Total Synthesis of 11β-Methyl-19-nor Steroids[1]

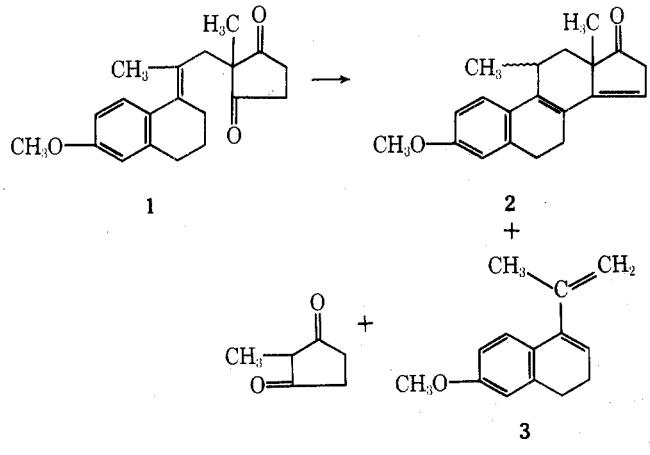
R. B. Garland,* J. R. Palmer, and R. Pappo*

Department of Chemical Research, Searle Laboratories, A Division of G. D. Searle & Co., P.O. Box 5110, Chicago, Illinois 60680

Received September 8, 1975

A total synthesis scheme for the preparation of 11β-methyl-19-nor steroids was developed. A key step in the synthesis involved the use of an allylic quaternary ammonium salt, **5**, to alkylate 2-methylcyclopentane-1,3-dione to produce the seco steroid, **6a**. Cyclization under mild conditions led to **7a** which after a series of stereospecific reductions produced racemic 11β-methylestradiol-3-methyl ether (**10a**). The method was also applied to the synthesis of previously inaccessible 11β,18-dimethyl-19-nor steroids.

The preparation of 11-methylated steroids from naturally available materials involves the reaction of an organometallic compound with a readily enolizable 11-ketone.[2] Attempts at applying the same series of reactions to the 18-homologues failed.[3] The problems encountered in the introduction of the 11β-methyl group as well as interest in obtaining the 13-ethyl analogues has prompted some efforts toward total synthesis. Because of the efficiency of the Smith-Torgov approach this method was tried but found unsuccessful for the 11-methyl derivatives.[3,4] The tricyclic compound, **1**, could be prepared with difficulty via the isothiouronium salt technique.[3,5] Various attempts at cyclization of **1** produced only traces of **2** (as a mixture of C_{11} isomers) together with 98–100% of cleavage products, **3** and 2-methylcyclopentane-1,3-dione.



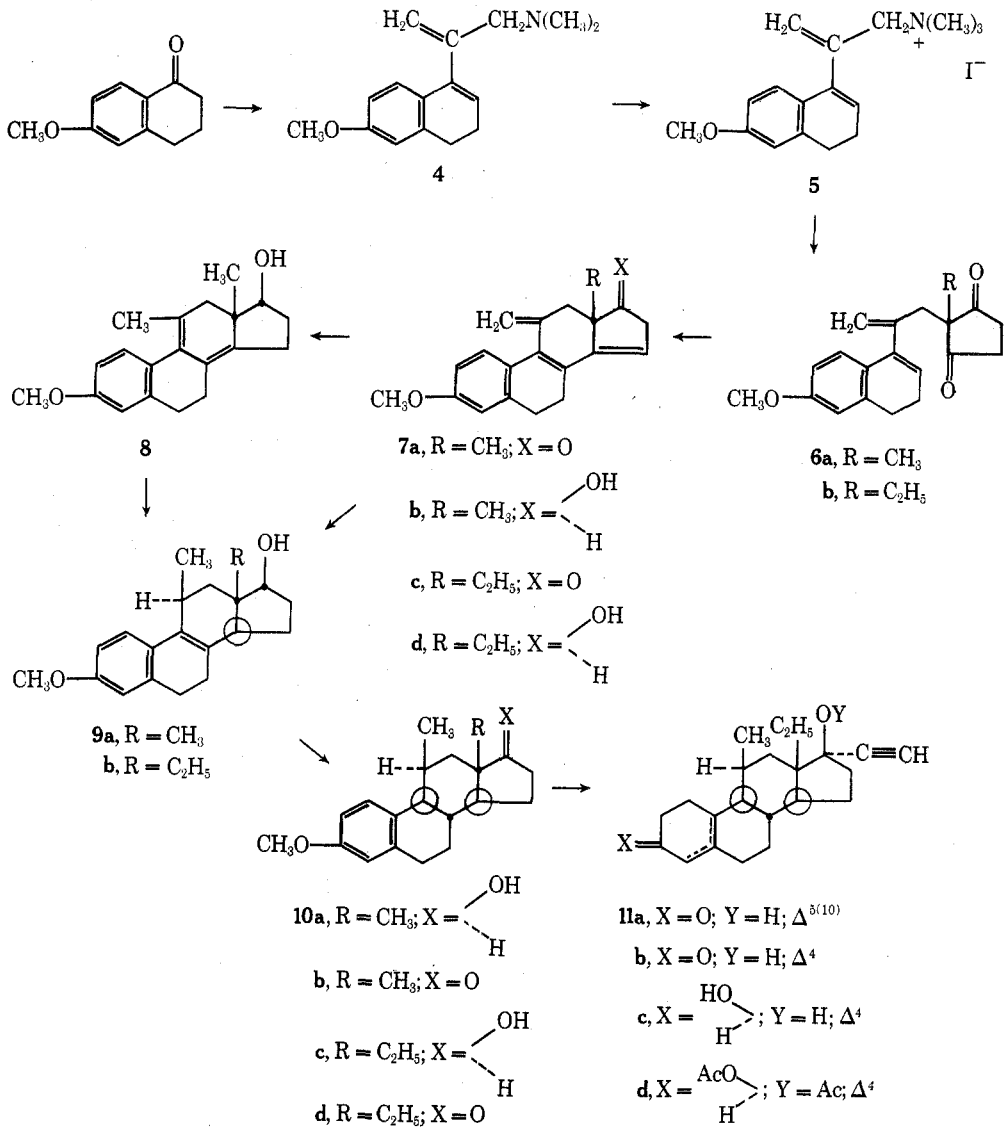
We postulated that if the 9,11 double bond could be forced into the 8,9 position the desired cyclization would become favorable and at the same time the cleavage reaction would become unlikely. Thus, we sought to prepare a diene such as **6a**.

