compound 3, which comprised 80% of the mixture, and a second unidentified component, which was neither 1 nor 2.

A plausible mechanism for the formation of 3 involves initial condensation of 1 with ethyl acetoacetate followed by Michael addition of another molecule of ethyl acetoacetate and subsequent rearrangement. Evidence supporting this mechanism was the conversion of 2 with excess ethyl acetoacetate in piperidine–EtOH to 3 in 70% yield (NMR).

While 3 represents only one example of this synthesis, in principle it should be applicable to the preparation of other similarly substituted *o*-hydroxybenzophenones.

Experimental Section

General. Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. The infrared and ultraviolet spectra were obtained on Perkin-Elmer 521 and Perkin-Elmer 350 recording spectrometers, respectively. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Mass spectra were obtained on a Finnigan 1015 quadrupole mass spectrometer. All compounds were analyzed for C and H and were within ±0.4% of the theoretical value.

3-(4-Oxo-4*H*-1-benzopyran-3-yl)-2-(1-oxoethyl)-2-propenoic Acid Ethyl Ester (2). Ethyl acetoacetate (13.0 g, 0.1 mol), NaOAc (8.2 g, 0.1 mol), and 1 (17.4 g, 0.1 mol) were heated and stirred in Ac_2O (50 ml) on the steam bath for 2 hr and diluted with H_2O (300 ml); the resulting tan solid was recrystallized from Et_2O to give 10.00 g of 2, mp 120–122°. Further concentration gave an additional 8.0 g, mp 95–100°. The first crop when recrystallized ($EtOH–H_2O$) gave tan needles of 2: mp 120–122°; ir (KBr) 1705, 1680, and 1650 cm^{-1} (ester, α,β-unsaturated ketone, and chromone carbonyl); NMR[3,5] ($CDCl_3$) δ 8.35 (s, 1 H, C_2 H), 8.18 (dd, 1, J = 7.0 Hz, benzene H_5), 7.28–8.05 (m, 4 H, benzene and olefinic), 4.3 (q, 2 H, J = 7.0 Hz, CH_2), 2 5 (s, 3 H, CH_3), 1.35 (t, 3 H, J = 7.0 Hz, CH_3); uv max (95% EtOH) 220 nm (ϵ 17 900). Anal. C, H.

5-(2-Hydroxybenzoyl)-2-methylbenzene-1,3-dicarboxylic Acid Diethyl Ester (3). To a stirred solution of 1 (26.2 g, 0.15 mol) and ethyl acetoacetate (35.4 g, 0.25 mol) in EtOH at 0–20° was added piperidine (10.0 ml). The resulting red solution was allowed to warm to room temperature over several hours, neutralized with HOAc, poured onto ice–H_2O (1 l.), and extracted with Et_2O (1 l.). The Et_2O layer was then washed with H_2O, 5% $NaHCO_3$, and brine and dried ($MgSO_4$). Concentration in vacuo gave a red oil. Boiling the oil with hexane followed by decantation gave, after cooling, 4.0 g of 3: mp 55–55.5°; ir (KBr) 1730 and 1630 cm^{-1} (ester and ketone carbonyl); NMR ($CDCl_3$) δ 8.3 (s, 2 H, H_4 and H_6), 7.8–6.8 (m, 4 H, aromatic) 4.5 (q, 4 H, J = 7.0 Hz, 2-CH_2), 2.8 (s, 3 H, CH_3), 1.35 (t, 6 H, J = 7.0 Hz, 2-CH_3); uv max 258 nm (ϵ 12 100); mass spectrum (70 eV) *m/e* 356 (P^+). Anal. C, H.

The residual red oil showed no trace of 3 by TLC (silica gel, Et_2O–hexane, 1:1). Attempts to crystallize it were unsuccessful. After prolonged standing it solidified to a waxy yellow solid yielding 18.5 g. GC analysis (2-ft 1% OV-22, 190°) showed that 80% of 3 was present.

3-[(4-Oxo-4*H*-1-benzopyran-3-yl)-methylene]-2,4-pentanedione (4). 2,4-Pentanedione (10.05 g, 0.1 mol), 1 (17.4 g, 0.1 mol), and NaOAc (8.2 g, 0.1 mol) were heated and stirred in Ac_2O (65.0 ml) for 3 h on the steam bath. The mixture was cooled and diluted with a two-phase $CH_2Cl_2–H_2O$ mixture. The CH_2Cl_2 was separated, extracted with saturated $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration in vacuo yielded a tan semisolid, which when recrystallized (EtOH, 300 ml) gave 5, 15.7 g (60%), mp 168–170°. Anal. C, H.

β-(Oxo-α-[(4-oxo-4*H*-1-benzopyran-3-yl)-methylene]benzenepropanoic Acid Ethyl Ester (5). Ethyl benzoylacetate (9.7 g, 0.05 mol), 1 (8.7 g, 0.05 mol), and NaOAc (4.2 g, 0.05 mol) were heated and stirred in Ac_2O (50 ml) for 4 h on the steam bath. Dilution with a two-phase $CH_2Cl_2–H_2O$ solution and separation of the CH_2Cl_2 followed by drying ($MgSO_4$), filtration, and concentration in vacuo yielded an oily residue. Recrystallization (CH_2Cl_2–heptane) gave 5, 5.0 g (30%), mp 111–112°. Anal. C, H.

