Steroid Total Synthesis. VI.[1] (+)-Estr-4-ene-3,17-dione[2]

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Reaction of (±)-9-(3,5-dimethyl-4-isoxazolyl)-7-hydroxynon-1-en-3-one (1) with (+)- and (−)-α-phenethylamine gave mixtures of the (2*S*,6*R*)- and (2*R*,6*S*)-2-[2-(α-phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)-ethyl]tetrahydropyran-2-ols **2**–**5**. The determination of the absolute configurations and optical purities of these Mannich bases is described. The resolved Mannich base **2** was converted, *via* (−)-*trans*-3-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-6a-methyl-1,2,3,5,6,6a-hexahydrocyclopenta[*f*][1]benzopyran-7(8*H*)-one (**8**) and (+)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (**14**), to (+)-estr-4-ene-3,17-dione (**23**).

In the accompanying paper,[1] we have described a total synthesis of racemic 19-nor steroids. In this paper we present the results of our attempts to modify this synthesis to allow the preparation of optically active 19-nor steroids, in particular (+)-estr-4-ene-3,17-dione (**23**).[3]

Results and Discussion

Reaction[4] of the racemic vinyl ketone **1**[1] with (−)-α-phenethylamine (Scheme I) gave the diastereomeric Mannich bases (2*S*,6*R*)- and (2*R*,6*S*)-2-[2-(*S*-α-phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]tetrahydropyran-2-ol (**2**, **3**). Similar reaction with (+)-α-phenethylamine gave the antipodal Mannich bases **4** and **5**. All four compounds were crystalline and were obtained in 50–70% of theoretical yield by fractional crystallization, once seed crystals were available.[5]

We believe that the Mannich bases possess the conformations and absolute configurations shown for the following reasons. That the Mannich bases exist mainly in the spirocyclic, internally hydrogen bonded hemiketal form is indicated by their infrared spectra (strong hydrogen bonded OH and NH absorption at 3200 cm^{-1}; weak carbonyl absorption at 1710 cm^{-1}). The absolute configurations of the α-phenethylamines are known.[6] The configurations at C-6 were determined by conversion of the Mannich bases to either (+)- or (−)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (*vide infra*). Our previous work[4] with related systems has shown that 6*R* Mannich bases give tricyclic compounds, and eventually steroids, of the natural series. Application of the principles of conformational analysis then allowed us to determine the absolute configurations at C-2, as well as the conformations of the molecules. Owing to the spirocyclic nature of these Mannich bases, each ring can individually undergo conformational inversion. Since the configuration of the hemiketal center C-2 is clearly invertible, at least under the reaction conditions under which it is formed (heating with excess α-phenethylamine in benzene at 50° for 3 hr), there are eight possible chair–chair forms for each of the Mannich bases **2**–**5**. The application of free-energy differences determined in cyclohexane systems to heterocyclic rings is a hazardous undertaking, at best. It is thus rather difficult to estimate by how much each of the conformations shown is more stable than its seven other forms. What is clear, however, is that these are the most stable conformers, since the three ethylidene substituents are in the more stable equatorial positions while the oxygen substituents at the anomeric center C-2 are in favored[7] axial orientations. An interesting consequence of this analysis is that the configuration at C-6 determines that at C-2. Since there are two asymmetric centers in addition to that of the α-phenethylamine in each Mannich base, it would be expected *a priori* that four diastereomers would be obtained with each amine. The fact that only two diastereomers were found provides support for our conformational arguments.

The nmr spectra of the Mannich bases present evidence of their homogeneity and optical purity. The spectra of the four compounds **2**–**5** are identical, except for the positions of the isoxazole methyl signals. In the spectra of the 6*R* bases **2** and **4**, these signals are at 134 and 140 Hz, while the corresponding signals of the 6*S* bases **3** and **5** are at 127 and 133 Hz. Diastereomeric mixtures of compounds show the expected summation of signals. In addition, there is a smaller set of signals (15–20% of the total) at 133 and 139 Hz in the spectrum of each Mannich base or mixture of Mannich bases. We assign this second set of signals to the open form **6** of the Mannich bases. The presence of compounds of type **6** in solution, which was previously shown by the infrared spectra of these compounds, indicates that the acyclic forms **6** are probably more stable than any of the ring-inverted conformers of the bases **2**–**5**. Molecular models indicate that the phenyl and isoxazole rings can come in quite close proximity in the spirocyclic forms **2**–**5**. Such immediate nearness would not be expected to occur in the open configuration **6**. If the isoxazole signals at 133 and 139 Hz are thus considered to be "normal," it appears that the isoxazole rings of the 6*S* bases **3** and **5** are being shielded, presumably by the phenyl ring, while those of the diastereomeric 6*R* bases are virtually unaffected. As yet, we have no explanation for this selective shielding. It has, however, allowed us to determine that we have obtained each of the Mannich bases in an optical purity of at least 95%.