Initially we approached this problem via the reaction of 3-dimethylaminopropen-2-yl magnesium bromide[6] with 6-methoxy-1-tetralone to produce **4** after acidic work-up. Subsequently we found it more convenient to utilize a lithium reagent prepared via halogen–metal interchange between 2-bromo-3-dimethylaminopropene and *n*-butyllithium.[7,8] In the course of our work we found that 2-chloro-3-dimethylaminopropene will also undergo exchange with *n*-butyllithium if the temperature is allowed to rise to 0°. (The bromo compound exchanges rapidly at −40°.) The use of the lithium reagent has the advantages of speed in preparation, easier work-up with a cleaner product, and more easily recovered 6-methoxy-1-tetralone. Owing to enolate formation there is always about 40% of the 6-methoxy-1-tetralone left at the end of the reaction. Presumably the high rate of enolate formation is due to the steric inhibition of the addition reaction. The crude product, **4**, could be quaternized directly with methyl iodide to form **5**.

Since the quaternary salt, **5**, is allylic, it was very likely that anionic attack would result in the displacement of trimethylamine. Most of the reported uses of quaternary ammonium salts for C-alkylation reactions involve quaternary salts of Mannich bases where an elimination–addition reaction mechanism is probable. The use of several benzylic quaternary ammonium salts to C-benzylate malonic ester or acetoacetic ester in up to 80% yield was the example closest to the reaction envisaged.[9,10] We treated the salt, **5**, with the sodium salt of 2-methylcyclopentane-1,3-dione in refluxing xylene with a trace of hexamethylphosphoric triamide (HMPT) and were able to isolate **6a** in 38% yield. The work-up was complicated by the presence of small amounts of complex amine by-products which were not readily removed by acid extraction and which hindered the crystallization of the product. We reasoned that these materials were formed by a dequaternization reaction induced by the iodide ion. This speculation was supported by the discovery of crystals of tetramethylammonium iodide high in the reflux condenser. In order to remove the iodide we converted **5** to a quaternary ammonium hydroxide, added the dione, and heated as before, thereby increasing the yield of **6a** to 55%. The use of more than 2% HMPT resulted in lowered yields as the amount of O-alkylation product and other undetermined by-products increased. The reaction of the amine, **4**, with 2-methylcyclopentane-1,3-dione with or without added base did not produce any of the desired product. In a similar manner 2-ethylcyclopentane-1,3-dione produced **6b**.

The tricyclic compounds, **6**, were indeed readily cyclized below 10° with 1 equiv of anhydrous *p*-toluenesulfonic acid in benzene or toluene. The tetracyclic hexaenes (**7a, 7c**) were isolated with caution or more conveniently were reduced directly to the more stable hydroxy compounds (**7b, 7d**). In both of these intermediates the 13-ethyl derivatives required somewhat greater caution in solution (low temperature, N_2 atmosphere, and avoidance of base) but all of these materials could be stored for extended periods in the crystalline state in a refrigerator.

Catalytic hydrogenation of **7b** led to **9a** as the major product. If the hydrogenation was stopped after 1 equiv of hydrogen the major product was **8** with the amount of material corresponding to structures **2** estimated at about 10% on the basis of NMR and uv analysis of the crude mixture. We can therefore presume that the hydrogenation proceeds by way of **8** with the entering hydrogen atoms going in by a 1,6 addition, followed by a 1,4 addition with both atoms on the same side of the molecule. In the ethyl series the yield of **9b** was slightly lower. This fact along with the decreased stability of **7c** and **7d** may be due to a slightly greater strain on the triene system caused by the bulkier ethyl group. This added strain could easily explain the decreased stabil-



ity and it might alter the route of hydrogenation leading to additional isomers.

Reduction of **9a** with sodium and aniline in ammonia[11] produced **10a.** The ir, uv, and NMR spectra of this material were identical with those of a sample of 3-methoxy-11β-methylestra-1,3,5(10)-trien-17β-ol from natural sources.[2] The 17-ketone, **10b,** was also prepared and again the spectra were identical with those of an authentic sample. The ethyl compounds, **10c** and **10d,** were likewise prepared. The similarity of the NMR bands corresponding to the 11-methyl protons in the methyl and ethyl series is evidence for the same relative stereochemistry.