Acknowledgment. The authors wish to thank Dr. Churby Clowers and Mr. Mike Gordon and associates of our analytical department for the analytical data. Thanks are also expressed to Dr. Fred Kaplan of the University of Cincinnati for spectral consultation.

Registry No.—1, 17422-74-1; 2, 57443-89-7; 3, 57443-90-0; 4, 57443-91-1; 5, 57443-92-2; ethyl acetoacetate, 141-97-9; 2,4-pentanedione, 123-54-6; ethyl benzoylacetate, 94-02-0.

References and Notes

(1) H. Harnisch, *Justus Liebigs Ann. Chem.*, **765**, 8 (1972).
(2) A. Nohara, T. Umetani, and Y. Sanno, *Tetrahedron Lett.*, 1995 (1973).
(3) A. Nohara, H. Kunki, T. Saijo, K. Ukawa, T. Murata, M. Kanno, and Y. Sonno, *J. Med. Chem.*, **18**, 34 (1975).
(4) A. Nohara, T. Ishiguro, and Y. Sonno, *Tetrahedron Lett.*, 1183 (1974).
(5) H. Cairns, D. Hunter, J. King, and N. H. Rogers, *Tetrahedron*, **30**, 79 (1974).

Total Synthesis of Steroids. XI.[1] Synthesis of Optically Active 11-Ketoestrane Derivatives

B. Aweryn, A. R. Daniewski, and M. Kocór*

Institute of Organic Chemistry, Polish Academy of Sciences, 00-961 Warszawa, Poland

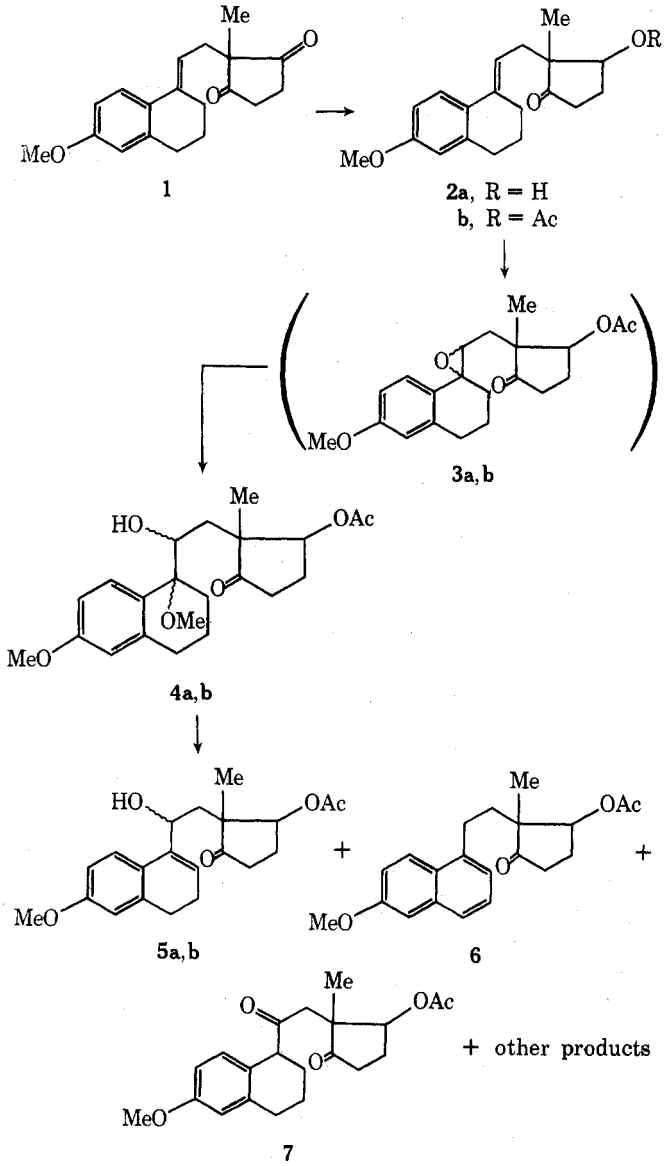
Received August 12, 1975

In addition to our work on the total synthesis of racemic 11-oxidized estrogens published recently,[2,3] we would like to report the total synthesis of optically active new estrane derivatives, which was based on the method applied to the synthesis of *rac*-14α-hydroxy-3-methoxy-8α-estra-1,3,5(10)-triene-11,17-dione.[2]