With the optically pure Mannich bases in hand, we turned our attention to the condensation of these materials with 2-methylcyclopentane-1,3-dione (**7**).[8]

(1) Part V: J. W. Scott and G. Saucy, *J. Org. Chem.*, **37**, 1652 (1972).

(2) Presented in part at the Third International Congress on Hormonal Steroids, Hamburg, Germany, 1970.

(3) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5366 (1953).

(4) Part III: G. Saucy and R. Borer, *Helv. Chim. Acta*, **54**, 2517 (1971).

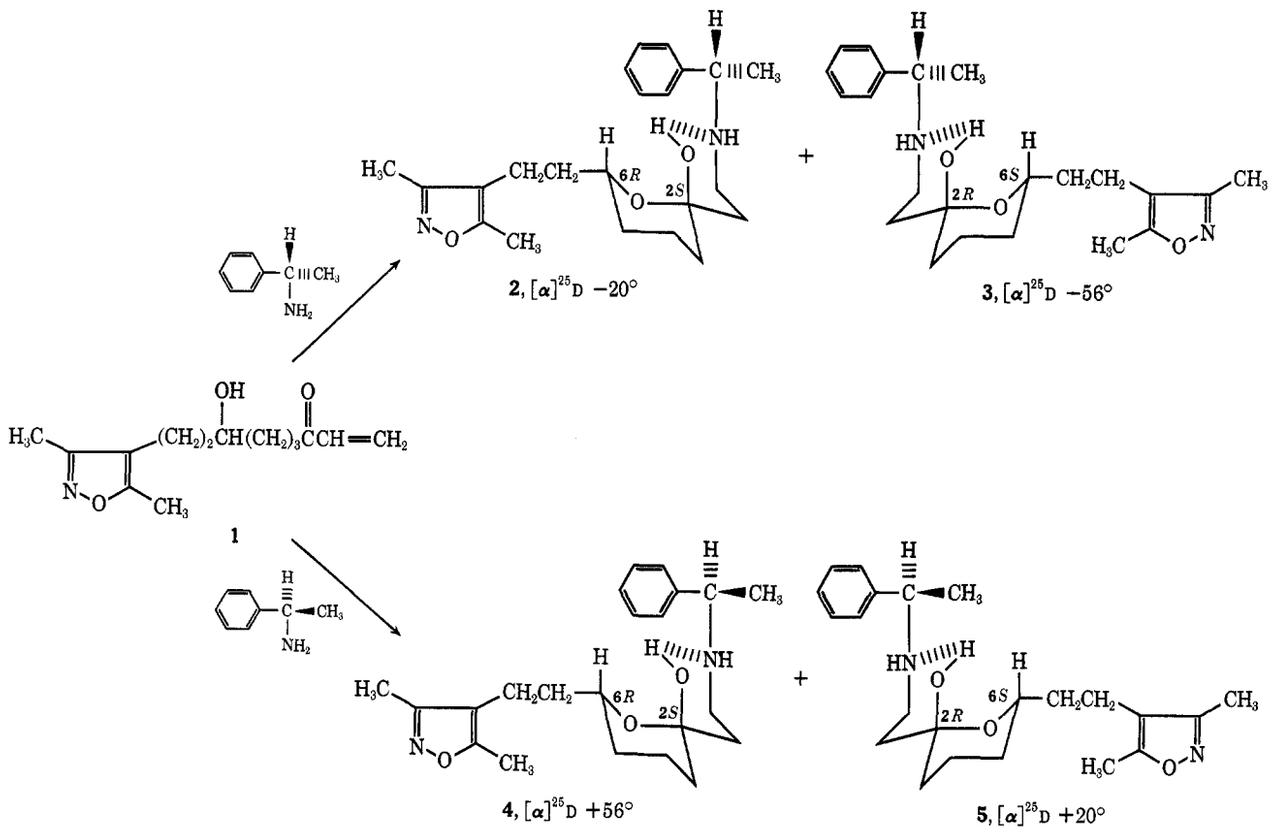
(5) The initial resolution was obtained by fractional crystallization of the oxalate salts of the diastereomeric mixtures. Regeneration of the free amines with dilute base then gave the pure crystalline Mannich base seed crystals.