The 3-methoxy-11β-methyl-13-ethylgona-1,3,5(10)-trien-17β-ol (**10c**) was converted by standard reactions to the progestational type compounds **11.**

Experimental Section

Microanalyses were performed by Mr. Emmanuel Zielinski and associates and spectra were run by Mr. John Damascus and associates of Searle Laboratories. All uv spectra were run in methanol on a Beckman DK-2A spectrophotometer and are reported as wavelength in nanometers (ϵ). Ir spectra were run in $CHCl_3$ on a Beckman IR-12 spectrophotometer and carbonyl region peaks are reported as wavelength in microns. NMR spectra were run in $CDCl_3$ except as noted on a Varian A-60A spectrometer and are reported in parts per million (δ) downfield from $(CH_3)_4Si$ as an internal standard. (Notation: s, d, t, etc. refer to singlet, doublet, triplet, etc., and br refers to a broad peak.) Column chromatography was done by "dry column" technique[12] on Mallinckrodt SilicAR CC-7, 100–200 mesh. Hydrogenations were carried out by Mr. Mike Scaros and associates of Searle Laboratories. Melting points were determined on a Fisher-Johns block and are uncorrected.

[2-(3,4-Dihydro-6-methoxy-1-naphthyl)-2-propenyl]trimethylammonium Iodide (5). To a solution of 326 g (2 mol) of 2-bromo-3-dimethylaminopropene[6] in 1200 ml of *n*-hexane at −40° was added 2.0 mol of *n*-butyllithium in hexane over a 45-min period. After 30 min of additional stirring a solution of 300 g (1.7 mol) of 6-methoxy-1-tetralone in 1500 ml of benzene was added at a rate to keep the temperature at −40 to −30°. After 1 hr the temperature was allowed to rise to 0° and ice water was added. The organic layer was separated and washed again with ice water, then extracted with a total of 1200 ml of 10% HCl. Normal work-up of the residual organic layer returned 107 g of 6-methoxy-1-tetralone, mp 78–79° from cyclohexane. The acid solution was cooled to 0° and made strongly basic with 50% NaOH solution. The liberated amine was extracted with ether and the solution was washed well with water. After drying over sodium sulfate the mixture was thoroughly stripped of solvent at 65° on the water pump to remove low-boiling amines. [This product was adequately pure for quaternization. When the reaction was run similarly with a Grignard reagent[6] prepared from 310 g of 2-bromo-3-dimethylaminopropene and 260 g of 6-methoxy-1-tetralone the product contained dark impurities and was distilled to yield 121 g of **4**: bp 130–133° (0.2 mm); uv λ_{max} 273 nm (ϵ 10800); NMR δ 2.25 (s, 6 H) superimposed on 2.1–2.9 (4 H), 3.06 (br s, 2 H), 3.79 (s, 3 H), 5.15–5.35 (2 H), 5.88 (t, J = 4.4 Hz, 1 H), 6.5–7.2 (3 H).] The crude oil (160 g) was dissolved in 3 l. of benzene and 100 g of methyl iodide was added. After standing at room temperature overnight, the solid was collected and washed with benzene to give 242 g (37% conversion, 57% yield from 6-methoxy-1-tetralone) of **5**: mp 182–183°; uv λ_{max} 218 nm (ϵ 27560), 268 (10000); NMR (CD_3OD) δ 2.1–2.9 (4 H), 3.15 (s, 9 H), 3.81 (s, 3 H), 4.32 (br s, 2 H), 5.84 (br s, 2 H), 6.25 (t, J = 4.6 Hz, 1 H), 6.7–7.2 (3 H).

Anal Calcd for $C_{17}H_{24}NOI$: C, 52.99; H, 6.28; N, 3.64; I, 32.94. Found: C, 52.75; H, 6.24; N, 3.66; I, 32.81.

When 2-chloro-3-dimethylaminopropene (bp 32°, 20 mm), prepared from 2,3-dichloropropene in the same manner as the bromo compound,[6] was substituted and the reaction run on a 0.1-mol scale with the same temperature as above, the yield of **5** was only 10% and the neutral layer contained a significant amount of 1-butyl-6-methoxy-1-tetralol as indicated by NMR analysis. In another 0.1-mol run, the solution of 2-chloro-3-dimethylaminopropene and butyllithium was allowed to warm to 0° for 20 min before the 6-methoxy-1-tetralone was added. The rest of the sequence was unchanged and the yield of **5** was 53% based on consumed 6-methoxy-1-tetralone.

13-Ethyl-3-methoxy-11-methylene-8,14-secogona-1,3,5(10),8-tetraene-14,17-dione (6b). To a solution of 76 g (0.197 mol) of **5** in 800 ml of methanol and 40 ml of water at 15° was added 24 g (0.103 mol) of silver oxide. The mixture was stirred at 15–20° for 2 hr, when a silver nitrate test was negative. The solid was removed by filtration washing well with methanol. To the filtrate was added 30 g (0.238 mol) of 2-ethylcyclopentane-1,3-dione and the resulting solution was concentrated to dryness on the water pump. The residue was suspended in 1400 ml of xylene and 10 ml of triethylamine (to neutralize the excess dione). The resulting mixture was heated to distill out ca. 100 ml through a short Vigreux column to remove methanol, water, and excess triethylamine. After the addition of 5 ml of HMPT ca. 100 ml more distillate was collected and the heat was adjusted to cause refluxing in the column. After 18 hr slow distillation was resumed until little more amine was detected in the distillate (in 6 hr ca. 400 ml was collected). After cooling the solution was washed with water and 5% $NaHCO_3$ solution. After drying over sodium sulfate, the solvent was removed and the residue crystallized from methanol to yield 35.2 g (54%) of **6b:** mp 100–100.5°; ir 5.66 (weak), 5.79 μ; uv λ_{max} 273 nm (ε 11000); NMR δ 0.73 (t, J = 7.5 Hz, 3 H), 1.62 (q, J = 7.5 Hz, 2 H), 1.9–2.4 (2 H), [2.60 (s, ca. 4 H) and 2.72 (br s, ca. 2 H) superimposed on 2.5–2.9 (ca. 2 H)], 3.81 (s, 3 H), 4.9–5.1 (2 H), 5.79 (t, J = 4.6 Hz, 1 H), 6.6–7.1 (3 H).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.98; H, 7.64.

