cholest-1-en-3-one, 16963-96-5; 3-methoxy-5α-cholest-2-en-1-one, 16963-97-6.

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A Synthesis of Estrone *via* Novel Intermediates. Mechanism of the Coupling Reaction of a Vinyl Carbinol with a β Diketone[1]

C. H. KUO, D. TAUB, AND N. L. WENDLER

Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey

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An investigation of the coupling reaction of vinylcarbinols with β diketones as exemplified by the condensation of 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene with 2-methylcyclopentane-1,3-dione is presented. Quantitative conversion of 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene into a crystalline isothiuronium salt has provided a versatile intermediate in an improved condensation providing the tricyclic precursor to estrone, **3**. Selective as well as stereospecific reduction of the latter system with lithium tri-*t*-butoxyaluminum hydride afforded the ketol **8**, a key optically resolvable intermediate in the synthesis of estrone.

Ten years have elapsed since Nazarov and collaborators[2] successfully prepared the important vinylcarbinol, 1-vinyl-1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**1**); their attempts, however, to convert **1** into the allylic bromide **4** (X = Br) for purposes of condensation with reactive enolates proved abortive.[3,4] Subsequently, Ananchenko and Torgov discovered that the vinylcarbinol **1** it selfwas capable of direct coupling with 2-methylcyclohexane-1,3-dione in the presence of strong base to give the homolog of the tricyclic diketone **3** in 50% yield.[5] These authors further examined a variety of catalysts to promote this condensation although they later employed Triton B (benzyltrimethylammonium hydroxide) almost exclusively.[6] This procedure has since been generally adopted by contemporaries in the field in its application to the synthesis of estrone employing 2-methylcyclopentane-1,3-dione (**2**) as donor component.[7]

The coupling of a vinylcarbinol with an enolate under presumed conditions of basic catalysis presented a unique reaction type for which a fitting analogy was lacking. By way of rationalization both a simulated Michael process[8] and an SN2′ displacement reaction[9] have been proposed. A close formal analogy of this condensation to the so-called Carroll reaction[10] has already been noted elsewhere.[11] In the latter reaction, for example, acetoacetic ester condenses with phenylvinylcarbinol in the presence of potassium acetate at 200° to give cinnamylacetone. The Carroll reaction has been shown to proceed *via* initial ester exchange to a derived acetoacetate followed by Cope rearrangement.[12] More pertinent to the case at hand are the observations of Marbet and Saucy[10b] that tertiary vinylcarbinols rearrange *via* their isopropenyl ethers to γ,δ-unsaturated carbonyl systems. The possibility of a formal Carroll reaction in the case of the condensation of **1** and **2** *via* an intermediate enol ether was ruled out by our own observations through the employment of vinylcarbinol possessing ^{18}O in the carbinol grouping. In the event of a formal Carroll reaction the carbinol ^{18}O would have been transferred to the pertinent carbonyl function of the cyclopentandione moiety, a consequence not observed.

It appeared to us on the basis of the prior art to be patently unsound that alkali should catalyze the condensation of **1** with **2**. To gain substantiation for this point of view the two components were allowed to react in the presence of 1 equiv of alkali instead of the fractional equivalent which had always been employed previously.[6,7] Under the conditions that employed 1 mol equiv of alkali *no condensation* whatsoever was observed between **1** and **2**. It was thereby evident that the condensation of Torgov and Ananchenko is not base catalyzed, but is in fact an acid-catalyzed reaction with the β diketone functioning autocatalytically. It was likewise evident that the previous success of this condensation was due to the extent that the β diketone had not been converted into its salt by added alkali, mistakenly believed to catalyze the reaction. In substantiation thereof we observed that, when **1** and **2** were warmed together in *t*-butyl alcohol in the absence of any external catalyst, coupling proceeded smoothly to give **3** directly

(1) For preliminary accounts of this work, see (a) C. H. Kuo, D. Taub, and N. L. Wendler, *Angew. Chem.*, **77**, 1142 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 1083 (1965); (b) *Chem. Ind.* (London), 1340 (1966).

(2) I. N. Nazarov, I. V. Torgov, and G. Verkhaletova, *Dokl. Akad. Nauk SSSR*, **112**, 1067 (1957).

(3) D. J. Crispin and J. S. Whitehurst [*Proc. Chem. Soc.*, 22 (1963)] have more recently reported on the preparation of this bromide in a preliminary note.

(4) For an excellent review of recent advances in the synthesis of 19-nor steroids, see T. B. Windholz and M. Windholz, *Angew. Chem. Intern. Ed. Engl.*, **3**, 353 (1964).

(5) S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk SSSR*, **127**, 553 (1959).

(6) S. N. Ananchenko, T'ao Jeng-O, and I. V. Torgov, *Izv. Akad. Nauk SSSR, Otd. Khim.*, 298 (1962).

(7) (a) T. B. Windholz, J. H. Fried, and A. A. Patchett, *J. Org. Chem.*, **28**, 1092 (1963); (b) G. H. Douglas, J. M. H. Groves, D. Hartley, G. A. Hughes, B. J. McLaughlin, J. Siddal, and H. Smith, *J. Chem. Soc.*, 5072 (1963). These workers employed alkali metal hydroxides and bicarbonate as catalysts: (c) T. Miki, K. Hiraga, and T. Asako, *Proc. Chem. Soc.*, 139 (1963); *Chem. Pharm. Bull. Jap.*, **13**, 1285 (1965); (d) S. N. Ananchenko and I. V. Torgov, *Tetrahedron Lett.*, 553 (1963).

(8) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 209.

(9) J. S. Whitehurst, *Ann. Rept. Chem. Soc.* (London), 426 (1963).

(10) (a) M. F. Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941); (b) R. Marbet and G. Saucy, *Chimia*, **14**, 362 (1960); *Helv. Chim. Acta*, **50**, 2091, 2095 (1967).

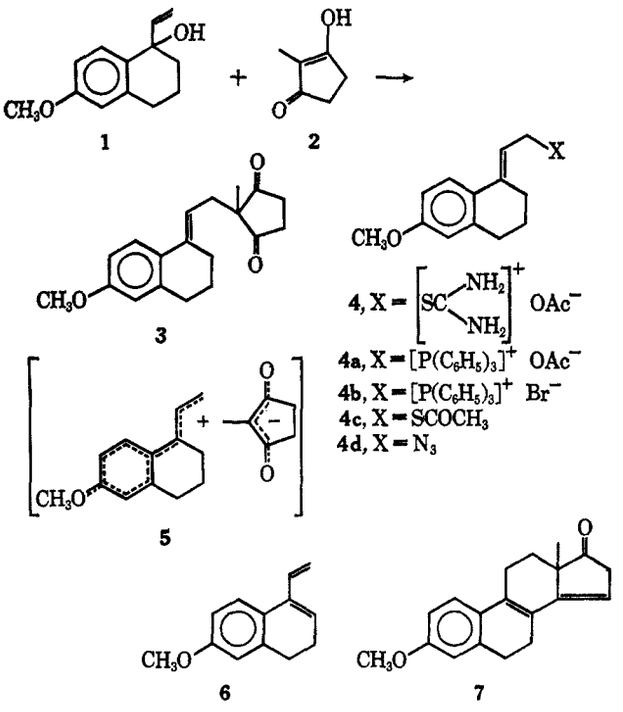
(11) D. P. Strike, T. Y. Jen, G. A. Hughes, C. H. Douglas, and H. Smith, *Steroids*, **8**, 309 (1966).

(12) W. Kimel and A. C. Cope, *J. Amer. Chem. Soc.*, **65**, 1992 (1943).

in over 70% yield.[13] On the other hand when **1** and **2** were heated in acetic acid and xylene at 120° there was afforded a 60% yield of the crystalline pentaene **7** resulting from coupling followed by cyclization. This method is actually the most convenient preparative procedure for this compound.