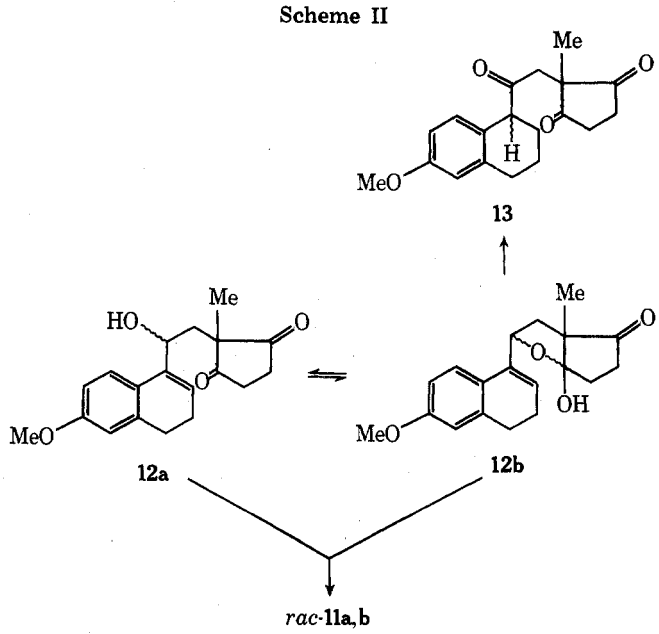
The Torgovs secodione 1[4] can be transformed easily by microbial reduction[5] to the secolone **2a**. The latter has been used as the starting material in the present synthesis. The acetate of the secolone **2b** obtained by standard method was subjected to the action of *m*-chloroperbenzoic acid (MCPBA) under the same conditions as we described earlier[6] for the secodione 1. Surprisingly, the reaction resulted in so many products that their separation was not rewarding, although some of them have been isolated and identified (**5a,b**, **6**, and **7**). In order to avoid the undesirable reactions we tried to carry out the oxidation in the presence of weak alkali and to vary the reaction solvent. The best results were obtained with methanol as solvent and pyridine *N*-oxide as weak base. Although it was not possible to prevent oxirane ring cleavage, the number of reaction products under these conditions was limited to only two, i.e., the methoxy alcohols **4a** and **4b**, obtained in ca. 90% yield. They could be separated very easily owing to their different polarities and they were reasonable stable. We suppose that they are formed by the cleavage of epoxides **3a** and **3b** with methyl alcohol; however, we were not able to assign an absolute configuration on the basis of our spectroanalytical data. One can conclude from the model studies that there is no special steric preference in formation of either of them, which also explains the 1:1 ratio of formation. These two products (**4a,b**) (Scheme I) proved to be very useful for further synthesis. Each of them undergoes in the presence of weak acid (acetic acid) in chloroform solution a methanol elimination to yield the allylic alcohols **5a** and **5b**, respectively; the more polar **4b** looses methanol more easily and produces a small amount of **7**, as by-product; the elimination of methanol from the less polar **4a** is not accompanied by any side reaction. The elimination reaction can be also conducted on **4a,b** mixture; however, the separation of the allylic alcohols is very difficult. Also in the case of the alcohols **5a** and **5b** we were not able to ascribe an absolute configuration to either of them.

Under the influence of strong acids at elevated temperature in benzene solution **5a** and **5b** undergo a rearrange-