3-Methoxy-11-methylene-8,14-secoestra-1,3,5(10),8-tetraene-14,17-dione (6a). In a manner similar to the above 13.3 g of **5**, 4.1 g of silver oxide, and 4.0 g of 2-methylcyclopentane-1,3-dione with 1 ml of triethylamine, 5 ml of HMPT, and 500 ml of xylene yielded 5.9 g (55%) of **6a:** mp 82.5–83° from aqueous methanol; ir 5.65 (weak), 5.78 μ; uv λ_{max} 274 nm (ε 10400); NMR δ 1.08 (s, 3 H), [2.67 (s, ca. 4 H) + 2.74 (br s, ca. 2 H) superimposed on 1.9–2.9 (ca. 4 H)], 3.81 (s, 3 H), 4.9–5.1 (2 H), 5.70 (t, J = 4.5 Hz, 1 H), 6.4–7.1 (3 H).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.23; H, 7.27.

In a similar run with 2.8 g of **5**, 0.85 g of silver oxide, 1.0 g of 2-methylcyclopentane-1,3-dione, 1 ml of triethylamine, and 20 ml of HMPT in 250 ml of xylene, the crude product contained several impurities as evidenced by TLC. After chromatographic purification developing with 5% ethyl acetate in benzene the product fraction was crystallized from methanol to yield 256 mg of **6a** identical with the above. The major by-product fraction moving somewhat slower amounted to 430 mg of a crude oil believed to be the isomeric O-alkylation product: ir 5.74 (weak), 5.88; 6.10 μ; uv λ_{max} 253 nm (ε 22650); NMR δ 1.66 (t, J = 1.4 Hz, 3 H), 2.0–2.9 (ca. 8 H), 3.82 (s, 3 H), 4.79 (t, J = 1.4 Hz, 2 H), 5.36 (d of t, J = 7 + 1.4 Hz, 2 H), 5.91 (t, J = 4.5 Hz, 1 H), 6.5–7.2 (3 H).

A solution of 2.25 g of 2-methylcyclopentane-1,3-dione and 1.08 g of sodium methylate in 10 ml of methanol was concentrated to dryness and 3.85 g of **5**, 250 ml of xylene, and 10 ml of HMPT were added. The mixture was slowly distilled over a 6-hr period adding xylene to maintain the volume at 200–250 ml. (From the stillhead a small amount of solid, mp ca. 330° dec, was identified as tetramethylammonium iodide, NMR in D_2O single band δ 3.20.) After cooling the mixture was washed with water, 5% HCl, and 5% $NaHCO_3$ and dried over sodium sulfate. The solvent was removed and the mixture was chromatographed to give first 210 mg of a crude amine by-product with NMR bands at δ 3.10 and 2.22 in the ratio of 4:3 suggesting bis[2-(3,4-dihydro-6-methoxy-1-naphthyl)-2-propenyl]methylamine. This was followed by the crude product which on crystallization from aqueous methanol gave 1.17 g (38%) of **6a** identical with the above.

Racemic 13-Ethyl-3-methoxy-11-methylenegona-1,3,5(10),-8,14-pentaen-17β-ol (7d). A solution of 35.2 g (0.108 mol) of **6b** in 750 ml of toluene was dried by distillation of ca. 50 ml and then chilled under nitrogen to −30°. A solution, previously dried by reflux under a Dean-Stark type trap, from 20.5 g (0.108 mol) of p-toluenesulfonic acid monohydrate and 1.5 l. of benzene was added over a short period with vigorous stirring while keeping the temperature below 0°. The mixture was stirred at 0° for 15 min. The precipitate of p-toluenesulfonic acid hydrate was removed by rapid filtration through a Supercell cake in a nitrogen atmosphere rinsing the solid with dry benzene. The filtrate was diluted with 500 ml of dry ether and chilled in an ice bath under nitrogen while 35 ml of 1 M $LiAlH_4$ in ether was added quickly with stirring. After 15 min the excess hydride was quenched and the mixture was washed with cold 5% HCl and then with ice water. After brief drying over sodium sulfate the solution was concentrated on the water pump to a small residue which was triturated with cold methanol. The solid was collected and recrystallized from methanol to yield 20.3 g of the hemimethanoloate of **7d,** mp 86–88°. (Other runs gave samples melting as low as 58–60° or as high as 102–104° with only slight variations in the amount of methanol as judged by the NMR spectrum.) Concentration of the mother liquors followed by quick chromatographic purification developing with 5% ethyl acetate in benzene and crystallization from methanol gave 6.3 g more material: mp 85–87°; uv λ_{max} 248 nm (ε 13700), 257 (11300), 312 (19600), 324 (22600), 338 (17900); NMR δ 0.97 (t, J = 7 Hz, 3 H), 1.61 (q, J = 7 Hz, 2 H), 1.7–2.9 (ca. 9.5 H), 3.48 (s, ca. 1.5 H), 3.81 (s, 3 H), 4.23 (t, J = 8.5 Hz, 1 H), 5.23 (d of t, J = 6 + 1.5 Hz, 2 H), 5.64 (t, J = 3 Hz, 1 H), 6.6–7.7 (3 H).

Anal. Calcd for $C_{21}H_{24}O_2 \cdot \frac{1}{2}CH_4O$: C, 79.59; H, 8.08. Found: C, 79.36; H, 7.99.