The vinylcarbinol **1** is extremely acid labile and when warmed in acetic acid readily undergoes dehydration to diene **6** which subsequently dimerizes *via* a Diels–Alder reaction.[14] That this diene, moreover, is not an intermediate in the coupling reaction of **1** with **2** was evident from its inability to react with dione **2** to give **3** under the prescribed reaction conditions. These facts suggested therefore that the coupling of 2-methylcyclopentane-1,3-dione **2** (pK_a 4.5) with vinylcarbinol **1** might be best interpreted as an acid–base reaction proceeding *via* an ion-pair intermediate **5**. In this context it was found that the vinylcarbinol **1** in acetic acid reacted rapidly with thiourea, added as a carbonium-ion scavenger, to give the crystalline isothiuronium salt **4**, mp 125–127°, in essentially quantitative yield. This salt in turn coupled in aqueous media at room temperature with the cyclopentanedione **2** to give crystalline **3** in 90% yield.

The reaction of **1** with **2** in *t*-butyl alcohol was further found to be essentially unaffected by the addition of triphenylphosphine, again added as carbonium-ion scavenger. On the other hand **1** itself rapidly formed the crystalline phosphonium salts **4a** and **4b** on reaction with triphenylphosphine in acetic acid and triphenylphosphine hydrobromide in methylene chloride, respectively. Likewise the thioacetate **4c** and azide **4d** were formed by treating **1** with thioacetic acid in *t*-butyl alcohol–xylene and sodium azide in acetic acid, respectively. The phosphonium salts **4a** and **4b**, in contrast to the isothiuronium salt **4**, were unreactive in attempted coupling with **2**. From these observation it appears reasonable to conclude that the ion-pair intermediate **5** involved in the coupling of **1** with **2** is associated and inaccessible to external nucleophiles.[15]

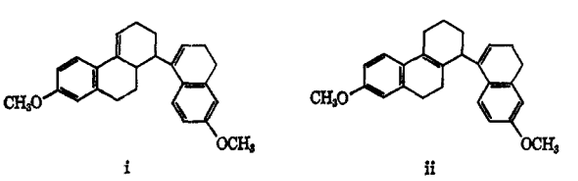


The advantages of employing the isothiuronium salt **4** in the coupling reaction, *inter alia*, with 2-methylcyclopentane-1,3-dione (**2**) are several. In the form of the crystalline isothiuronium salt the otherwise labile carbinol **1** can be easily handled and stored without deterioration; secondly, superior yields in the coupling reactions are observed; and finally, this salt exhibits a greater versatility in the application of this condensation reaction to other enolate systems. In the latter connection several instances of derived cyclopentane-1,3-diones, *e.g.*, 4-acetoxy-2-methylcyclopentane-1,3-dione[16] and cyclopentane-1,3-dione itself, either do not couple at all with **1** or only in very poor yield. By contrast the isothiuronium salt **4** condenses with these same diones in good to acceptable yields to afford the desired products. Recently, **4** has been utilized in a condensation with α,γ-dimethyltetronic acid to provide an efficient synthesis of bisdehydrodoisynolic acid.[17]

In pursuit of a novel approach to estrone from the tricyclic diketone **3**, the latter was submitted to reduction with lithium tri-*t*-butoxyaluminum hydride. Surprisingly, this reduction not only proved to be completely selective in reducing exclusively one carbonyl group but was also found to be highly stereospecific in yielding one epimer (85–90%), namely, the *dl*-17α-ketol **8** (steroid nomenclature).[18] The structure of the latter was established by cyclization of its acetate derivative **8c** to *dl* **9a** which was found to be distinct from its 17β counterpart and could in turn be further transformed indepen-

(13) Yields obtained by previous workers employing Triton B as recommended by Ananchenko and Torgov[5] have been of the order of magnitude of 50–60% (see ref 7). Smith, *et al.*,[11] have recently claimed to have achieved yields as high as 80%, although an experimental account supporting this does not appear to have been published.

(14) Previous references to the dimerization of **6** [*cf.* I. V. Torgov and I. N. Nazarov, *Zh. Obshch. Khim.*, **29**, 787 (1959)] do not include specific structural proposals. We observed the formation of two dimers: i [mp 168–170° (reported, *ibid.*, mp 168–170°); λ_{max}^{MeOH} 265 mμ (ϵ 30,500), 212 (36,400); nmr δ 5.82 (1 H triplet, J = 7 cps) and 6.25 (1 H multiplet), 2-vinyl protons (Found: C, 83.63; H, 7.53. Calcd for $C_{28}H_{28}O_2$: C, 83.83; H, 7.58)] and ii [mp 135–137° (reported, *ibid.*, mp 134–135°); λ_{max}^{MeOH} 272.5 mμ (ϵ 24,200); nmr δ 5.76 (1 H triplet, J = 7 cps), 1-vinyl proton (Found: C, 83.71; H, 7.80; mol wt, 378 (vapor phase osmometry). Calcd for $C_{28}H_{28}O_2$: C, 83.83; H, 7.78; mol wt, 372.5]. The perhydro-1-naphthyl- rather than -2-naphthylphenanthrene structures are selected by virtue of the Alder–Stein rule: K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).



i ii

(15) Subsequent to the publication of our original communication[1a] on the mechanism of this coupling reaction, pertinent papers have appeared in which the acid-catalyzed character of this reaction has also been recognized and earlier points of view correspondingly accommodated. See ref 11 and A. V. Zakharychev, D. R. Logidze, and S. N. Ananchenko, *Tetrahedron Lett.*, 803 (1967).

(16) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **32**, 3074 (1967).

(17) W. R. J. Simpson, D. Babbe, J. A. Edward, and J. H. Fried, *Tetrahedron Lett.*, 3209 (1967). For the use of the isothiuronium salt **4** in a synthesis of 13-amino-19-nor steroids, see D. B. R. Johnston, F. S. Waksmunski, T. B. Windholz, and A. A. Patchett, *Chimia*, **22**, 84 (1968). See also the synthesis of A-nor-1-thia-3-aza steroids: C. Lehmann, H. Schick, B. Lücke, and C. Hilgetag, *Chem. Ber.*, **101**, 787 (1968).

(18) While our original communication[1b] was still in press, a preliminary note [H. Gibian, *et al.*, *Tetrahedron Lett.*, 2321 (1966)] appeared noting the stereospecific semireduction of **3** microbiologically to give optically active 17β-ol of the natural series and 17α-ol in the unnatural series, the latter having no utility in a synthesis of *d*-estrone.

