Notes

Total Synthesis of Steroids. VIII. Synthesis of Optically Active 19-Norsteroids Oxidized in Position 11

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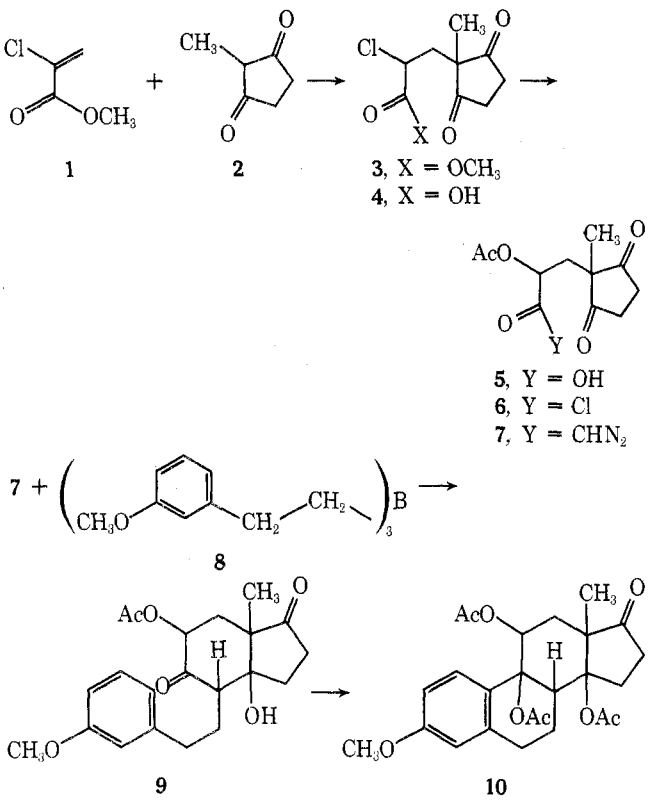
The total synthesis of 11-oxidized *rac*-19-norsteroids was recently described.[1-3] One of the substrates in that work was *rac*-2-methyl-2-(β-acetoxy-β-carboxyethyl)cyclopentane-1,3-dione (**5**) (Scheme I). In the present paper we report resolution of the compound **5** into enantiomers by means of α-phenylethylamine as a resolving agent. When the synthesis was carried out with optically pure acid **5**, optically pure steroids were obtained.