Racemic 13-Ethyl-3-methoxy-11-methylenegona-1,3,5(10),-8,14-pentaen-17-one (7c). Under similar conditions from 4.76 g of **6b** and 2.78 g of p-toluenesulfonic acid monohydrate, the intermediate was isolated by taking the filtrate after removal of tosyl acid hydrate, washing with ice water, and drying over sodium sulfate. After removal of solvents on the water pump the residue was triturated with methanol and the solid was recrystallized from CH_2Cl_2–CH_3OH to yield 3.68 g (82%) of **7c:** mp 117.5–118°; ir 5.73 μ; uv λ_{max} 248 nm (ε 12900), 257 (11000), 312 (16900), 325 (19000), 339 (15400); NMR δ 0.86 (t, J = 7 Hz, 3 H), 1.64 (q, J = 7 Hz, 2 H), 1.9–3.4 (ca. 8 H), 3.81 (s, 3 H), 5.31 (br d, J = 7 Hz, 2 H), 5.92 (t, J = 2.8 Hz, 1 H), 6.6–7.6 (3 H).

Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.22; H, 7.30.

Racemic 3-Methoxy-11-methyleneestra-1,3,5(10),8,14-pentaen-17-one (7a). In a manner similar to the preparation of **7c** above, 4.71 g of **6a** and 2.85 g of p-toluenesulfonic acid monohydrate yielded 3.80 g (86%) of **7a:** mp 161–163° from CH_2Cl_2–CH_3OH; ir 5.73 μ; uv λ_{max} 246 nm (ε 15200), 255 (12700), 325 (23700), $\lambda_{shoulder}$ 313 (20400), 338 (19300); NMR δ 1.14 (s, 3 H) [2.43 (br s, ca. 2 H) superimposed on 2.1–2.9 (ca. 4 H)], 3.13 (d of d, J = 12 + 3 Hz, 2 H), 3.80 (s, 3 H), 5.33 (br d, J = 4 Hz, 2 H), 5.89 (t, J = 3.3 Hz, 1 H), 6.6–7.6 (3 H).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 82.00; H, 7.13.

Racemic 3-Methoxy-11-methyleneestra-1,3,5(10),8,14-pentaen-17β-ol (7b). To a solution of 2.32 g of **7a** in 20 ml of benzene and 50 ml of ether under nitrogen was added 5 ml of 0.9 M $LiAlH_4$ in ether. After 5 min the product was isolated in the normal manner to give 2.32 g (89%) of a methanol solvate, mp 102–110°. A portion was boiled in hexane and then recrystallized from ether to give a sample: mp 120–124°; uv λ_{max} 247 nm (ε 13400), 257 (10900), 312 (20000), 324 (23300), 339 (18700); NMR δ 1.00 (s, 3 H), 1.78 (OH, 1 H), 2.0–2.8 (ca. 8 H), 3.81 (s, 3 H), 4.12 (br t, J = 8.5 Hz, 1 H), 5.1–5.3 (2 H), 5.54 (t, J = 3.3 Hz, 1 H), 6.6–7.7 (3 H).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60: H, 7.53. Found: C, 81.59; H, 7.59.

Racemic 13-Ethyl-3-methoxy-11β-methylgona-1,3,5(10),8-tetraen-17β-ol (9b). A solution of 7.55 g (23 mmol) of the hemimethanoloate of **7d** in 250 ml of ethanol was hydrogenated in the presence of 3.7 g of a 5% Pd/Al_2O_3 catalyst at 2 psi and room temperature. After 3 hr 49.5 mmol of H_2 had been taken up. The catalyst was removed by filtration and the filtrate was concentrated to a small residue which was triturated with methanol. The crude solid was recrystallized from CH_2Cl_2–CH_3OH to yield 4.0 g of a solvate, mp 131–142°. Recrystallization from CH_2Cl_2–cyclohexane gave 3.47 g (48%) of **9b:** mp 147–148°; uv λ_{max} 278 nm (ε 17600), $\lambda_{shoulder}$ 271 (17200); NMR δ [1.21 (d, J = 7.5 Hz, ca. 3 H) + 1.52 (OH, ca. 1 H) superimposed on 0.9–2.9 (ca. 17 H)], 3.80 (s, 3 H) superimposed on 3.82 (br t, J = 6 Hz, 1 H), 6.6–7.3 (3 H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.59; H, 8.83.

Racemic 3-Methoxy-11β-methylestra-1,3,5(10),8-tetraen-17β-ol (9a). A solution of 1.48 g (5 mmol) of **7b** in 50 ml of benzene was hydrogenated over 0.74 g of 5% Pd/Al_2O_3 at 2 psi. After 4 hr 10 mmol of H_2 had been consumed. The catalyst was removed by filtration and the filtrate was concentrated to a small residue which was crystallized from aqueous methanol to give 870 mg (58%), mp 159–161°. A sample recrystallized from aqueous methanol melted at 162–163°; uv λ_{max} 278 nm (ε 13900), $\lambda_{shoulder}$ 270 (13600); NMR δ 0.93 (s, 3 H), 1.21 (d, J = 7.5 Hz, 3 H), 1.57 (OH, ca. 1 H) superimposed on 1.4–2.9 (ca. 13 H), 3.80 (s, 3 H) superimposed on 3.6–3.9 (ca. 1 H), 6.6–7.3 (3 H).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.36; H, 8.74.