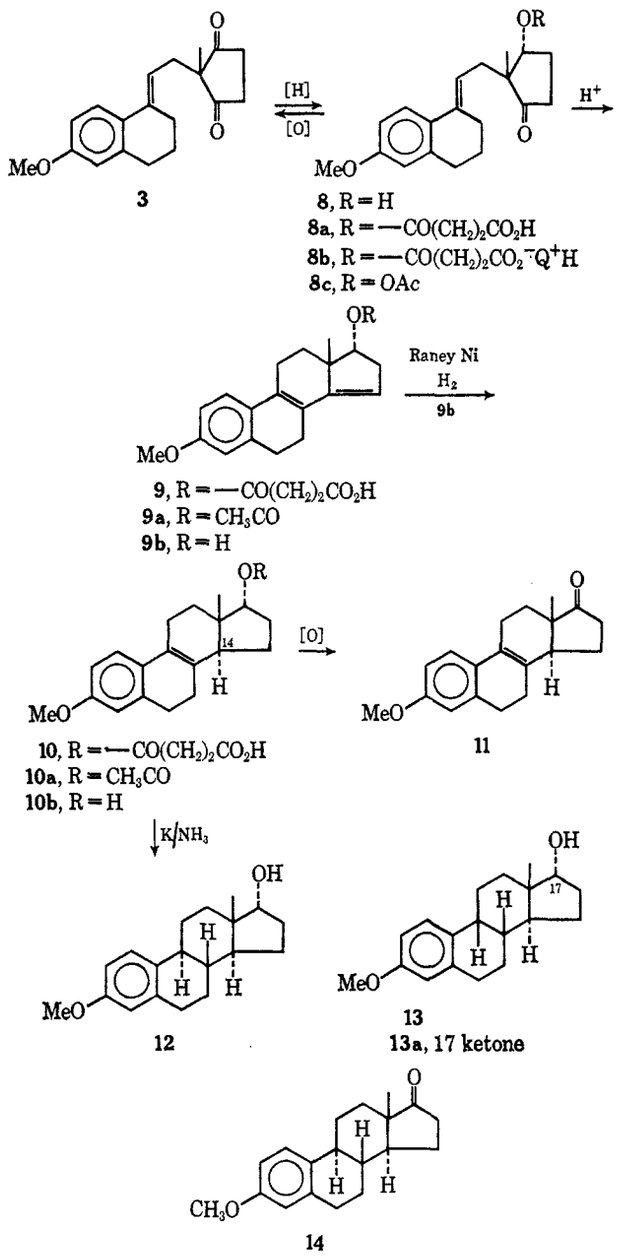
dently to *dl*-estrone **14** *via* the sequence **9a** → **10a** → **12** → **14**.

The ketol, **8**, provided the key intermediate in our sequence, not only for purposes of optical resolution, but also in providing a novel sequence of intermediates *en route* to estrone. The ketol was converted essentially quantitatively into its hemisuccinate derivative **8a** which in turn was resolved *via* the corresponding quinine salt **8b** (Q = quinine). Although the desired enantiomorph appeared in the mother liquors after initial separation of its dextrorotatory isomer, it could nevertheless be isolated in good yield and in turn hydrolyzed to the (−)-ketol **8**: mp 100–102°; $[\alpha]_D$ −45° (dioxane). Hydrolysis of the undesired enantiomeric hemisuccinate in turn provided the corresponding (+)-ketol: mp 100–102°; $[\alpha]_D$ +45° (dioxane) {lit.[18] $[\alpha]_D$ +47° (ethanol)}. The latter ketol together with extraneous hydrolyzed hemisuccinate residue could be essentially quantitatively reoxidized to starting diketone **3** by the method of Moffatt and Pfitzner (see Experimental Section). The latter sequence thereby permits utilization of the unwanted isomer by recycling it in the resolution process *via* the indicated oxidation–reduction pathway (**3** ⇌ **8**).

Cyclization of the (−)-ketol **8** could be effected either as its acetate derivative **8c** or as the hemisuccinate **8a** obtained from the resolution step. Ring closure was carried out by the conventional technique[7] with *p*-toluenesulfonic acid in benzene to give both the 17-hemisuccinate (**9**) and 17-acetate (**9a**) of 8,14-bisdehydro-17-isoestradiol-3-methyl ether, both in 85–90% yield. Hydrogenation of the latter **9a** over palladium on carbon afforded essentially a 70:30 mixture[19] of 14α and 14β **10a**, respectively, which was very difficult to separate. The hemisuccinate derivative **9** gave an even poorer ratio (55:45) of the corresponding 14α and 14β **10**. These ratios were determined by integration of the C-18 methyl peaks at δ 0.76 and 1.00 for 14α and 14β, respectively, in the nmr spectra. Initial removal of the ester function at C-17, either hydrolytically or reductively with $LiAlH_4$, followed by hydrogenation of the free 17α-ol **9b** in dioxane over Raney nickel, afforded a 92:8 (14α:14β) ratio of the desired 8-dehydro-17-isoestradiol-3-methyl ether (**10b**): mp 118–120°; $[\alpha]_D$ −36°. This result demonstrates that, contrary to expectations based on the usual steric considerations, hydrogenation of the 14,15 double bond in the 17α-OH series from the α face can be made to proceed with a selectivity equal to that in the 17β-OH series.

Oxidation of the 17α-ol **10b** either by the Oppenauer procedure or that of Moffatt and Pfitzner led to optically active 8-dehydroestrone methyl ether **11** which, as the racemate, had previously been converted into estrone.[7] Chromium trioxide treatment of **10b**, either in pyridine or acetone–sulfuric acid, produced only minor amounts of **11**. The major reaction pathway was dehydrogenation to napthalenoid products (*cf.* ref 7c).

Reduction of the 8,9 double bond of **10b** with lithium or potassium in liquid ammonia produced preponderantly 17-isoestradiol 3-methyl ether **12**, mp 103–106°, $[\alpha]_D$ +55° (MeOH),[20] together with a minor amount of the 9β isomer **13**, $[\alpha]_D$ −75.4° (MeOH), identified by comparison of the ir spectrum of the corresponding 17



ketone **13a**, $[\alpha]_D$ +43° (MeOH), with that reported for the *dl* isomer.[21,22] Oxidation of **12** with chromic acid yielded *d*-estrone methyl ether **14** identical in all respects with an authentic specimen.

Experimental Section

Melting points were taken on a microscope hot-stage apparatus and are uncorrected. Uv spectra were determined in MeOH on a Cary Model II PMS spectrometer and ir spectra on a Perkin-Elmer Infracord instrument. Nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Optical rotations were measured with a Zeiss photoelectric

(19) C. Ruter, E. Schröder, and R. Vössing, *Ann.*, **701**, 206 (1967).

(20) (a) A. Butenandt and C. Groergens [*Z. Physiol. Chem.*, **248**, 129 (1937)] reported mp 109–110°. (b) C. H. Robinson, O. Gnoj, and E. P. Oliveto [*J. Org. Chem.*, **25**, 2247 (1960)] reported $[\alpha]_D$ +53° (dioxane).

(21) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. Jones, *J. Amer. Chem. Soc.*, **80**, 661 (1958).

(22) Use of lithium as the reductant generally produced some phenolic material by methyl ether cleavage [*cf.* K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, *Khim. Prirodn Soedin, Akad. Nauk Uz SSR*, **1**, 172 (1965)] isolated in our *dl* series and identified as 1,3,5(10),8-estratetraene-3,17α-diol. In the previously described metal–ammonia reductions of the analogous 8-dehydro-17β-ol and 17-one systems (see ref 7) the formation of 9β-estratriene by-product has not been noted, although the 9β isomer of 19-nortestosterone was a significant by-product in the further reduction of the above 8-dehydro systems [K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, *ibid.*, 180 (1965)].

polarimeter employing a 0.5-dc tube. Tlc was carried out on silica gel G coated glass plates. We wish to thank Mr. R. N. Boos and his associates for the elemental analyses, Mr. A. Kalowsky for the ultraviolet spectra, and Dr. N. R. Trenner and Mr. J. Beck for the ^{18}O mass spectral determinations.

6-Methoxy-1,2,3,4-tetrahydronaphthylideneethylisothiuronium Acetate (4).—To a stirred mixture of purified vinyl carbinol 1,[23] (3.06 g, 15 mmol) and thiourea (1.14 g., 15 mmol) was added 12 ml of acetic acid, and the reaction mixture was stirred at 25° for 4 hr.[24] At the end of this period 80 ml of ether was added with stirring and the precipitated salt was filtered to afford 3.73 g of **4**. The filtrate was concentrated to a solid residue, triturated with benzene–ether, and filtered to give an additional 1.04 g which was combined with the first crop to give a total of 4.77 g of **4** (98%): mp 125–127°; λ_{max} 300 mμ (ε 8590), 275 (19,400); nmr (DMSO-d_6), δ 1.79 [s, $CH_3C(=O)$-], 3.75 (s, MeO–), 5.98 (t, vinylic proton).