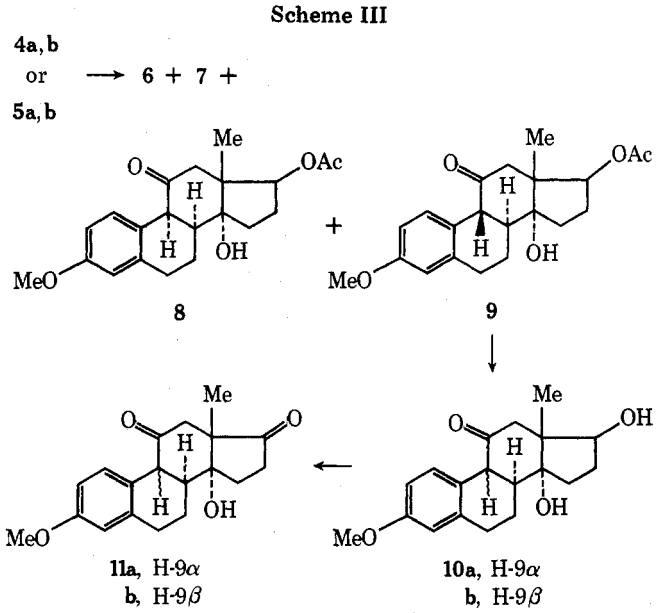
Scheme I



Scheme II



Scheme III



ment to a mixture of 6 and 7 (ratio ca. 1:1, checked by TLC). The racemic alcohols **12a,b** under similar conditions gave only the 17-keto analogue of 7, i.e., the triketone **13** (Scheme II). The cyclization of **4a,b** or **5a,b** with Meerwein reagent, i.e., $Et_3O^+BF_4^-$, gives four products: the desired tetracyclic compounds 8 and 9 and the two rearrangement products 6 and 7 in a ratio 3:5:5:5 (Scheme III). The yield of the tetracyclic compounds 8 and 9 is ca. 40%, i.e., only half of that obtained by the cyclization of **12a,b** in our previous work.[2] Apparently the allylic alcohols **5a** and **5b** underwent more easily the side reactions leading to 6 and 7 as compared with the racemic compounds **12a,b.** The mechanism of the cyclization is most probably the same as proposed before; the first step is the formation of 11-ethyl ether followed by nucleophilic attack of the double bond on the keto group, accompanied by proton elimination from C-11 and subsequent hydrolysis of the 11-enol ether grouping. The tetracyclic compound 9 has a trans B/C ring junction, which follows from the relatively large coupling constant $J_{9,8}$ = 10 Hz, whereas in the other isomer 8 the signals of H-9 and H-8 are coupled by J = 5 Hz (cis B/C junction). Compounds 8 and 9 can be interconverted in the presence of acids.

In order to prove the stereochemistry of all chiral centers in 8 or 9 we transformed them in a two-step reaction sequence (hydrolysis of the acetoxy group and Jones oxidation[7]) to diketone **11b.** The same diketone was obtained as a racemate by us before[2] and all uv, ir (in $CHCl_3$), and ^1H NMR data of the latter were in good agreement with the new optically active tetracyclic diketone **11b.** Since the absolute stereochemistry at the C-13 chiral center for the starting material **2a** is known and the reaction sequences described above do not involve any racemization reaction at this particular carbon atom, the absolute configuration of all new compounds must be as presented in all schemes.

Further transformations of 11 (in racemic form) have been reported earlier;[2,3] so the present work describes a facile, stereospecific synthesis of 11-ketoestrane derivatives from a known and easily accessible substrate **2a.**

Experimental Section[8]

17β-Acetoxy-3-methoxy-8,14-secoestra-1,3,5(10),9(11)-tetraen-14-one (2b). The secolone **2a** (5.1 g, 17.0 mmol) was acetylated with acetic anhydride–pyridine under standard conditions, yielding 5.7 g of **2b** (98%): ir 1740 and 1735 cm^{-1}; ^1H NMR 1.00 (s, 3, CH_3), 1.97 (s, 3, $OCOCH_3$), 3.70 (s, 3, OCH_3), 5.17 (t, 1, H-17), 5.64 (t, 1, H-11), 6.50 (m, 2, H-2 and H-4), 7.32 ppm (d, 1, $J_{1,2}$ = 10 Hz, H-1).

17β-Acetoxy-3,9ξ-dimethoxy-8,14-secoestra-1,3,5(10)-trien-11ξ-ol-14-one (4a and 4b). To a methanol (120 ml) solution of **2b** (5.7 g, 16.6 mmol) and pyridine *N*-oxide (9.51 g, 100 mmol), 88% MCPBA (6.55 g, 38.0 mmol) was added at room temperature. The reaction mixture was left for 3 h. One-half of the methanol was removed in vacuo at room temperature and the excess of MCPBA was destroyed with the 10% aqueous solution of Na_2SO_3. The products **4a,b** were extracted with 300 ml of benzene, and the benzene layer was shaken with saturated sodium hydrogen carbonate, dried over anhydrous Na_2SO_4, and evaporated in vacuo, giving 6.00 g (92.5%) of the oily mixture of **4a** and **4b**. This mixture (0.200 g) was separated by preparative TLC with benzene and acetone (9:1) as eluents yielding the oily, less polar **4a** (0.090 g): $[\alpha]D$ −55.4° (*c* 2.25, $CHCl_3$); uv max (95% EtOH) 229, 275, and 282 nm; ir 3500, 1740, and 1730 cm^{-1}; ^1H NMR 0.95 (s, 3, CH_3), 1.98 (s, 3, $OCOCH_3$), 3.09 (s, 3, OCH_3, at C-9), 3.72 (s, 3, OCH_3 at C-3), 4.78 (t, 1, H-17), 6.42 (d, 1, $J_{4,2}$ = 3 Hz, H-4), 6.65 (dd, 1, $J_{2,4}$ = 3, $J_{2,1}$ = 8 Hz, H-2), 7.45 ppm (d, 1, $J_{1,2}$ = 8 Hz, H-1).

The oily, more polar **4b** (0.095 g): $[\alpha]D$ +25.2° (*c* 2.62, $CHCl_3$); uv max (95% EtOH) 229, 275, and 282 nm; ir 3480, 1740, and 1720 cm^{-1}; ^1H NMR 0.91 (s, 3, CH_3), 1.95 (s, 3, $OCOCH_3$), 2.98 (s, 3, OCH_3 at C-9), 3.71 (s, 3, OCH_3 at C-3), 4.85 (t, 1, H-17), 6.42 (d, 1, $J_{4,2}$ = 3 Hz, H-4), 6.65 ppm (dd, 1, $J_{2,4}$ = 3, $J_{2,1}$ = 8 Hz, H-2).