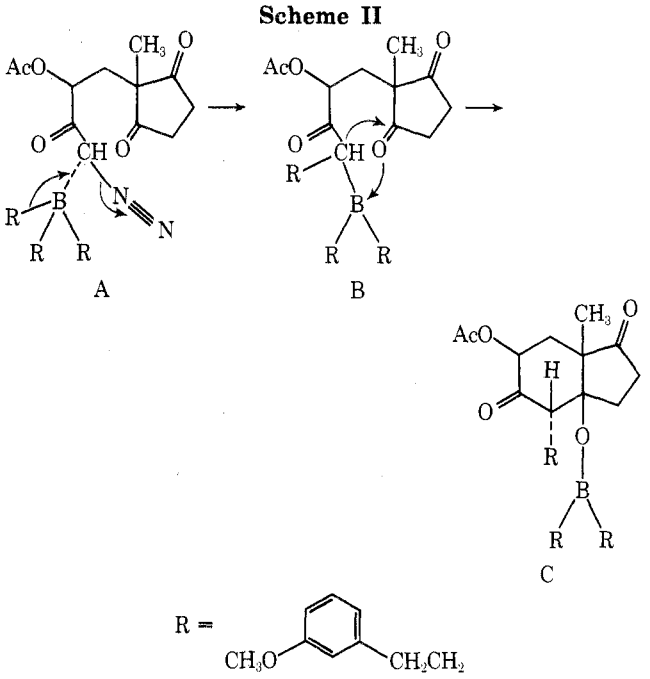
Scheme I



In the case of racemic acid **5** the seco compound **9** was obtained in crystalline form but when the starting acid **5** was optically active, the seco compound was an oil. The optical purity of triacetate **10** was determined by examination of the NMR spectrum of its mixture with tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium. In the NMR spectrum of the racemic triacetate **10** containing the chiral europium complex, the signals of protons of the angular methyl group as well as those of the two acetoxy groups appeared as doublets. In the case of optically active triacetate **10** the corresponding signals in the NMR spectrum of **10** containing the chiral europium complex were shifted but appeared as singlets. The optical purity of the triacetate **10** was at least 95%, which indicates that the asymmetric induction of the creation of new chiral centers was also 95%. The (−) diazo ketone **7** and then the (+) triacetate **10** were obtained from the (−) acid **5**. The (+) triacetate **10** was transformed by known[2] reactions to (+)-3-methoxy-14β-estra-1,3,5(10)-trien-17-one, the specific rotation of which was identical with the reported value.[4] Since the structure of triacetate **10** is known, it was possible to ascertain that the acid **5** with negative specific rotation has the *S* configuration and is a precursor of steroids with the natural configuration at the chiral centers.

In addition to the preceding papers[1-3] we would like to suggest a reaction mechanism for the reaction of diazo ketone **7** with the boron compound **8** which leads to tricyclic secodione **9**. As the first step we propose the formation of complex A, which rearranges stereospecifically with elimination of molecular nitrogen to intermediate B. (Scheme II). The latter undergoes cyclization to the next intermediate C, which under hydrolytic conditions is converted to secodione **9**. The boron compound **8** attacks diazo ketone **7** only from the less hindered side (opposite to the acetoxy group); thus a new chiral center is formed at the 8 carbon atom of compound **9**. The next step is most probably a concerted and stereospecific 1,2 shift of one phenylethyl group, accompanied by nitrogen elimination. The intermediate B thus formed undergoes further rearrangement owing to complexing of boron by the carbonyl oxygen, which is the driving force for the cyclization to intermediate C in a stereospecific manner.

Scheme II



Experimental Section

2-Methyl-2-(β-carbomethoxy-β-chloroethyl)cyclopentane-1,3-dione[6] (3). A solution of 2-methylcyclopentane-1,3-dione (**2**, 16.8 g, 0.15 mol) and 2.0 g of KOH in 150 ml of methanol and methyl α-chloroacrylate (**1**, 12 g, 0.1 mol) was refluxed for 12 hr under nitrogen. Methanol was distilled off, and 100 ml of benzene was added to the residue. The unreacted 2-methylcyclopentane-

1,3-dione (2, 6 g) was filtered off and the filtrate after distillation in vacuo afforded 18.6 g (80%) of 3: bp 100° (0.14 mmHg); mp 48–49.5°; NMR δ 1.17 (s, 3, CH_3), 2.36 (d, 2, CH_2), 2.77 (s, 4, CH_2CH_2), 3.67 (s, 3, CH_3O), 4.30 ppm (t, 1, CHCl).

Anal. Calcd for $C_{10}H_{13}ClO_4$: C, 51.65; H, 5.60. Found: C, 51.49; H, 5.61.

2-Methyl-2-(β-carboxy-β-chloroethyl)cyclopentane-1,3-dione[6] (4). A mixture of compound 3, (23.3 g, 0.1 mol) and 50 ml of concentrated hydrochloric acid was heated under reflux for 0.5 hr and then 10 ml of the acid was distilled off. Compound 4 crystallized out upon cooling; it was filtered and washed with 20 ml of ice-water. The product was dried in air: yield 17.5 g (80%); mp 117–119°; NMR δ 1.15 (s, 3, CH_3), 2.46 (d, 2, CH_2), 2.80 (s, 4, CH_2CH_2), 4.40 ppm (t, 1, CHCl).

Anal. Calcd for $C_9H_{11}ClO_4$: C, 49.6; H, 5.04. Found: C, 50.08; H, 5.09.

2-Methyl-2-(β-carboxy-β-acetoxyethyl)cyclopentane-1,3-dione (5). Compound 4 (21.85 g, 0.1 mol) was dissolved in an aqueous solution of 16.8 g (0.20 mol) of sodium bicarbonate and the mixture was refluxed for about 2 hr until all the substrate disappeared (checked by TLC). Then the solution was evaporated and the residue was treated with 60 ml of acetic acid and 15 ml of acetic anhydride. The mixture was refluxed for about 0.4 hr to convert the hydroxy acid completely into the acetoxy acid 5. Then the acetic acid was almost completely removed by distillation under reduced pressure and the residue was treated with 100 ml of acetone and 10 ml of concentrated hydrochloric acid. Sodium chloride was filtered off and the acetone was evaporated in order to reduce the volume of the solution to about 50 ml. Then 50 ml of benzene was added, and the crystals of acetoxy acid 5 were filtered off and recrystallized from a mixture of benzene and acetone. The pure product melted at 162–163°: yield 20.6 g (85%); NMR δ 1.15 (s, 3, CH_3), 2.03 (s, 3, CH_3CO), 2.33 (d, 2, CH_2), 2.77 (s, 4, CH_2CH_2), 4.97 ppm (t, 1, CH).

Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.5; H, 5.78. Found: C, 54.8; H, 5.80.

(−)-S-2-Methyl-2-(β-carboxy-β-acetoxyethyl)cyclopentane-1,3-dione (5). The solution of (−)-α-phenylethylamine (35.5 g, 0.293 mol) in ethanol (100 ml) was mixed with the solution of racemic acetoxy acid 5 (71.0 g, 0.293 mol) in 400 ml of ethanol and allowed to crystallize in the cold for 3 hr. The crystalline precipitate was recrystallized twice from ethanol (130 ml), yielding 33.0 g (62%) of the salt. The free (−) acid 5 was obtained by stirring the methanolic solution of salt with Dowex 50W, filtering off the resin, and concentrating the filtrate to afford 22.0 g of pure (−) acetoxy acid 5: mp 139–141°; $[\alpha]^{18}D$ −16.15° (c 9.5, MeOH).

Acid Chloride of 2-Methyl-2-(β-carboxy-β-acetoxyethyl)-cyclopentane-1,3-dione (6). The acetoxy acid 5 (2.42 g, 0.01 mol) was treated with 25 ml of dry $CHCl_3$ and 3 ml of thionyl chloride and the mixture was refluxed for about 0.5 hr. Then the excess thionyl chloride and chloroform were distilled off, using reduced pressure at the end of the distillation. The crystalline acid chloride 6 was used in further reactions.

2-Methyl-2-(2′-acetoxy-3-keto-4′-diazobutyl)cyclopentane-1,3-dione (7). Acid chloride 6 obtained by the above described method from 2.42 g (0.01 mol) of acid 5 dissolved in 25 ml of dry ether and was added dropwise at 0–10° to a solution of diazomethane in ether prepared from 6 g (0.058 mol) of nitrosomethylurea. Then the mixture was cooled to −50° and 2.30 g (86.7%) of diazo ketone 7 (mp 66–67°) was filtered off, $[\alpha]^{18}D$ −55.7° (c 6.5, CH_3OH).

11β-Acetoxy-14β-hydroxy-3-methoxy-9,10-secoestra-1,3,5(10)-triene-9,17-dione (9). A solution of $LiAlH_4$ (0.228 g, 0.006 mol) in 20 ml of anhydrous THF was treated dropwise at −10° with BF_3·Et_2O (1.134 g, 0.008 mol) and then a solution of *m*-methoxystyrene (3.3 g, 0.0230 mol) in 10 ml of anhydrous THF was added. The mixture was stirred under argon for about 1 hr at room temperature and subsequently a solution of diazo ketone 7 (1.8 g, 0.007 mol) in 10 ml of dry benzene was dropped in, causing an evolution of nitrogen. The mixture was allowed to stand for 3 hr, and then 6 ml of glacial acetic acid was added. The solvents were removed in vacuo, and the residual liquid was poured into 100 ml of water and extracted with benzene (3 × 50 ml). The organic layer was washed with water (3 × 50 ml) and dried with anhydrous Na_2SO_4. After evaporation of solvents in vacuo the residue was washed with pentane (3 × 20 ml) and hexane (2 × 20 ml) in order to remove low molecular weight impurities. The remaining oil was dissolved in 50 ml of benzene, and 5 ml of *t*-BuOOH was added. The mixture was left overnight and filtered and then the solvents were removed from the filtrate in vacuo. The residue was again washed with hexane (2 × 20 ml) and the remaining resin was pure enough for the next step.[2]

All the compounds listed below[5] were obtained using the procedures described for the racemic compounds.[2,3]