Concentration of the mother liquors led to 614 mg of an oil. A study of the methyl bands in the NMR spectrum indicated about 46% of the above material, δ 0.93 (s) and 1.21 (d, J = 7.5 Hz) together with 25% of an isomeric component with δ 1.06 (s) and 0.69 (d, J = 5 Hz) and 29% of a third component with δ 0.99 (s) and 0.83 (d, J = 6 Hz). In some other runs very little of the third component was observed. On the basis of the ratios of the components from various runs, the third component may have arisen from the uptake of a third mole of hydrogen by the isomeric by-product.

Racemic 3-Methoxy-11-methylestra-1,3,5(10),8(14),9(11)-pentaen-17β-ol (8). A solution of 463 mg (1.5 mmol) of **7b** in 40 ml of benzene was hydrogenated over 50 mg of 5% $Pd/CaCO_3$ at atmospheric pressure. After 1 hr 1.55 mmol of H_2 had been consumed and uptake stopped. The catalyst was removed and the solution was concentrated to dryness. The residue was crystallized twice from aqueous methanol to yield 392 mg (63%) of **8**: mp 124–127°; uv λ_{max} 244 nm (ε 20800), 285 (7600), $\lambda_{shoulder}$ 250 (20500); NMR δ 0.89 (s, 3 H), 1.61 (OH, 1 H), [2.00 (br s, ca. 3 H) + 2.24 (br s, ca. 2 H) superimposed on 1.7–2.8 (ca. 8 H)], 3.80 (s, 3 H), 3.8–4.1 (1 H), 6.7–7.4 (3 H).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.06; H, 8.31.

Hydrogenation of this material over Pd/Al_2O_3 as described above resulted in an 80% yield of **9a** by an NMR analysis or 62% yield of crystallized **9a**.

Concentration of the mother liquors left 112 mg of a crude oil. The uv spectrum of this material was similar to the above with an additional maximum at 311 nm with shoulders at 300 and 324 nm. The NMR spectrum showed, in addition to the above (ca. 60%), bands at δ 0.83, 0.92, 0.99, 1.11, 1.20, 1.32, and 5.1–5.3 and 5.4–5.6 which may be accounted for by structures **2**.

Racemic 13-Ethyl-3-methoxy-11β-methylgona-1,3,5(10)-trien-17β-ol (10c). To a solution of 2.0 g of sodium metal in ca. 250 ml of refluxing ammonia was added a solution of 6.117 g of **9b** in 15 ml of aniline and 100 ml of THF over a 5-min period. After 30 min the flask was cooled well in a dry ice bath and 10 g of solid ammonium chloride was added cautiously. The ammonia was allowed to evaporate under a nitrogen stream at room temperature and 50 ml of water was added. The mixture was concentrated on the water pump to remove most of the THF. The mixture was made acidic with 10% HCl and stirred until the supernatant liquid was clear. The solid was collected and washed well with water. After drying, recrystallization from methanol yielded 5.93 g of the hemimethanoloate of **10c**: mp 124–125°; uv λ_{max} 220 nm (ε 8400), 278 (1970), 287 (1900); NMR δ [0.90 (d, J = 7.5 Hz, ca. 3 H) + 1.50 (OH, ca. 1.5 H) superimposed on 0.8–2.9 (ca. 19 H)], 3.47 (CH_3OH, 1.5 H), 3.78 (s, 3 H) superimposed on 3.6–3.9 (1 H), 6.6–7.2 (3 H).

Anal. Calcd for $C_{21}H_{30}O_2 \cdot \frac{1}{2}CH_4O$: C, 78.13; H, 9.76. Found: C, 78.35; H, 9.85.

Racemic 11β-Methylestradiol-3-methyl Ether (10a). In a manner similar to the above procedure, 253 mg of **9a** and 500 mg of sodium metal yielded 2.2 mg of **10a**: mp 143–145° from aqueous methanol; uv λ_{max} 279 nm (ε 1920), 288 (1960); NMR δ 0.89 (d, J = 7.5 Hz, 3 H), 0.92 (s, 3 H), 1.58 (OH, 1 H) superimposed on 1.2–3.0 (ca. 14 H), 3.78 (s, 3 H) superimposed on 3.5–3.9 (1 H), 6.6–7.2 (3 H). These spectra and ir spectra are indistinguishable from those of a sample derived from natural sources.[2]

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.70; H, 9.40.

Racemic 11β-Methylestrone-3-methyl Ether (10b). Jones reagent oxidation[13] of 132 mg of **10a** produced 100 mg of **10b**: mp 150–153° from aqueous methanol; ir 5.74 μ; uv λ_{max} 278 nm (ε 2000), 287 (1940); NMR δ 0.89 (d, J = 7.5 Hz, 3 H), 1.00 (s, 3 H), 1.2–3.1 (ca. 14 H), 3.77 (s, 3 H), 6.6–7.3 (3 H). These spectra are indistinguishable from those of a sample derived from natural sources.[2]

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.43; H, 8.78.

Racemic 13-Ethyl-3-methoxy-11β-methylgona-1,3,5(10)-trien-17-one (10d). Jones reagent oxidation[13] of 560 mg of the hemimethanoloate of **10c** produced 453 mg of **10d**: mp 144.5–145° from aqueous methanol; ir 5.75 μ; uv λ_{max} 220 nm (ε 8400), 278 (1970), 287 (1900); NMR δ 0.85 (t, J = 5.5 Hz, ca. 3 H) superimposed on 0.90 (d, J = 7 Hz, ca. 3 H), 1.1–3.0 (ca. 16 H), 3.77 (s, 3 H), 6.6–7.2 (3 H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.68; H, 9.22.