Anal. Calcd for $C_{16}H_{22}O_3N_2S$: C, 59.60; H, 6.88; N, 8.69; S, 9.95. Found: C, 59.47; H, 6.95; N, 8.59; S, 9.73.

6-Methoxy-1,2,3,4-tetrahydronaphthylidineethyltriphenylphosphonium Acetate (4a).—A solution of 1-vinyl-6-methoxy-1-tetralol (**1**, 1.02 g, 5 mmol) and triphenylphosphine (1.31 g, 5 mmol) in 10 ml of acetic acid was magnetically stirred at 25° for 3 hr. The reaction mixture was concentrated *in vacuo* to a yellow oil which was triturated with ether. The residual oil crystallized from acetone–ether to afford **4a**: first crop, 1.11 g; mp 101–106°; λ_{max} 303 mμ (ε 10,900), 275 (17,100), 270 (16,450), 225 (34,600), $\lambda_{max}^{chloroform}$ 2.8 (w), 3.1–3.3 (bonded), 5.9, 6.22, 6.38, 6.70, 6.98, 7.25, 7.60, 7.85, 8.10, 8.60, 8.98, 9.60, 10.0, 14.45 μ. This material was difficult to obtain in a solvent-free form suitable for elemental analysis, but could be converted into the corresponding bromide by salt exchange in acetone with an equivalent of lithium bromide at room temperature. The bromide so obtained was identical with an authentic sample (see below).

6-Methoxy-1,2,3,4-tetrahydronaphthylideneethyltriphenylphosphonium Bromide (4b).—To a stirred solution of triphenyl phosphine hydrobromide (1.37 g, 4 mmol; prepared from triphenylphosphine and hydrogen bromide in ethyl acetate at 25°) in 15 ml of methylene chloride under nitrogen, was added a solution of vinylcarbinol **1** (1.02 g, 5 mmol) in 10 ml of methylene chloride at 0–10°. The reaction mixture was then stirred at 25° for 16 hr. The solvent was removed under reduced pressure and the crystalline residue was filtered from acetone to afford 1.514 g of **4b**: mp 189–192°; $\lambda_{max}^{chloroform}$ 2.80 (w), 3.05 (m), 6.21 (s), 6.37 (w), 6.69 (s), 6.83 (w), 6.96, 8.98, 9.60, 9.99, 10.70, 14.45 μ. An analytical sample was prepared by recrystallization from acetone–ether: mp 190–192° (needles); λ_{max}^{MeOH} 301 mμ (ε 13,400), 276 (22,000), 268 (22,200), 250 (24,600), 226 (105,700); nmr, δ 1.50 (2 H, multiplet), 3.78 (3 H, singlet), 4.68, 4.92, (2 H, two doublets), 5.75 (1 H, multiplet).

Anal. Calcd for $C_{31}H_{30}OPBr$: C, 70.32; H, 5.71; P, 5.71 Br, 15.04. Found: C, 70.13; H, 5.59; P, 5.86; Br, 15.32.

6-Methoxy-1,2,3,4-tetrahydronaphthylidineethyl Thioacetate (4c).—A solution of 1-vinyl-6-methoxy-1-tetralol (**1**, 408.5 mg, 2 mmol), thioacetic acid (152.2 mg, 2 mmol), 1.5 ml of dry xylene, and 0.7 ml of *t*-butyl alcohol was refluxed for 3 hr. The solvents were removed *in vacuo* and the residue was extracted into ether. The latter was washed with water, 5% $NaHCO_3$, and aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to an oil which was purified chromatographically (10 g of silica gel, 15-ml fractions). The benzene eluates gave 400 mg of single-spot **4c** as an oil: λ_{max} 269 mμ (ε 19,750), $\lambda_{max}^{chloroform}$ 5.95, 6.21, 6.28, 6.7 μ.

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C, 68.70; H, 6.89; S, 11.29.

In the same manner 408.5 mg of vinylcarbinol in 3 cc of acetic acid reacted with 130 mg of sodium azide at 25° for 3 hr. After the usual work-up **6-methoxy-1,2,3,4-tetrahydronaphthylidineethyl azide (4d)** was obtained as an oil: $\lambda_{max}^{chloroform}$ 4.78, 5.99, 6.20, 6.38, 6.68, 6.81, 7.00 μ.

The ^{18}O Series. 6-Methoxytetralone-^{18}O.—Oxygen-18-labeled water (0.3 ml, 20% $H_2{}^{18}O$) was added to a stirred solution of 6-methoxytetralone (528 mg, 3 mmol) in 3 ml of anhydrous methanol. One drop of concentrated HCl was added and the reaction mixture was heated at 80° for 20 min. The solvent was removed *in vacuo* and the residue was triturated with dry benzene to provide crystalline-labeled 6-methoxytetralone, mp 74–76°. Recrystallization from ether gave 456 mg, mp 76–78°. Mass spectrometry indicated 19 atom % ^{18}O content.

1-Vinyl-6-methoxytetralol-^{18}O (1) was obtained by reaction of the above 6-methoxytetralone-^{18}O (740 mg, 4.2 mmol) with vinylmagnesium bromide in tetrahydrofuran under the standard conditions.[7,25] The product (1.20 g of pale yellow oil) was purified by short-path distillation, bp 111° (0.02 mm). Direct mass spectral ^{18}O determination could not be performed because of elimination of the tertiary hydroxyl group as water. However, analysis by $H_2O \rightleftarrows CO_2$ equilibration of the eliminated water showed 1 to contain 17–18% ^{18}O.

3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (3). A.—A mixture of the above vinylcarbinol-^{18}O (198 mg, 0.97 mmol), 2-methylcyclopentane-1,3-dione (**2**, 109 mg, 0.97 mmol), dry xylene (0.9 ml), and *t*-butyl alcohol (0.9 ml) was refluxed under nitrogen for 3 hr. Solvents were removed at reduced pressure and the residue was triturated with benzene. Ether was added and the crystals were filtered to give 51 mg of recovered **2**. The filtrate was washed with water, 5% $NaHCO_3$, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford 110 mg of **3**, mp 75–77°. Direct mass spectrometry showed the product to contain 1.6 mol % ^{18}O. As shown in the control experiment (B) this small percentage of ^{18}O is attributable to exchange with the ^{18}O liberated during the condensation and present in the reaction medium.

B.—To a stirred mixture of normal dione **3** (448 mg, 1.5 mmol), 2-methylcyclopentane-1,3-dione (**2**, 506 mg, 4.5 mmol) in 2.6 ml of dry xylene, and 2.5 ml of *t*-butyl alcohol was added 0.027 ml (1.5 mmol, 20% H_2O^{18}) of H_2O^{18}. The system was refluxed for 3 hr under nitrogen, concentrated *in vacuo*, and triturated with benzene. Ether was added and the recovered crystalline dione **2** was removed by filtration. The filtrate was washed with water, 5% $NaHCO_3$, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 326 mg of **3**, mp 76–78°, which mass spectrometry indicated to have 2 mol % of ^{18}O.

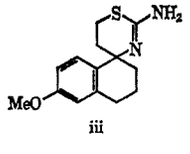
Attempted Condensation of 1 and 2 in the Presence of 1 *M* Equiv of Base.—A stirred mixture of vinylcarbinol **1** (530 mg, 2.6 mmol), 2-methylcyclopentane-1,3-dione (**2**, 290 mg, 2.6 mmol), and 1.60 ml of 1.7 *M* methanolic Triton B in 3 ml of xylene and 0.8 ml of *t*-butyl alcohol was refluxed under nitrogen for 2 hr. The mixture was cooled, treated with ethyl acetate and water, extracted with excess 5% $KHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to dryness. The neutral oily residue (520 mg) possessed no carbonyl absorption in its infrared spectrum ($CHCl_3$) which was identical with that of vinylcarbinol **1**. From the aqueous extract, **2** could be recovered on acidification and concentration.