9β,11β,14β-Triacetoxy-3-methoxyestra-1,3,5(10)-trien-17-one (10), mp 244–245°, $[\alpha]D$ (room temperature) 61.4° (c 5.4, $CHCl_3$); **14β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione,** mp 227–229°, $[\alpha]D$ (room temperature) 355.0° (c 6.4, HMPT); **3-methoxy-14β-estra-1,3,5(10)-triene-11,17-dione,** mp 172–173°, $[\alpha]D$ (room temperature) 435.0° (c 4.7, $CHCl_3$); **11,11,17,17-bis(ethylenedioxy)-3-methoxy-14β-estra-1,3,5(10)-triene,** mp 127–128°, $[\alpha]D$ (room temperature) 145.0° (c 0.5, $CHCl_3$); **11,11,17,17-bis(ethylenedioxy)-3-methoxyestra-1,3,5(10)-trien-14β-ol,** mp 164–166°, $[\alpha]D$ (room temperature) 106.2° (c 0.32, EtOH); **11,11-ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraen-17-one,** mp 121–122°, $[\alpha]D$ (room temperature) 301.0° (c 0.46, EtOH); **11,11-ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one,** mp 133–134°, $[\alpha]D$ (room temperature) 185.0° (c 0.23, EtOH); **17α-hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-11-one,** mp 175–176°, $[\alpha]D$ (room temperature) 270.0° (c 0.1, $CHCl_3$); **14β-estra-4-ene-3,11,17-trione,** mp 226–227; $[\alpha]_{578}$ (room temperature) 375.0° (c 0.13, $CHCl_3$); **14β-hydroxyestra-4-ene-3,11,17-trione,** mp 202–204°, $[\alpha]_{578}$ (room temperature) 278.0° (c 0.42, $CHCl_3$); **11,11-ethylenedioxy-14β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one,** mp of crude 196–204°, $[\alpha]D$ (room temperature) 121.0° (c 0.21, EtOH); **3-methoxy-14β-estra-1,3,5(10)-trien-17-one,** mp 112–114°, $[\alpha]D$ (room temperature) 180.0° (c 0.2, $CHCl_3$) [lit.[4] mp 112–113°, $[\alpha]D$ (room temperature) 179° (c 0.2, $CHCl_3$)].

Registry No.—1, 80-63-7; 2, 765-69-5; 3, 55836-13-0; 4, 55836-14-1; (±)-5, 55836-15-2; (−)-(S)-5, 55902-71-1; (−)-(S)-5 (−)-α-phenylethylamine, 55902-72-2; 6, 55836-16-3; 7, 55836-17-4; 8, 55836-18-5; 9, 55836-19-6; 10, 55836-20-9; (−)-α-phenylethylamine, 2627-86-3; 14β-hydroxy-3-methoxyestra-1,3,5(10)-triene-11,17-dione, 55902-73-3; 3-methoxy-14β-estra-1,3,5(10-triene-11-17-dione, 55902-74-4; 11,11,17,17-bis(ethylenedioxy)-3-methoxy-14β-estra-1,3,5(10)-triene, 55836-21-0; 11,11,17,17-bis(ethylenedioxy)-3-methoxyestra-1,3,5(10)-trien-14β-ol, 55902-75-5; 11,11-ethylenedioxy-3-methoxyestra-1,3,5(10),14-tetraen-17-one, 55902-76-6; 11,11-ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-trien-17-one, 55836-22-1; 17α-hydroxy-3-methoxy-14β-estra-1,3,5(10)-trien-11-one, 56452-85-8; 14β-estra-4-ene-3,11,17-trione, 55902-78-8; 14β-hydroxyestra-4-ene-3,11,17-trione, 55836-23-2; 11,11-ethylenedioxy-14β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one, 55902-79-9; 3-methoxy-14β-estra-1,3,5(10)-trien-17-one, 17748-69-5.

References and Notes

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(2) Part VI: A. R. Daniewski, *J. Org. Chem.*, **40**, 3124 (1975).
(3) Part VII: A. R. Daniewski, *J. Org. Chem.*, **40**, 3127 (1975).
(4) P. Grabbe, A. Cruz, and J. Iriarte, *Can. J. Chem.*, **46**, 349 (1968).
(5) Melting points were determined on a micro hot plate, and are not corrected. Specific rotations were determined on a Perkin-Elmer 141 polarimeter.
(6) A. R. Daniewski and M. Kocór, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **20**, 395 (1972).

Total Synthesis of Steroids. X.[1] Synthesis of 3-Methoxyestra-1,3,5(10),8,14-pentaen-17-one

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We recently published a series of papers[1-3] on the total synthesis of 11-oxygenated steroids, which were obtained either as racemates or as optically active compounds. Now we wish to describe the total synthesis of pentaene **10,**