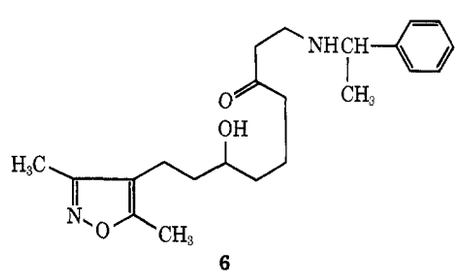
(6) J. C. Craig, R. P. K. Chan, and S. K. Roy, *Tetrahedron*, **23**, 3573 (1967).

(7) C. B. Anderson and D. T. Sepp, *Tetrahedron*, **24**, 1707 (1968); E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

(8) J.-J. Panouse and C. Sannié, *Bull. Soc. Chim. Fr.*, 1036 (1955).

SCHEME I





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Reaction of the base **2** with the dione **7** in a toluene–pyridine–acetic acid mixture (Scheme II) gave a mixture of trans and cis dienol ethers (**8**, **9**), $[\alpha]^{25}D$ −171°. In the racemic series,[1] it had been possible to isolate the pure trans dienol ether by crystallization, but unfortunately this was not possible with compounds **8** and **9**. Since we thus had no means of accurately determining the extent of optical induction obtained during the condensation reaction,[9] the mixture of dienol ethers was converted, as previously described[1] in the racemic series, to the (+) enedione **14**. Thus, the dienol ethers **8** and **9** were reduced with lithium aluminum hydride (→**10**[10]), hydrogenated over palladium on carbon (→**11**), hydrated with dilute sulfuric acid in acetone (→**12**), oxidized with Jones reagent[11] (→**13**), and cyclized with methanolic sodium hydroxide. An optically pure comparison sample of the (+) dione **14**, $[\alpha]^{25}D$ +93.6°, was synthesized by alkylation of enone **17**[12] with 4-chloromethyl-3,5-dimethylisoxazole,[13] followed by acid-catalyzed cleavage of the ether group and oxidation[11] of the resulting alcohol **16**. The rotation of the crude enone **14** prepared from the dienol ether mixture indicated that this material was approximately 44% optically pure; in other words, an optical induction of 72% had occurred. The extent of optical induction was quite sensitive to the reaction conditions.[4] After considerable experimentation, we were able to obtain dienol ether mixtures of $[\alpha]^{25}D$ −186.5°, corresponding to 89% optical induction. This was done by first quaternizing the Mannich base **2** with methyl iodide and potassium carbonate. The crude quaternary salt was then treated with 2-methylcyclopentane-1,3-dione in aqueous *tert*-butyl alcohol to give a mixture of compounds whose spectral data were in accord with the general structure **18**.[4] Treatment of this mixture with *p*-toluenesulfonic acid then gave the dienol ethers **8** and **9** in 46% yield from the Mannich base **2**. The enone **14** prepared from this mixture was fractionally crystallized to give optically pure (+)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione, mp 85.5–88.5°, in 31% yield from the dienol ether mixture.

Conversion of the optically pure enedione **14** to (+)-estr-4-ene-3,17-dione (**23**) was carried out (Scheme III) as previously described for the racemic series.[1] Thus, hydrogenation of compound **14** over palladium on carbon in ethanol–triethylamine gave the dione **19**, mp 107–110.5°. Ketalization (→**20**, mp 148–150°),

(9) The nmr method previously described[1] was probably accurate at best to ±10%, owing to the overlap of the signals to be integrated. Despite numerous attempts, the materials could not be separated by gas chromatography.