Racemic 13-Ethyl-17-hydroxy-11β-methyl-18,19-dinor-17α-pregn-5-en-20-yn-3-one (11a). Under Birch reduction conditions,[14] 6.2 g of **10c** in 75 ml of THF and 75 ml of 2-propanol was treated with a total of 9.5 g of sodium metal in 150 ml of ammonia. The crude dry product (5.9 g, mp 155–158°) in 350 ml of dry toluene was oxidized by 60 ml of cyclohexanone in the presence of 6 g of aluminum isopropoxide during 1 hr at reflux. After some cooling 45 ml of a saturated Rochelle salt solution was added and the mixture was steam distilled under nitrogen until the distillate was clear. After cooling the mixture was extracted with ether. The extract was washed with water and dried over sodium sulfate and the solvent removed in vacuo. The residue was crystallized from benzene–cyclohexane to give 5.35 g of material melting at 142–144°. A solution of this material in 50 ml of dry THF was added to a solution previously prepared by addition of 25 ml of 3.1 M ethylmagnesium bromide in ether to ca. 20 g of acetylene in 100 ml of THF at −78° and then allowed to warm to 10°. The resulting mixture was stirred for 4 hr at room temperature. After cooling in an ice bath, 100 ml of ice-cold saturated NH_4Cl was added slowly with stirring. The mixture was extracted twice with ether and the extracts were washed with water, dried over sodium sulfate, and concentrated in vacuo. Crystallization from benzene–cyclohexane gave 3.79 g, mp 161–164°. This material was suspended in 150 ml of methanol and 10 ml of a 10% oxalic acid solution was added. After 30 min of stirring at room temperature the solution was complete and the mixture was diluted with 100 ml of water and concentrated on the water pump to remove most of the methanol. Normal extraction and crystallization from benzene-cyclohexane gave 3.38 g of **11a**: mp 135–136°; ir 5.81 μ; uv λ_{max} 288 nm (ε 111); NMR δ 2.64 (s, 1 H), 2.77 (br s, 2 H), 0.8–2.6 (ca. 27 H including OH at 2.05 and strong bands at 0.84, 0.96, 1.08, 1.18, 2.02, and 2.40).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.79; H, 9.35.

Racemic 13-Ethyl-17-hydroxy-11β-methyl-18,19-dinor-17α-preg-4-en-20-yn-3-one (11b). To a solution of 860 mg of **11a** in 30 ml of methanol was added 10 ml of 4 N HCl. After 6 hr at room temperature crystals had formed, and 10 ml more of 4 N HCl was added. After 2 hr more the mixture was chilled an the solid collected and washed well with water. Recrystallization from aqueous methanol yielded 687 mg: mp 208–210°; ir 5.99, 6.17 μ; uv λ_{max} 240.5 nm (ε 16700); NMR δ 2.61 (s, 1 H), 5.87 (br s, 1 H), 0.8–2.9 (ca. 34 H including OH at 2.15 and strong bands at 1.03, 1.17, 1.22, 2.02, 2.30, 2.39).

Anal Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.03; H, 9.31.

Racemic 13-Ethyl-11β-methyl-18,19-dinor-17α-pregn-4-en-20-yne-3β,17-diol (11c). To a solution of 909 mg of **11b** in 40 ml of THF was added 2 g of lithium tri-*tert*-butoxyaluminum hydride and the mixture was stirred at room temperature for 18 hr and worked up in the normal manner. After chromatographic purification developing with 5% ethyl acetate in benzene, the major fraction (faster moving) was crystallized twice from cyclohexane to yield 638 mg of **11c**: mp 176–178°; NMR δ 2.60 (s, 1 H), 3.98–4.32 (1 H), 5.3–5.5 (1 H), 0.7–2.5 (ca. 29 H including strong bands at 0.99, 1.10, 1.17, 1.46, 1.97, and 2.11).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.25; H, 9.63.

Racemic 3β,17-Diacetoxy-13-ethyl-11β-methyl-18,19-dinor-17α-pregn-4-en-20-yne (11d). A solution of 344 mg of **11c** and 11 mg of 4-dimethylaminopyridine in 5 ml of acetic anhydride and 5 ml of triethylamine was heated under nitrogen for 24 hr at 40° and then for 16 hr more at 45°. After cooling 20 ml of 2-propanol was added and after 30 min 100 ml of water was added and the mixture was extracted with ether. The extract was washed with water and dried over sodium sulfate and the solvent removed. The mixture was chromatographed developing with 2% ethyl acetate in benzene. The major fraction was crystallized from methanol to yield 230 mg of **11d**: mp 147–149°; NMR δ 2.05 (s, ca. 6 H) superimposed

on 0.9–2.4 (ca. 27 H), 2.63 (s, 1 H), 5.35–5.45 (ca. 1 H) superimposed on 5.0–5.6 (ca. 1 H).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.97; H, 8.80.

Registry No.—**2** isomer A, 57346-08-4; **2** isomer B, 57346-09-5; **4**, 57346-10-8; **5**, 57346-11-9; **6a**, 57346-12-0; **6b**, 57346-13-1; **7a**, 57346-14-2; **7b**, 57346-15-3; **7c**, 57346-16-4; **7d** ½MeOH, 57346-18-6; **8**, 57346-19-7; **9a**, 57346-20-0; **9b**, 57346-21-1; **10a**, 57378-55-9; **10b**, 57346-22-2; **10c**, 57346-23-3; **10c** ½MeOH, 57427-66-4; **10d**, 17253-49-5; **11a**, 57362-17-1; **11b**, 57346-24-4; **11c**, 23163-43-1; **11d**, 23163-53-3; 2-bromo-3-dimethylaminopropene, 14326-14-8; 6-methoxytetralone, 1078-19-9; 2-ethylcyclopentane-1,3-dione, 823-36-9; 2-methylcyclopentane-1,3-dione, 765-69-5; (±)-13-ethyl-3-methoxy-11β-methylgona-2,5(10)-dien-17β-ol, 57346-25-5; (±)-13-ethyl-3-methoxy-11β-methylgona-2,5(10)-dien-17-one, 57346-26-6; (±)-13-ethyl-3-methoxy-11β-methyl-17-hydroxy-18,19-dinor-17α-pregna-2,5(10)-dien-20-yne, 53762-18-2.