Direct Condensation of 1 and 2 without External Catalyst.—A stirred mixture of 1-vinyl-6-methoxytetralol (**1**,[25] 700 mg, 3.7 mmol) and 2-methylcyclopentane-1,3-dione (**2**, 420 mg, 3.7 mmol) in 4 ml of xylene and 2 ml of *t*-butyl alcohol was refluxed under nitrogen for 90 min. The mixture was cooled, ether was added, and precipitated, unreacted dione **2** was removed by filtration (115 mg). The filtrate was washed with water, 5% $KHCO_3$, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to dryness. Crystallization of the residue from methanol gave 575 mg of **3**, mp 76–78°, in two crops (70% based on **2** consumed) with additional material in the mother liquor.

(±)-3-Methoxy-1,3,5(10),8,14-estrapentaene-17-one (7). One-Step Process from 1 and 2.—To a stirred solution of 7.00 g of

(23) This material was purified by short-path distillation: bp 111° (0.02 mm); λ_{max}^{MeOH} 283 mμ (ε 2060), 276 (2210), 227 (8,950), 223 (8760) (*Anal.* Calcd for $C_{18}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.30; H, 7.93). *Cf.* R. Seltzer and W. J. Considine, *Chem. Ind.* (London), 1729 (1965).

(24) Under hot conditions (refluxing xylene–acetic acid 2:1) no isothiuronium salt was obtained. The product was the spiran iii: mp 253–255°; λ_{max} 284 mμ (ε 1700), 275 (2200), 244 (18,500); λ_{max}^{Nujol} 3.21, 6.20, 6.40, 6.45, 6.57, 6.69, 6.86, 7.30, 7.50, 7.95, 8.30, 8.85, 9.65 μ (*Anal.* Calcd for $C_{14}H_{18}ON_2S$: C, 64.08; H, 6.91; N, 10.68; S, 12.22. Found: C, 63.81; H, 6.69; N, 10.91; S, 11.60).



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(25) I. N. Nazarov, I. V. Torgov, and G. N. Verkholetova, *Dokl. Akad. Nauk SSSR*, **112**, 1067 (1957). Vinylcarbinol **1** is normally *ca.* 85–90% pure as prepared by Grignard reaction of 6-methoxytetralone and vinyl magnesium bromide.

vinylcarbinol 1 (*ca.* 90% pure, 30 mmol) in 40 ml of xylene was added 3.90 g (35 mmol) of 2-methylcyclopentane-1,3-dione (**2**) and 20 ml of acetic acid. The mixture was refluxed under nitrogen for 2 hr and concentrated to a small volume, ether–benzene 1:1 was added, and the precipitated unreacted **2** was recovered by filtration and washed with ether (1.11 g). The combined filtrate and washes were extracted with 5% $KHCO_3$ and saturated salt solution, dried over $MgSO_4$, and concentrated to dryness. Trituration with ether gave 3.73 g of single-spot (tlc with $CHCl_3$) **7**, mp 106–108°. Concentration of the mother liquor to dryness and crystallization of the residue from methanol gave an additional 1.32 g of single-spot **7**: mp 106–108°; total yield 5.05 g (60% based on **1**, 70% based on **2** consumed); λ_{max} 332 mμ infl (ε 24,600), 311 (29,000), 239 infl (11,000), 233 (13,600), 228 (13,300); identical with an authentic sample.[7]

dl **Series. 3-Methoxy-8(14)-seco-1,3,5-(10),9(11)-estratetraene-14,17-dione (3). By the Isothiuronium Salt Method A.**—To a stirred mixture of the isothiuronium acetate **4** (645 mg, 2.0 mmol) and 2-methylcyclopentane-1,3-dione (**2**, 449 mg, 4.0 mmol) was added 14 ml (1:1) of aqueous ethanol. A clear solution was observed within 5 min followed by precipitation of product after an additional 5 min. The reaction mixture was stirred at room temperature for 3 hr, chilled, and filtered to give 476 mg of dione **3**, mp 76–78°. The ethanol was removed from the filtrate under reduced pressure and the aqueous phase was saturated with NaCl and extracted with ethyl acetate. The latter extract was washed with 5% $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to give 140 mg of partly crystalline residue which was purified by tlc (silica gel, chloroform) to provide an additional 59 mg of **3**, mp 76–78° (total yield 90%).

B.—A mixture of 1.63 g (5 mmol) of isothiuronium salt **4**, 700 mg (6.3 mmol) of 2-methylcyclopentane-1,3-dione (**2**), 30 ml of water, 15 ml of benzene, and 15 ml of ether was stirred at 20–25°.[26] Essentially all of the material dissolved after 30 min. After a total time of 1.5 hr, 50 ml of water and 25 ml of 1:1 ether–benzene were added, and the layers were separated. The aqueous layer was extracted twice with 1:1 ether–benzene. The combined organic layers were washed with excess 5% $KHCO_3$ and saturated aqueous NaCl and dried over $MgSO_4$. Concentration to dryness on the water pump gave a yellow oil, 1.44 g, which solidified on cooling and scratching. Crystallization from methanol gave 1.05 g of dione **3**: mp 77–79°; λ_{max} 295 mμ (ε 5640), 267 (17,500); tlc (silica gel 5% acetone–chloroform) showed the mother liquor to be rich in product.

(±)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (8).—A solution of 4.20 g of lithium tri-*t*-butoxyaluminum hydride in 150 ml of freshly distilled tetrahydrofuran was added to a magnetically stirred solution of 4.48 g of 3-methoxy-8-(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (**3**), in 120 ml of tetrahydrofuran at 0° under nitrogen during ~45 min. The reaction mixture was stirred at 20–25° for 16 hr. Saturated aqueous Na_2SO_4 (210 ml) was then added dropwise at 0°. Inorganic salts were removed by filtration and washed thoroughly with benzene and ether. The combined organic phase was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 4.52 g of (±) **8**: λ_{max} 295 mμ (ε 3970), 265 (18,200), 210 (19,400). The composition of this product as ~85–90% of the 17α epimer was determined by cyclization of its acetate derivative (see below) to tetracyclic pentaene followed by chromatographic isolation of the desired 17α isomer **9a**. Purification of the reduction product *via* its hemisuccinate derivative followed by hydrolysis (see below under Optically Active Series) afforded crystalline (±) **8**: mp 74–76°; $\lambda_{max}^{chloroform}$ 2.82, 2.95 (sh), 5.75, 6.21, 6.36, 6.69, 6.82 μ.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.83; H, 7.95.

In subsequent reductions (±) **8** could be obtained crystalline directly by seeding.

The (±)-ketol **8** afforded a **semicarbazone** crystallized from EtOAc–$CHCl_3$: mp 196–199°; λ_{max}^{MeOH} 295 mμ (ε 3520), 266 (20,420), 214 (28,800); λ_{max}^{Nujol} 2.95, 3.15, 5.95, 6.22, 6.40, 6.60, 6.70, 6.88 μ.

Anal. Calcd for $C_{20}H_{27}O_3N_3$: C, 67.20; H, 7.61; N, 11.76. Found: C, 67.58; H, 7.60; N, 11.67.