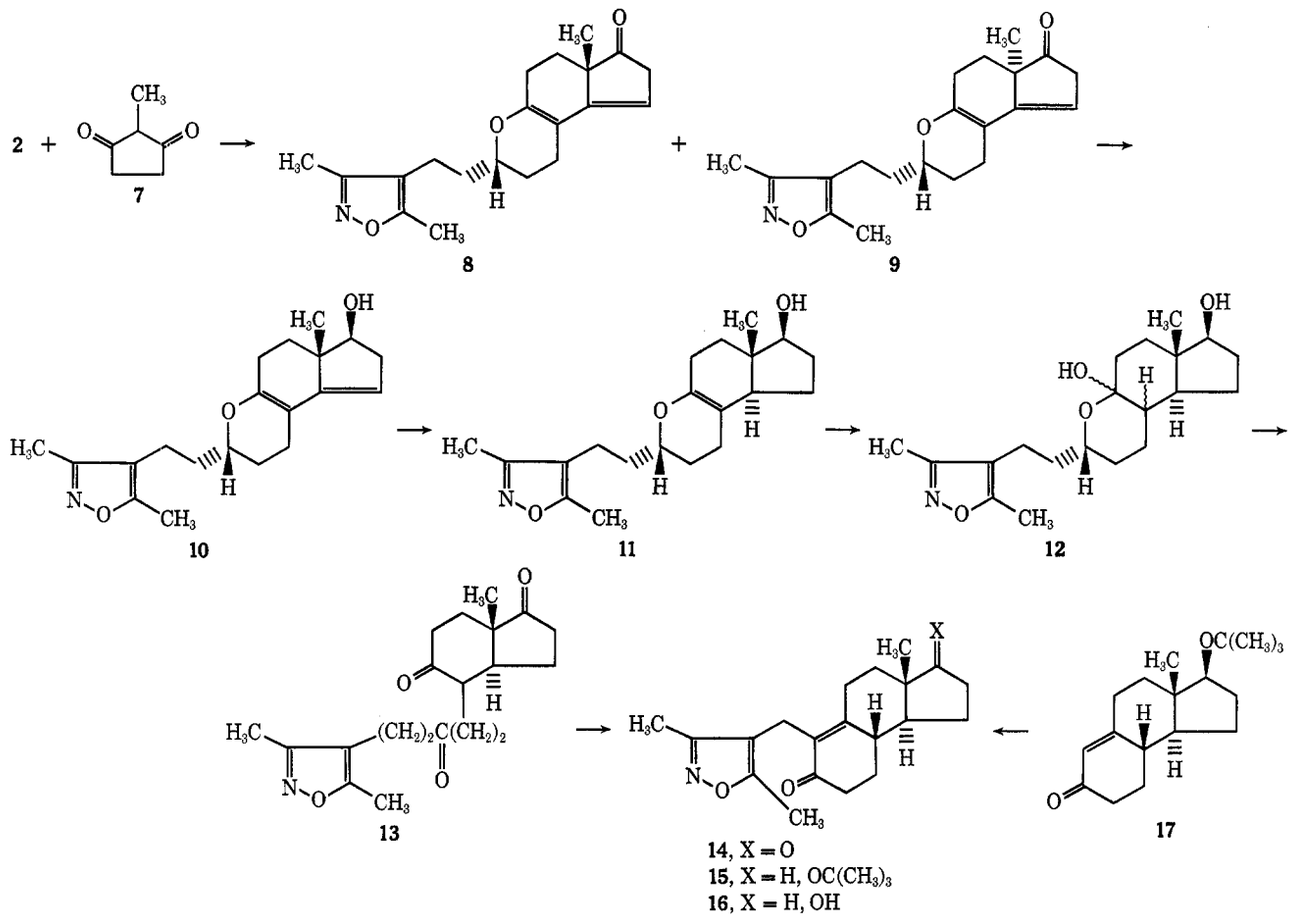
(10) For convenience, only the trans isomers of compounds **10–12** are shown.

(11) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(12) J. W. Scott, W. Vetter, W. E. Oberhänsli, and A. Furst, *Tetrahedron Lett.*, in press.

(13) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, **28**, 2762 (1958).

SCHEME II



followed by hydrogenation in 4% ethanolic sodium hydroxide solution, gave the vinylogous amide **21**. Treatment of this compound with aqueous base at reflux (→**22**, mp 85.5–86.5°) and then heating with methanolic hydrochloric acid to effect deketalization and ring closure gave (+)-estr-4-ene-3,17-dione (**23**)[3] in 66% yield. The material thus obtained was identical in all respects with a sample obtained by Jones oxidation of 17β-hydroxyestr-4-en-3-one.[14]