References and Notes

(1) Presented in part at the 4th International Congress on Hormonal Steroids, Mexico City, 1974; R. B. Garland and R. Pappo, *J. Steroid Biochem.*, **5**, 299 (1974).
(2) J. S. Baran, H. D. Lennon, S. E. Mares, and E. F. Nutting, *Experientia*, **26**, 762 (1970).
(3) J. S. Baran and C. D. Liang, private communication.
(4) R. V. Coombs and R. P. Danna, reported at the 4th International Congress on Hormonal Steroids, 1974. We also confirmed these results.
(5) C. H. Kuo, D. Taub, and N. L. Wendler, *Angew. Chem., Int. Ed. Engl.*, **4**, 1083 (1965).
(6) D. Bar, P. Marcinal, and A. Marcinal-Lefebvre, *Bull. Soc. Chim. Fr.*, 2484 (1972).
(7) E. J. Corey, D. E. Cane, and L. Libit, *J. Am. Chem. Soc.*, **93**, 7016 (1971).
(8) We are indebted to Dr. Robert Chorvat of these Laboratories for suggesting this reaction, which was discovered independently by him.
(9) H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944).
(10) See also the intramolecular alkylation of a ketone by a quaternary ammonium salt resulting in an *i*-steroid: R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959).
(11) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).
(12) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).
(13) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).
(14) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

Claisen Rearrangement with Hydroxymethylpyridines and Hydroxymethylpyridones

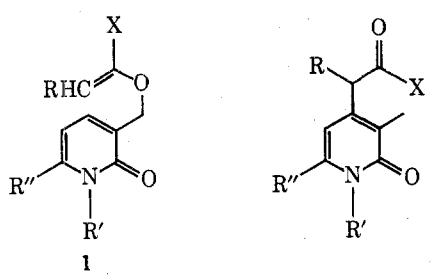
C. Richard Costin, Cary J. Morrow, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received August 19, 1975

The Claisen rearrangement has been applied to 2-, 3-, and 4-hydroxymethylpyridines, using triethyl orthoacetate to generate the intermediate ketene acetals. In all three cases, the major products resulted from normal rearrangement, with the 3-hydroxymethylpyridine being the most reactive. Similar results were obtained using amide acetals in place of ortho esters. 3-Hydroxymethyl-1-methyl-2-pyridone took a different course in reaction with orthoesters, giving only thermal rearrangement to the corresponding propionates. This reaction path became minor with amide acetals and acid catalysis, normal Claisen rearrangement predominating. These rearrangements proceed more readily than with benzyl alcohols and are synthetically useful.

In the course of work directed toward the total synthesis of camptothecin, we were led to examine the Claisen rearrangement of substituted vinyl ethers prepared from 3-hydroxymethyl-2-pyridone systems, **1**. As the products of



1

this reaction were found to be strongly dependent on the nature of R and X as well as on the presence or absence of acid catalysts, we decided to examine in some detail the general question of Claisen rearrangement in systems where the allylic double bond of the allyl vinyl ether is contained in a heterocyclic aromatic ring. In the extension of the Claisen rearrangement reported here, the allylic double bond is contained in a pyridine or pyridone nucleus. The method provides a convenient synthesis of alkyl-substituted pyridylacetates which are otherwise available by a rather tedious route.[1]

The Claisen rearrangement has been the subject of considerable research over six decades and has proved to be a highly versatile method in synthesis.[2] Most of this early work was concerned with the rearrangement of allyl phenyl ethers, and to date only a few, mostly unsuccessful, attempts have been made to extend the Claisen rearrangement to systems which have the allylic double bond incorporated in an aromatic ring. For example, benzyl vinyl ether was found[3] to rearrange to 3-phenylpropanal rather than *o*-tolylacetaldehyde. Similarly, α-benzyloxystyrene rearranges thermally to give β-phenylpropiophenone.[4] More recently, 5-benzyloxy-1,3-dimethyluracil was reported[5] not to undergo the Claisen rearrangement but to partially rearrange to 6-benzyl-1,3-dimethyl-5-hydroxyuracil. It is clear from these results that the thermal rearrangement of benzyl vinyl ethers does not proceed by a Claisen pathway, but may follow a free-radical scission–recombination mechanism[3] similar to that established for the thermal rearrangement of benzyl phenyl ether.[6]

Modification of the aromatic ring by substitution with electron-donating groups promotes the Claisen rearrangement. The thermal rearrangement of 3,5-dimethoxybenzyl isopropenyl ether provides 2,4-dimethoxy-6-methylphenylacetone and a minor amount of 3,5-dimethoxybenzylacetone.[7] Similarly, 3-methoxybenzyl isopropenyl ether gave a 1:1 mixture of the two corresponding ketones.[7]

In addition to the aromatic substituent effect, variations in the vinyl moiety also influence the course of the reaction. Whereas benzyl vinyl ether failed to give any Claisen product, the thermal rearrangement of benzyldiethyl orthoace-