(±)-3-Methoxy-1,3,5(10),8,14-estrapentaene 17α-Acetate (9a).—Total crude lithium tri-*t*-butoxyaluminum hydride reduction product **8** (4.52 g) was acetylated with acetic anhydride (2 ml) in 8 ml of dry pyridine at 25° for 16 hr. The reaction mixture was concentrated *in vacuo* to a brown oil, **9a**, which was cyclized without further purification with anhydrous *p*-toluenesulfonic acid (17.3 g) in 300 ml of dry benzene at 25° for 16 hr. After filtration of the formed *p*-toluenesulfonic acid monohydrate, the organic phase was washed with 5% Na_2CO_3, dried over $MgSO_4$, and concentrated *in vacuo* to 4.85 g of product which was chromatographed on 500 g of silica gel, and the eluates were collected in 500-ml fractions. The initial compound eluted was **3-methoxy-1,3,5(10),8,14-estrapentaene 17β-acetate**:[27] 227 mg; mp 110–112° (from acetone–methanol); nmr ($CDCl_3$), δ 1.00 (s, CH_3–C–), 2.13 [s, CH_3–C(=O)–], 5.07 (t, J = 8 cps, 17α-H), 5.51 (m, vinyl H). This was followed by the 17α-acetate **9a**: 2.17 g; mp 95–98° (analytical sample needles were recrystallized from acetone–methanol, mp 97–99°); λ_{max} 320 mμ (ε 23,600), 311 (30,800), 302 (25,800), 240 (10,520), 239 (13,580), 228 (13,600), 220 (13,500); $\lambda_{max}^{chloroform}$ 5.80, 6.22, 6.40, 6.70, 6.85, 7.00, 7.95, 8.00 μ; nmr ($CDCl_3$), δ 1.04 (s, CH_3–C–), 2.05 (s, CH_3C=O), 3.83 (s, CH_3O), 5.17 (d, J = 5 cps, 17β-H), 5.60 (m, vinyl H).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.66; H, 7.51.

(±)-3-Methoxy-1,3,5(10),8-estratetraene 17α-Acetate (10a).—The (±)-pentaene acetate **9a** (324 mg, 1 mmol) in 10 ml of dry benzene was hydrogenated over 10% palladium on charcoal at atmospheric pressure. Uptake of 1 mol of hydrogen was realized within 10 min. The reduction was terminated and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* to an oil which crystallized upon addition of ether. The crystals were filtered to give a first crop of 207 mg, mp 103–110° (*ca.* 70:30 mixture of **10a** and its 14β epimer by comparison of the respective nmr 18-methyl singlets at δ 0.76 and 1.00). Pure **10a** (rosettes) was obtained by preparative tlc: mp 112–115°; λ_{max} 320 mμ (ε 1140), 308 (2980), 278 (16,000), 213 (18,600); $\lambda_{max}^{chloroform}$ 5.82, 6.22, 6.40, 6.70, 8.05, 8.20 μ.

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.14; H, 8.06.

(±)-17-Isoestradiol 3-Methyl Ether (12).—To a stirred solution of 200 mg of (±)-3-methoxy-1,3,5(10),8-estratetraene 17α-acetate (**10a**) in 14 ml of drytetrahy drofuran and 25 ml of NH_3 was added 56 mg of lithium at −50°. At the end of 2 hr, the deep blue color of the reaction mixture was discharged by addition of solid NH_4Cl. Following evaporation of the ammonia, water (80 ml) was added and the mixture was extracted with ether. The ether extract was washed with water and saturated aqueous Na_2SO_4, dried over $MgSO_4$, and concentrated *in vacuo* to an oil. Partial crystallization took place upon addition of ether to give 42 mg of **1,3,5(10),8-estratetraene-3,17α-diol**: mp 233–235°; λ_{max}^{MeOH} 276 mμ (ε 14,900), 212 (19,000); λ_{max}^{Nujol} 3.00, 3.30, 6.23, 6.70, 6.90, 7.30, 9.60 μ.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.34; H, 8.34.

Preparative thin layer chromatography (5% ether in $CHCl_3$) of the mother liquor gave 64 mg of pure **12** (needles): mp 92–95°; λ_{max} 287 mμ (ε 1760), 279 (1840), 219 (7700); $\lambda_{max}^{CHCl_3}$ 2.85, 3.40, 3.50, 3.55, 6.20, 6.36, 6.69, 6.84, 6.90 μ.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.88; H, 9.32.

(±)-Estrone Methyl Ether (14).—To a stirred solution of (±)-17-isoestradiol 3-methyl ether (**12**, 30 mg) in acetone (3 ml) was added 0.08 ml of Jones' reagent.[28] The reaction mixture was stirred at 25° for 5 min and excess reagent was destroyed by addition of 1.5 ml of MeOH and dilution with 15 ml of water to give a colorless crystalline precipitate which was filtered and air dried to yield 20.4 mg of **14**: mp 139–141°; $\lambda_{max}^{CHCl_3}$ 5.75, 6.18, 6.22, 6.65, 6.81, 6.86 μ; tlc (5% ether in $CHCl_3$), R_f 0.65; identical with an authentic sample (mixture melting point, ir spectroscopy, tlc).

Optically Active Series. (±)-3-Methoxy-8(14)-seco-1,3,5-(10),9(11)-estratetraene-17α-ol-14-one 17-Hemisuccinate (8a).—(±)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (**8**, 300 mg, 1 mmol, mp 74–76°) and succinic anhydride (450 mg, 2.5 mmol) in dry pyridine (8 ml) was stirred and

(26) Comparable results were obtained on refluxing the reactant in *t*-butyl alcohol for 3 hr.

(27) K. K. Koshoev, S. N. Ananchenko, A. V. Platonova, and I. V. Torgov [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 2058 (1963)] report mp 110–111°.

(28) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

heated under nitrogen at 100° for 52 hr.[29] The dark reaction mixture was concentrated *in vacuo* to a residue. Ether and water were added and the reaction mixture was made acidic with 2 *N* sulfuric acid. Precipitated excess succinic anhydride was removed by filtration. The ether extract was washed with water and 5% K_2CO_3, dried over $MgSO_4$, and concentrated to a neutral residue (11 mg). The acidic product was isolated from the carbonate extract by acidification with 2 *N* H_2SO_4 and extraction with ether. The ether extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to afford 398 mg of crystalline succinate **8a**, mp 101–104°. The analytical sample was prepared by recrystallization from ether–petroleum ether: mp 102–104°; λ_{max} 293 mμ (ε 3940), 265 (20,000), 213 (20,200); $\lambda_{max}^{chloroform}$ 2.9–3.3, 5.75, 5.80 (sh), 6.21, 6.36, 6.69, 8.15, 8.65, 9.41, 9.60 μ; nmr ($CDCl_3$), δ 1.07 (s, 3 H, CH_3–C–).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.21; H, 7.15.

Saponification of the crystalline (±) hemisuccinate **8a** (801 mg, 2 mmol) was effected by treatment with cold aqueous KOH (1.36 g in 40 ml of water) under nitrogen at 25°. (Neutral product precipitated in part.) After stirring for 15 min, the reaction mixture was briefly warmed on the steam cone for 15 min and cooled to room temperature and the residue was dissolved in methylene chloride. The latter solution was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford 612 mg of colorless oil which completely crystallized from ether–petroleum ether, mp 70–72°. Recrystallization from ether–petroleum ether gave a first crop of 517 mg of the racemic ketol **8**, mp 74–76°. (See above for earlier description of this substance.)

(−)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one 17-Hemisuccinate (8a).—(±) hemisuccinate **8a** (41.48 g, 104 mmol), quinine trihydrate (39.17 g, 104 mmol), and acetone (1 l.) were warmed briefly on the steam bath to achieve homogeneity. The reaction mixture was cooled slowly with stirring. The resulting precipitate was aged before filtration to provide 40.65 g of the (+)-quinine salt **8b**: mp 160–162°; $[\alpha]^{29}D$ −39.2° (MeOH); $\lambda_{max}^{chloroform}$ 3.0–3.4 (broad), 5.75, 6.16, 6.21, 6.25, 6.35, 6.62, 6.68 μ. The filtrate was concentrated to a foam {39.00 g, $[\alpha]D$ −121° (MeOH)}, dissolved in benzene–ethyl acetate (1:1), and washed four times with 10% H_2SO_4, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford 21.8 g of crude noncrystalline hemisuccinate (−) **8a**: $\lambda_{max}^{chloroform}$ 2.8–3.3, 5.75, 5.80 (sh), 6.21, 6.38 μ. The ir spectrum was similar to that of (±) **8a**.