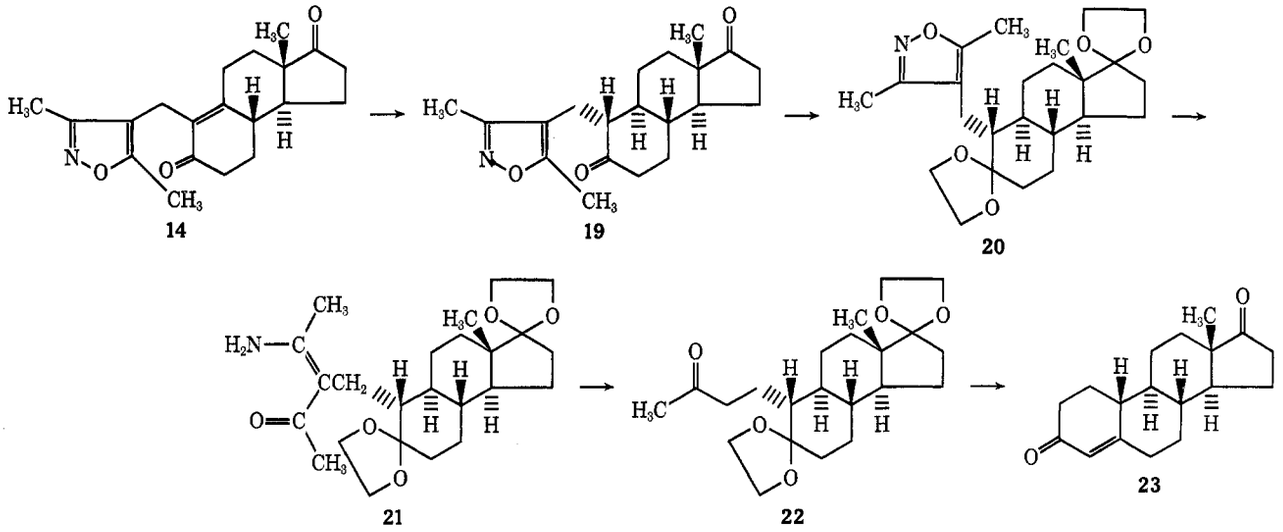
Experimental Section[15]

(2*S*,6*R*)-2-[2-(*S*-α-Phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]tetrahydropyran-2-ol (2) and (2*R*,6*S*)-2-[2-(*S*-α-Phenethylamino)ethyl]-6-[2-(3,5-dimethyl-4-isoxazolyl)ethyl]-tetrahydropyran-2-ol (3).—A solution of 13.4 g (0.06 mol) of (±)-7-(3,5-dimethyl-4-isoxazolyl)-5-hydroxyheptanoic acid lactone[1] in 200 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) was cooled under nitrogen in a Dry Ice–isopropyl alcohol bath to −60°. A 2 *N* vinylmagnesium chloride in tetrahydrofuran solution (55 ml = 0.11 mol; Peninsular ChemResearch, Inc.) was added at a rate such that the temperature remained at −50 to −55° (5 min). The resulting pale yellow solution was stirred at −55 to −60° for 20 min, cooled to −70°, and cautiously hydrolyzed with 15 ml of methanol (temperature < −50°). The solution was poured into a mixture of ice, 30 g of NH_4Cl, and 10 ml of acetic acid and extracted with ether. The ether solutions were washed with saturated brine, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal at 30° gave the vinyl ketone **1** as a pale yellow oil. This material was taken up in 100 ml of benzene, degassed, and placed under nitrogen. To the flask was added 7.50 g (0.062 mol) of (−)-α-phenethylamine (Aldrich Chemical Co.) and the resulting solution was stirred at 50–55° for 3 hr. The solvent was removed at reduced pressure and the residual orange resin was chromatographed on 1.5 kg of Woelm neutral alumina III. After prior elution with 1:1 hexane–benzene and benzene, benzene–ether mixtures gave a mixture of diastereomeric Mannich bases **2** and **3** as 18.0 g of pale yellow resin. To a solution of this material in 90 ml of ether was added a solution of 7.55 g (0.060 mol) of oxalic acid dihydrate in 60 ml of ether, at which point an oil precipitated. The ether layer was decanted and the oil was shaken twice with 50-ml portions of ether. The oil was then crystallized from 50 ml of acetone and 100 ml of benzene to give 15.4 g of white solid, mp 111–114°,[15] $[\alpha]^{20}D$ −28.2° (*c* 1.0, CH_3OH). Four crystallizations of this material from methanol–ether gave the pure oxalate of the Mannich base **2** as heavy, white needles, mp 118–120°, $[\alpha]^{20}D$ −28.5° (*c* 1.0, CH_3OH). A 110-mg sample of this material was shaken with benzene and 20 ml of 1 *N* KOH until all the solid dissolved. The benzene layer was washed with saturated brine and dried (Na_2SO_4). Solvent removal gave 82 mg of pale yellow resin which was crystallized from isopropyl ether to give the Mannich base **2** as 50 mg of white prisms, mp 65.5–69.5°, $[\alpha]^{25}D$ −19.8° (*c* 1.2, C_6H_6). The mother liquors from the

(14) G. D. Searle and Co.