17β-Acetoxy-11ξ-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),8-tetraen-14-one (5a and 5b). A chloroform solution of **4a** (0.12 g, 0.31 mmol) was refluxed with 1.5 ml of glacial acetic acid, and after 4 h worked up in the standard manner, giving 0.10 g (91%) of the oily, less polar **5a** which was purified by preparative TLC using benzene–acetone (9:1) as eluent. The product was crystallized from Et_2O, yielding 0.08 g of **5a** (72%): mp 110–113°; $[\alpha]D$ +24.3° (*c* 0.944, $CHCl_3$); uv max (95% EtOH) 219, 226, and 272 nm; ir 3450, 1740, and 1720 cm^{-1}; ^1H NMR 0.91 (s, 3, CH_3), 2.02 (s, 3, $OCOCH_3$), 3.75 (s, 3, OCH_3), 5.08 (m, 2, H-11 and H-17), 6.06 ppm (t, 1, H-8); *m/e* 358.

The same procedure was used for transformation of **4b** into **5b** and the crude product **5b** was separated by preparative TLC from the side product **7**, yielding 72% of **5b** and 14% of **7**.

5b: $[\alpha]D$ −0.136°, $[\alpha]_{578}$ −0.498°, $[\alpha]_{546}$ −0.908°, $[\alpha]_{436}$ −4.84° (*c* 2.21, $CHCl_3$); uv max (95% EtOH) 217, 226, and 272 nm; ir 3480, 1740, and 1720 cm^{-1}; ^1H NMR 1.05 (s, 3, CH_3), 1.98 (s, 3, $OCOCH_3$), 3.73 (s, 3, OCH_3), 4.98 (m, 2, H-11 and H-17), 6.01 ppm (t, 1, H-8); *m/e* 358.

17β-Acetoxy-3-methoxy-8,14-secoestra-1,3,5(10),6,8-pentaen-14-one (6) and 17β-Acetoxy-3-methoxy-8,14-secoestra-1,3,5(10)-triene-11,14-dione (7). A solution of **5a** (0.200 g, 0.56 mmol) in 20 ml of benzene was refluxed with *p*-TsOH (catalytic amount) for about 1 h. When **5a** completely disappeared the reaction mixture was worked up in the standard manner, yielding the mixture of **6** and **7**, which were separated by preparative TLC. The plates were developed five times with hexane–ethyl acetate (5:1) giving **6** and **7**.

6 (0.085 g, 44%): $[\alpha]D$ −13.0° (*c* 1.68, $CHCl_3$); uv max (95% EtOH) 230, 256, 278, 288, 317, 326, and 332 nm; ir 1748 cm^{-1}; ^1H NMR 1.05 (s, 3, CH_3), 2.05 (s, 3, $OCOCH_3$), 3.84 (s, 3, OCH_3), 5.37 (t, 1, H-17), 7.1 (m, 4, H in ring B), 7.42 (d, 1, H-2), 7.78 ppm (d, 1, $J_{1,2}$ = 9 Hz, H-1); *m/e* 340.

7 (0.090 g, 45%): $[\alpha]D$ −43.6° (*c* 2.51, $CHCl_3$); uv max (95% EtOH) 205, 224, 278, and 285 nm; ir 1750 and 1735 cm^{-1}; ^1H NMR 0.78 (s, 3, CH_3), 1.99 (s, 3, $OCOCH_3$), 3.70 (s, 3, OCH_3), 5.35 ppm (m, 1, H-17); *m/e* 358.

17β-Acetoxy-3-methoxy-8α-estra-1,3,5(10)-trien-14α-ol-11-one (8) and 17β-Acetoxy-3-methoxy-8α,9β-estra-1,3,5(10)-trien-14α-ol-11-one (9). To a solution of the mixture **4a,b** (5.00 g, 12.8 mmol) in 2.5 l. of acetone, $Et_3O^+BF_4^-$ (35 g, 184 mmol) was added in small portions and the solution was left overnight at room temperature. The solution was then refluxed for 45 min, the solvent was removed in vacuo, and the residue was dissolved in 250 ml of benzene, shaken with saturated sodium hydrogen carbonate, and dried over anhydrous Na_2SO_4. After evaporation of the solvents in vacuo the residue was washed with pentane (3 × 15 ml) and then hexane (3 × 15 ml) in order to remove the acetone condensation products. The remaining oil was chromatographed on 500 g of silica gel with benzene and acetone as eluents giving the mixture of both desired tetracyclic compounds **8** and **9** and the mixture of two rearrangement products **6** and **7**. The tetracyclic compounds **8** and **9** were separated by preparative TLC using hexane–ethyl acetate (2:1) as eluents. Elution from the plates with methanol gave **8** and **9**.