(−)- and (+)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (8).—Cold aqueous base (37.2 g of KOH in 1 l. of water) was added to 21.80 g of the crude (−) hemisuccinate **8a** with swirling under nitrogen. The cloudy reaction mixture was heated on the steam bath for 15 min with occasional swirling resulting in precipitation of neutral **8**. The mixture was chilled before filtration. The precipitate was washed with water and air dried to give 14.72 g of crude (−)-ketol **8** (91%), mp 94–98°. The filtrate was saturated with NaCl and extracted with methylene chloride and the extract was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to give an additional 120 mg of product. The total ketol was recrystallized from acetone–ether–petroleum ether to provide 13.12 g of prismatic needles, mp 98–100°. An analytical sample was prepared by recrystallization from ether–petroleum ether: mp 100–102°; $[\alpha]D$ −45° (dioxane).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.11; H, 7.75.

The (+) hemisuccinate (319 mg) was saponified in a similar manner to afford 218 mg of (+) **8** (92%): mp 100–102°; $[\alpha]D$ +45° (dioxane).

Oxidative Reconversion of (+) 8 into 3.—(+)-3-Methoxy-8(14) seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one (**8**, 300 mg, 1 mmol) was dissolved in anhydrous dimethyl sulfoxide (1.5 ml) and benzene (1.5 ml) containing pyridine (0.08 ml), and trifluoroacetic acid (0.04 ml) was added. After addition of 0.62 g of dicyclohexylcarbodiimide, the reaction mixture was kept at 25° for 16 hr.[30] Ether (25 ml) was added, followed by a solution of oxalic acid (270 mg, 3 mmol) in methanol (2.5 ml). After gas evolution had ceased (~30 min), water (25 ml) was added and the insoluble dicyclohexylurea was removed by filtration. The organic phase was then extracted twice with 5% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to dryness to provide 300 mg of crude crystalline **3** which was filtered from ether–petroleum ether to give 291 mg in three crops: mp 75–77°; tlc ($CHCl_3$), R_f 0.5.

3-Methoxy-1,3,5(10),8,14-estrapentaene 17α-Hemisuccinate (9).—(+)-3-Methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-17α-ol-14-one 17-hemisuccinate (**8a**, 2.0 g, 5 mmol) in 50 ml of dry benzene was added to a stirred slurry of anhydrous *p*-toluenesulfonic acid (from 5.71 g of the monohydrate in 40 ml of dry benzene taken to dryness) in 40 ml of dry benzene under nitrogen and the reaction mixture was stirred at 25° for 16 hr. The *p*-toluenesulfonic acid hydrate which precipitated was filtered and the filtrate was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 1.93 g of crystalline solid. The product was triturated with ether–petroleum ether and filtered to give 1.74 g of tetracyclic acid **9**: mp 133–135°; $[\alpha]D$ 0° ($CHCl_3$); λ_{max} 324 mμ (ε 24,100), 311 (31,700), 302 infl (26,300), 242 (10,580), 235 (13,730), 228 (13,500), 223 (12,510); $\lambda_{max}^{chloroform}$ 2.9–3.3, 5.8, 6.21, 6.39 μ; nmr, $\delta^{C_{13}}$ 1.0 (s, 3 H, >C–CH_3), 3.81 (s, 3 H, –O–CH_3), 5.17 (broad doublet, 1 H, –CH–O–), 5.57 (m, 1 H, vinylic), 10.3 (1 H, –CO–OH).

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.33; H, 6.82.

(−)-3-Methoxy-1,3,5(10),8,14-estrapentaene 17α-Acetate (9a).—Acetylation of (−) **8** (1.00 g) and cyclization as described above for (±) **8** gave (−) 17α-acetate **9a** (860 mg): mp 125–127°; $[\alpha]D$ −182° ($CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.33; H, 7.40.

(−)-3-Methoxy-1,3,5(10),8,14-estrapentaene-17α-ol (9b). A.—The pentaene acetate **9a** (1.30 g, 3 mmol) in dry tetrahydrofuran (52 ml) was added dropwise to a stirred slurry of lithium aluminum hydride (656 mg) in ether (104 ml) at 25°, and the reaction mixture was stirred at room temperature for 3 hr. With caution, ethyl acetate (24 ml) was added followed by 40 ml of saturated aqueous Na_2SO_4. Sufficient solid $MgSO_4$ was added to remove all the water. Inorganics were removed by filtration and the filtrate was concentrated *in vacuo* to 1.22 g of solid **9b**: mp 89–94°; $\lambda_{max}^{chloroform}$ 2.85, 3.0, 6.21, 6.26 (sh), 6.40, 6.70, 6.85, 7.00 μ. This compound became purple on standing. Because of its instability, further purification was not attempted and it was immediately hydrogenated.

B.—Under nitrogen, methanolic KOH (1.70 ml, 0.85 *N*) was added to a stirred solution of the hemisuccinate **9** (382 mg, 1 mmol) in 3 ml of methanol. The clear reaction mixture was stirred at 25° for 3 hr. Water was then added and methanol was removed *in vacuo*. The final aqueous solution was saturated with NaCl and extracted with ethyl acetate. The latter was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 238 mg of crude 17α-ol **9b**; because of its instability **9b** was immediately hydrogenated without further purification.

(−)-3-Methoxy-1,3,5(10),8-estratetraene-17α-ol (10b).—(−)-3-Methoxy-1,3,5(10),8,14-estrapentaene-17α-ol (**9b**, 850 mg, 3 mmol) in 16 ml of dry dioxane was added to Raney nickel catalyst (850 mg) in 20 ml of dry dioxane pre-equilibrated with hydrogen, and the reaction mixture was hydrogenated at 1 atm of pressure in a wrist-action shaker. Three millimoles of hydrogen were absorbed within 5 hr. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to a crystalline residue: 859 mg; mp 107–117°; nmr, δ 0.68 (s), 0.93 (s); ratio 92:8 of **10b** and its 14 β epimer. Vpc of the trimethylsilyl ether (t, 210°; 5% F 60 silicone oil on Gas-Chrom P) confirmed the nmr result. Recrystallization from ether–petroleum ether gave 738.7 mg of **10b** in two crops, mp 116–119°. The analytical sample was recrystallized from ether–petroleum ether: mp 118–120°; $[\alpha]D$ −36° ($CHCl_3$); λ_{max}^{MeOH} 278 mμ (ε 14,000), 214 (16,400).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.20; H, 8.43.

(−)-3-Methoxy-1,3,5(10),8-estratetraene 17α-Acetate (10a).—(−)-3-Methoxy-1,3,5(10),8-estrapentaen-17α-ol (**10b**, 950 mg)

(29) In earlier runs in which esterification was effected at 100° for 18 hr, 80% yields of the hemisuccinate resulted, whereas, when the crude ketol **8** was employed under the same conditions, a yield of 65% was realized. Therefore, in the preparation of this hemisuccinate employing total reduction product, an over-all yield of 80% of 17α-succinate can be expected.

(30) Procedure of K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).

was acetylated with acetic anhydride (1.5 ml) in dry pyridine (6 ml) at 25° for 16 hr. The reaction mixture was concentrated *in vacuo* to a crystalline residue. Recrystallization from ether–petroleum ether gave a first crop of 875 mg of 17α-acetate **10a**: mp 116–118°; $\lambda_{max}^{chloroform}$ 5.80, 6.20, 6.36, 6.68, 6.82, 7.00 μ.

