5] which had successfully oxidized a 3-formyl-5-hydroxyindole to the corresponding *o*-quinone and a 3-formyl-4-aminoindole to a *p*-quinone,[2a] effected only a partial conversion of VI



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