8 (0.70 g, 15%): mp 147–152° (from ethyl ether); $[\alpha]D$ +26.2° (*c* 1.197, $CHCl_3$); uv max (95% EtOH) 221 nm (ε 9200), 229 (6900), 278 (1610), and 285 (1430); ir 3550, 1740, and 1710 cm^{-1}; ^1H NMR 1.10 (s, 3, CH_3), 2.10 (s, 3, $OCOCH_3$), 3.75 (s, 3, OCH_3), 3.87 (d, 1, $J_{9,8}$ = 5 Hz, H-9), 4.88 (d, 1, H-17), 6.7 ppm (m, 3, H-1, H-2 and H-4).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.38; H, 7.43; *m/e* 358.

9 (1.25 g, 27%): mp 143–146° (from ethyl ether); $[\alpha]D$ −133.4° (*c* 1.140, $CHCl_3$); uv max (95% EtOH) 221 nm (ε 8400), 227 (7710), 278 (1690), and 285 (1600); ir 3450, 1735, and 1700 cm^{-1}; ^1H NMR 1.12 (s, 3, CH_3), 2.00 (s, 3, $OCOCH_3$), 3.72 (s, 3, OCH_3), 3.95 (d, 1, $J_{9,8}$ = 10 Hz, H-9), 4.65 (t, 1, H-17), 6.58 (m, 2, H-2 and H-4), 7.05 ppm (d, 1, H-1).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.49; H, 7.29; *m/e* 358.

The products **6** and **7** were separated on the preparative plates with hexane–ethyl acetate (5:1) as eluents, yielding 1.26 g (29%) of **6** and 1.25 g (27%) of **7**.

14α,17β-Dihydroxy-3-methoxy-8α-estra-1,3,5(10)-trien-11-one (10a) and 14α,17β-Dihydroxy-3-methoxy-8α,9β-estra-1,3,5(10)-trien-11-one (10b). To a methanol solution of the mixture **8** and **9** (0.150 g, 0.42 mmol) a methanol (2 ml) solution of KOH (0.023 g, 0.42 mmol) was added and left for 4 h at room temperature. The solution was then acidified with acetic acid, the solvent was evaporated in vacuo, and the products were extracted with chloroform. The extract was neutralized, dried over anhydrous Na_2SO_4, and evaporated in vacuo. After chromatography on one preparative plate with benzene–acetone (85:15) as developing solvent we obtained **10a** and **10b**.

10a: 0.011 g (8.3%); mp 167–172° (from ethyl ether); $[\alpha]D$ +37.4° (*c* 0.78, $CHCl_3$); uv max (95% EtOH) 223, 279, and 285 nm; ir 3420 and 1705 cm^{-1}; *m/e* 316.

10b: 0.105 g (79%); $[\alpha]D$ −105° (*c* 1.34, $CHCl_3$); uv max (95% EtOH) 227, 278, and 285 nm; ir 3500 and 1705 cm^{-1}; ^1H NMR 1.05 (s, 3, CH_3), 3.72 (s, 3, OCH_3), 4.02 (d, 1, $J_{9,8}$ = 11 Hz, H-9), 6.52 (d, 1, $J_{4,2}$ = 3 Hz, H-4), 6.65 (dd, 1, $J_{2,1}$ = 8.5, $J_{2,4}$ = 3 Hz, H-2), 6.97 ppm (d, 1, $J_{1,2}$ = 8.5 Hz, H-1); *m/e* 316.

The same procedure was used for the hydrolysis of **8** and **9** separately and in every case a mixture of **10a** and **10b** was obtained.

14α-Hydroxy-3-methoxy-8α,9β-estra-1,3,5(10)-triene-11,17-dione (11b). Oxidation of 0.050 g (0.158 mmol) of the mixture **10a** and **10b** with Jones reagent[7] under standard conditions yielded 0.037 g (74% yield) of the mixture **11a** and **11b**. The crystallization from ethyl ether yielded 0.020 g of **11b**: mp 154–156°; $[\alpha]D$ −116.5° (*c* 1.02, $CHCl_3$); uv max (95% EtOH) 276 and 283 nm; ir ($CHCl_3$) 3500, 1740, and 1720 cm^{-1}; ^1H NMR 1.18 (s, 3, CH_3), 3.73 (s, 3, OCH_3), 4.05 (d, 1, $J_{9,8}$ = 12 Hz, H-9), 6.53 (d, 1, $J_{4,2}$ = 2.5 Hz, H-4), 6.68 (dd, 1, $J_{2,1}$ = 8.7, $J_{2,4}$ = 2.5 Hz, H-2), 6.95 ppm (d, 1, $J_{1,2}$ = 8.7 Hz, H-1). Uv, ir ($CHCl_3$), and ^1H NMR data of the latter were in good agreement with the physical data obtained for the same racemic diketone.[2]

Conversion of the Diketone 7 into the Triketone 13. To a methanol solution of **7** (0.030 g, 0.084 mmol) a methanol solution of KOH (0.005 g, 0.09 mmol) was added and left for 2 h at room temperature. Standard work-up gave the crude product, which was oxidized with Jones reagent[7] under standard conditions yielding 0.017 g (65%) of the triketone **13**. The spectroanalytical data for this compound were the same as for the earlier obtained racemic triketone **13**.[6]

Acknowledgment. We are indebted to our technical assistant Mr. Jacek Kinowski for his skillful help in conducting some experiments.