(+)-17-Isoestradiol 3-Methyl Ether (12) and (−)-17-Iso-9β-estradiol 3-Methyl Ether (13). A.—To a stirred solution of 326.4 mg of 3-methoxy-1,3,5(10),8-estratetraene 17α-acetate (**10a**) in 23 ml of dry tetrahydrofuran and 40 ml of ammonia was added 91.5 mg of lithium ribbon at −50°. At the end of 2 hr, the deep blue color of the reaction mixture was discharged with solid ammonium chloride and the ammonia was evaporated yielding a solid residue. Water (~130 ml) was added and the organic mixture was extracted into ether. The latter extract was washed with water and saturated aqueous Na_2SO_4, dried over $MgSO_4$, and concentrated *in vacuo* to give a solid residue, mp 101–104°, which was separated by preparative tlc (silica gel, 5% ethyl acetate–chloroform) into two isomers, (+)-17-isoestradiol 3-methyl ether (**12**)[20] as needles {171.3 mg; mp 103–106°; [α]D +55° (MeOH); λ_{max} 288 mμ (ε 1770), 279 (1840), 218 (7730); $\lambda_{max}^{chloroform}$ 2.83, 2.98, 6.21, 6.35, 6.69 μ} and the corresponding 9β epimer **13** {52 mg; mp 84–95, 98–116°; [α]D −75.4 (MeOH); λ_{max} 288 μ (ε 1520), 279 (1675), 223 (6980); $\lambda_{max}^{chloroform}$ 2.82, 3.00, 6.2, 6.35, 6.69 μ}.

B.—A solution of (−)-3-methoxy-1,3,5(10),8-estratetraene 17α-ol (**10b**, 284.4 mg, 1 mmol) in 16 ml of tetrahydrofuran and 9 ml of ether was added at a temperature of −40 to −50° to ~18 ml of liquid ammonia which had been dried by passing through a soda lime tube. At −50 to −60°, 312 mg of potassium, in small pieces was added to the resulting solution and the mixture was allowed to stand for 1.5 hr at the same temperature. Solid ammonium chloride (882 mg) was carefully added. After evaporation of the ammonia, the residue was treated with water (at −5 to 0°) and was extracted with ether. The ethereal extract was neutralized with solid carbon dioxide, washed with water, and dried over sodium sulfate. After removal of the solvent, an oil was obtained which readily crystallized upon addition of ether to give 286.9 mg of product. Vpc of the trimethylsilyl derivative indicated two major peaks comprising about 90% of the total area with retention time 6.4 min (**12**) and 7.8 min (**13**) in the ratio of 4:1 (column temperature 222°; 6 ft × 0.25 in. glass column; packing, 3% F-60, 1.5% SE-30 on silonized Gas-Chrom P).

***d*-Estrone Methyl Ether (14).**—To a magnetically stirred solution of 17-isoestradiol 3-methyl ether (**12**, 60 mg) in 6 ml of acetone was added 0.16 ml of Jones' reagent[28] and the reaction mixture was stirred at 25° for 5 min. Excess chromic acid was destroyed with *ca.* 2 ml of methanol and 25 ml of water was added. The green chromate complex gradually dissolved followed by precipitation of colorless crystals which were filtered and washed with water to give 55 mg of *d*-estrone methyl ether (**14**), mp 158–162°. A sample crystallized from methanol had mp 164–166°; [α]D +156° (dioxane) {authentic sample had [α]D +159° (dioxane)}; nmr δ 0.97 (3 H) 3.78 (3 H). The infrared spectrum was identical with that of an authentic sample.

(+)-9β-Estrone Methyl Ether (13a).—A solution of 3-methoxy-9β-estradiol (**13**, 30 mg) in 3 ml of acetone was oxidized in the described manner with 0.08 ml of Jones' reagent for 5 min to give 31 mg of oil which was further purified by preparative tlc to afford 21 mg of a colorless oil: [α]D +43° (MeOH). The infrared spectrum of this material was identical with that of *dl*-9β-estrone 3-methyl ether prepared by W. S. Johnson, *et al.*,[21] with $\lambda_{max}^{chloroform}$ 2.9–3.0 (w), 3.39, 3.48, 5.76 (s), 6.20, 6.34, 6.68, 6.81, 6.88, 7.11, 7.29, 7.41, 7.60, 7.70, 7.75, 7.78, 8.02, 8.43, 8.59, 8.70, 8.85, 8.99, 9.19, 9.33, 9.45, 9.60, 9.80, 9.98, 10.18, 10.30, 10.47, 10.73, 11.0, 11.28, 11.47, 11.63, 12.1–12.3 μ; nmr δ 0.97, 3.78.

3-Methoxy-1,3,5(10),8-estratetraen-17-one (11). A.—3-Methoxy-1,3,5(10),8-estratetraen-17α-ol (**10b**, 286.4 mg, 1 mmol) was dissolved in anhydrous dimethyl sulfoxide (1.5 ml), benzene (1.5 ml) containing dry pyridine (0.08 ml), and trifluoroacetic acid (0.04 ml). After addition of dicyclohexylcarbodiimide (0.62 g, 3 mmol), the reaction mixture was stirred at 25° for 16 hr. Ether (25 ml) was then added, followed by a solution of oxalic acid (270 mg, 3 mmol) in methanol (2.5 ml). After gas evolution had ceased, 25 ml of water was added, solid dicyclohexylurea was filtered off, and the organic phase was washed with 5% $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, and concentrated to give a crystalline residue (472.4 mg) which still contained a small amount of dicyclohexylurea. After filtration from a benzene–ether mixture (1:1) the crystalline product from the filtrate was recrystallized from ether–petroleum ether plus a few drops of methanol. The ketone **11** was obtained in two crops totaling 158 mg (56% of theory): mp 116–119° (needles); [α]D +30.4° ($CHCl_3$); λ_{max} 320 mμ (ε 700), 280 (16,420), 275 (15,750), 213 (18,050), 208 (18,630); $\lambda_{max}^{chloroform}$ 2.79, 2.8–3.0, 5.75, 6.20, 6.35, 6.68, 6.85, 7.0 μ.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.63; H, 7.72.

B.—To a boiling solution of aluminum isoproxide (408.5 mg, 2 mmol) in 11.7 ml of Na-dried toluene and 2.67 ml of freshly distilled cyclohexanone under nitrogen was added over a 10-min period 286.4 mg of the tetraene alcohol **10b** in 8 ml of dry toluene. The reaction mixture was stirred and refluxed for an additional 2 hr (reflux temperature 108°). Saturated aqueous Rochelle salt solution (2.0 ml) was added dropwise and the reaction mixture was mechanically pumped to near dryness. Cyclohexylidinecyclohexanone was removed by steam distillation for 4 hr. The aqueous solution was extracted with benzene–ether (2:1) and the organic extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to 301 mg of a reddish oil which crystallized from ether to afford a first crop of 86 mg of **11**, mp 116–119°. The filtrate was purified by tlc (silica gel, 2% methanol–chloroform) to provide an additional 86.6 mg, mp 116–119° (totaling 172.6 mg or 61%).

Registry No.—**1**, 16973-91-4; **3**, 4820-46-6; **4**, 5060-00-4; **4a**, 5541-17-3; **4b**, 16976-23-1; **4c**, 16976-24-2; **4d**, 16994-39-1; **7**, 1456-50-4; (±) **8**, 16976-26-4; (±) **8** semicarbazone, 16976-27-5; (−) **8**, 16976-39-9; (+) **8**, 6563-81-1; (±) **8a**, 16976-28-6; (−) **8a**, 16976-29-7; **8b**, 16976-30-0; **9**, 16976-31-1; **9a**, 10003-15-3; **9b**, 17004-84-1; **10a**, 10003-16-4; **10b**, 17021-76-0; **11**, 6885-44-5; **12**, 16994-40-4; **13**, 7021-78-2; **13a**, 1923-52-7; **14**, 1091-94-7; estrone, 53-16-7; 6-methoxytetralone-O^{18}, 16973-92-5.