Registry No.—**2a**, 6563-82-2; **2b**, 57549-39-0; **4a**, 57474-04-1; **5a**, 57474-05-2; **5b**, 57525-82-3; **6**, 57474-06-3; **7**, 57474-07-4; **8**, 57474-08-5; **9**, 57525-83-4; **10a**, 57474-09-6; **10b**, 57525-84-5; **11b**, 57525-85-6; acetic anhydride, 108-24-7.

References and Notes

(1) Part X: A. R. Daniewski and M. Kocór, *J. Org. Chem.*, **40**, 3136 (1975).
(2) A. R. Daniewski, M. Guzewska, and M. Kocór, *J. Org. Chem.*, **39**, 2193 (1974).
(3) A. R. Daniewski, *J. Org. Chem.*, **40**, 3124, 3127 (1975).
(4) S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk SSSR*, **127**, 553 (1959); S. N. Ananchenko and I. V. Torgov, *Tetrahedron Lett.*, 1553 (1963); S. N. Ananchenko, V. Ye. Limanov, V. N. Leonov, V. N. Rzheznikov, and I. V. Torgov, *Tetrahedron*, **18**, 1355 (1962).
(5) H. Gibian, K. Kieslich, H. J. Koch, H. Kosmol, C. Rufer, E. Schroder, and R. Vossing, *Tetrahedron Lett.*, **No. 21**, 2321 (1966).
(6) A. R. Daniewski, M. Guzewska, M. Kocór, and J. S. Baran, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **19**, 313 (1971).

(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 142.
(8) All melting points were measured on a micro hot plate, and are not corrected. The ^{1}H NMR spectra were recorded with a JEOL 100-MHz spectrometer in parts per million (δ) in $CDCl_3$ solution with Me_4Si as an internal standard. The ir spectra were obtained with a Unicam Sp 200 spectrophotometer. All the reactions were controlled by thin layer chromatography. The uv spectra were measured in 95% EtOH. The microanalyses were performed in our microanalytical laboratory (head Z. Celler, M.S.). Specific rotations were determined on a Perkin-Elmer 141 polarimeter.

Stereochemistry of Bockmühl's Synthesis of Methadone

Charles J. Barnett* and Jeffrey C. Smirz

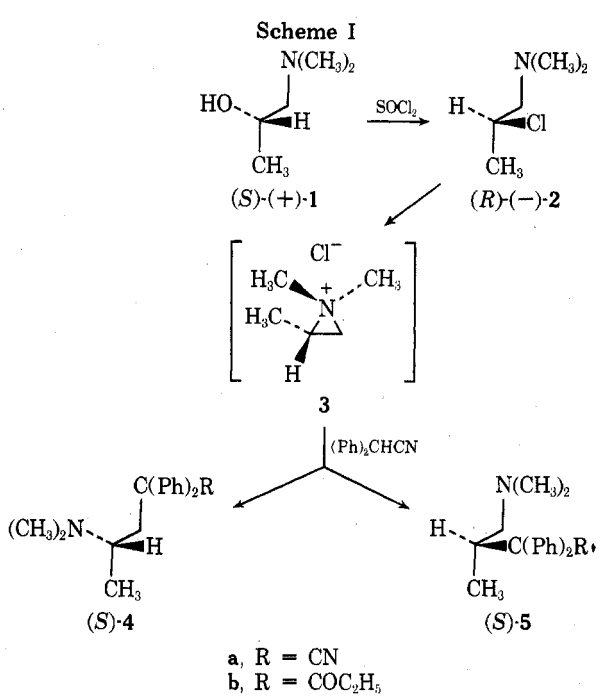
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received June 27, 1975

Methadone (**4b**) was first prepared in racemic form by Bockmühl and Erhardt[1] according to the approach outlined in Scheme I. The chloro amine **2** obtained from chlorination of (±)-1-dimethylamino-2-propanol (**1**) with thionyl chloride was treated with sodium diphenylacetonitrile to give a mixture of aminonitriles **4a** and **5a**. The aziridinium ion intermediate **3** has been proposed to account for the rearranged product **4a**.[2] Grignard reaction of **4a** with ethylmagnesium bromide followed by acid hydrolysis afforded methadone (**4b**). Similar treatment of **5a** gave rise to isomethadone (**5b**). More recently, amino alcohol (+)-**1** has been obtained from ethyl L-(−)-lactate (aminolysis, reduction) and thus assigned the (*S*)-(+) configuration.[3] The absolute configurations (shown in Scheme I) of the aminonitriles **4a**[4] and **5a**[5] and thus methadone and isomethadone have also been established. We have found that the conversion of **1** to **4a** and **5a** via **2** is stereospecific and proceeds with the stereochemistry as depicted in Scheme I.

Treatment of (*S*)-(+)-**1** with thionyl chloride in chloroform by the method of Schultz and Sprague[2] afforded (−)-1-dimethylamino-2-chloropropane (**2**) hydrochloride, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O), which was converted to the free base, $[\alpha]^{25}D$ −43.9° (*c* 2.55, $CHCl_3$), and treated with sodium diphenylacetonitrile in toluene essentially by the original procedure.[1] The mixture of aminonitriles thus obtained was separated by preparative thin layer chromatography on silica gel, affording substantially optically pure (*S*)-(+) ≡ L-(+)-**4a** and (*S*)-(+) ≡ D-(+)-**5a** by comparison of optical rotations with the literature values (see Experimental Section).

Scheme I



a, R = CN
b, R = COC_2H_5

The opposite configurations and identical optical purity of the nitriles **4a** and **5a** constitute compelling evidence that the aziridinium ion pathway is the exclusive mode of product formation in the alkylation step. It follows that unrearranged **5a** was formed with net retention of configuration (double inversion) while **4a** has the inverted configuration since the opening of the aziridinium ion **3** at the unsubstituted carbon would not alter the asymmetric center.[6] Thus the chloride **2** must have the (*R*)-(−) configuration and must have been obtained from **1** with inversion.

The present results clearly exclude the formation of an intermediate aziridine during chlorination of **1** and are best rationalized by SN2 displacement of the chlorosulfite ester of **1** hydrochloride. The high local concentration of chloride ion enforced by the internal ammonium ion of **1** should enhance the SN2 displacement process and may have been a factor in the high degree of stereospecificity observed in this case.[7]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were measured on a Rudolph polarimeter having a readability of ±0.01°, using a 1-dm tube. ^{1}H NMR spectra were obtained with Varian A-60 and T-60 instruments.

(−)-1-Dimethylamino-2-chloropropane Hydrochloride (2). To a solution of 3.77 g (0.0366 mol) of (*S*)-(+)-1-dimethylamino-2-propanol (**1**),[3] $[\alpha]^{25}D$ +24° (*c* 2.17, EtOH), in 10 ml of chloroform stirred and cooled in an ice–salt bath was slowly added 5.72 g (0.048 mol) of freshly distilled thionyl chloride in 2 ml of chloroform. When addition was complete a precipitate formed. The flask was allowed to warm to room temperature over 30 min, then heated to reflux for 30 min. The precipitated material redissolved on heating but the product crystallized from the boiling solvent shortly thereafter. The cooled mixture was diluted with ether and filtered. The crude product, 5.5 g (95%), was recrystallized from 2-propanol, giving 3.73 g (64%) of (−)-1-dimethylamino-2-chloropropane hydrochloride (**2**), mp 192–193°, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O) [lit.[2] mp for (±) hydrochloride 185–186°].

(−)-1-Dimethylamino-2-chloropropane (2). To a solution of 2.2 g of (−)-**2** hydrochloride in an equal volume of water was added 1.5 ml of 20% sodium hydroxide solution until the mixture was distinctly alkaline to pH paper. The free amine was extracted with two 5-ml portions of ether. The combined ether layers were dried over anhydrous potassium carbonate and distilled to give 0.8 g of (−)-1-dimethylamino-2-chloropropane (**2**): bp 115° [lit.[2] bp for (±) 62–63° (100–110 mmHg)]; $[\alpha]^{25}D$ −43.9° (*c* 2.55 $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.5 (d, 3, J = 6 Hz, CCH_3), 2.28 (s, 6, NCH_3), 2.50 (m, 2), 4.07 (m, 1), identical with an authentic racemic sample.

Alkylation of Diphenylacetonitrile with (−)-2. A 1.0-g sample of the hydrochloride salt of (−)-**2**, $[\alpha]^{25}D$ −65° (*c* 2.01, H_2O), was converted to the base as previously described and treated with sodium diphenylacetonitrile by the Bockmühl procedure.[1] A 0.52-g portion of the crude mixture of aminonitriles was separated by preparative thin layer chromatography (silica gel, E. Merck, benzene–methanol 8:2) affording 145.7 mg of (*S*)-(+)-**4a**, recrystallized from petroleum ether, mp 100–101°, $[\alpha]^{25}D$ +49° (*c* 0.68, absolute EtOH) [lit.[8] mp 100–101°, $[\alpha]^{25}D$ +50° (*c* 1.5, absolute EtOH)], and 156.5 mg of (*S*)-(+)-**5a**, $[\alpha]^{25}D$ +70° (*c* 0.82, 95% EtOH) [lit.[8] $[\alpha]^{25}D$ +70° (*c* 1.5, USP EtOH].

Registry No.—(*S*)-(+)-**1**, 53636-15-0; (*R*)-(−)-**2**, 57496-00-1; (*R*)-(−)-**2** HCl, 57496-01-2; (*S*)-(+)-**4a**, 7576-08-1; (*S*)-(+)-**5a**, 6134-96-9; diphenylacetonitrile, 86-29-3.

References and Notes

(1) M. Bockmühl and G. Ehrhart, *Justus Liebigs Ann. Chem.*, **561**, 52 (1949).
(2) E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948).