(15) Melting points were determined on a Kofler hot stage and are not corrected. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter.

SCHEME III



initial oxalate crystallization were shaken with benzene and 1 *N* KOH as above to give 12.0 g of yellow oil. A 3.0-g sample of this material was chromatographed on 90 g of Woelm neutral alumina I. The material eluted with benzene was crystallized twice from isopropyl ether to give the Mannich base **3** as 115 mg of white prisms, mp 70–72.5°, $[\alpha]^{25}D$ −55.2° (*c* 1.0, C_6H_6).

A sample of the mixed diastereomers **2** and **3** (30.75 g), which was prepared as described above, was dissolved in 100 ml of hot isopropyl ether, cooled to 20°, and seeded with isomer **2**. Crystallization was allowed to proceed at 20° overnight and then for 48 hr at 0°. Careful decantation of the mother liquors (to avoid initiation of crystallization of isomer **3**) gave 10.60 g of Mannich base **2** as large, white prisms. Recrystallization of this material from 150 ml of 2:1 hexane–ether gave 9.35 g (61%) of large white prisms, mp 69.5–75°, $[\alpha]^{25}D$ −20.4° (*c* 1.26, C_6H_6).[16] Seeding of the mother liquors from the original crystallization of compound **2** with isomer **3** gave, after 3 hr at 0°, 10.5 g of slightly orange solid. Two recrystallizations of this material from 120 and 90 ml of 2:1 hexane–ether gave 7.40 g (48%) of the Mannich base **3** as long white prisms, mp 68.5–75.5°, $[\alpha]^{25}D$ −56.2° (*c* 1.14, C_6H_6). An additional 1.58 g (10%) of Mannich base **2**, mp 69.5–75.5°, $[\alpha]^{25}D$ −21.1° (*c* 1.33, C_6H_6), was obtained by fractional crystallization of the material recovered from the mother liquors.

The analytical samples of compounds **2** and **3** were obtained respectively as large white prisms, mp 69.5–73.5°, $[\alpha]^{25}D$ −21.3° (*c* 1.26, C_6H_6), and as a white, crystalline solid: mp 70–72.5°; $[\alpha]^{25}D$ −55.2° (*c* 1.0, C_6H_6); uv max (C_2H_5OH) 220 nm (ε 7500), 250 (280), 256 (285), and 262–263 (200); ir ($CHCl_3$) 3400–2400 (OH and NH, hydrogen bonded), 1710 (C=O, weak), and 1640 cm^{-1} (isoxazole).

Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.92; H, 8.66; N, 7.52. Found: **2**, C, 71.10; H, 8.47; N, 7.40; **3**, C, 71.07; H, 8.69; N, 7.52.

The isoxazole methyl nmr signals for these compounds are given and discussed fully in the discussion. Other signals ($CDCl_3$) are at δ 1.39 (d, 3, $CHCH_3$) and 7.25 ppm (s, 5, C_6H_5).

(+)-19-(3,5-Dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione (14). A. From 17β-*tert*-Butoxy-de*A*-estr-9-en-5-one (17).—In a dry flask under nitrogen, a mixture of 520 mg (12.0 mmol) of 55% NaH in mineral oil and 2.76 g (10.0 mmol) of the enone **17**[12] in 100 ml of 1,2-dimethoxyethane (freshly distilled from $LiAlH_4$) was heated at reflux for 1.0 hr to give a cloudy, light brown solution. Heating was continued as a solution of 1.75 g (12.0 mmol) of 4-chloromethyl-3,5-dimethylisoxazole[13] in 20 ml of 1,2-dimethoxyethane was added over 4.5 hr. The resulting suspension was heated at reflux for another 1.5 hr, cooled, poured into H_2O, and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave an orange resin which was chromatographed on 200 g of E. Merck 0.05–0.2 mm silica gel. Elution with 19:1 benzene–ether gave 619 mg (22.5%) of enone **17**. Continued elution with this solvent mixture gave the desired isoxazole enone **15** as a light yellow solid. Crystallization from ether–hexane gave 1.72 g (45%) of white prisms: mp 125.5–126.5°; $[\alpha]^{25}D$ +18.4° (*c* 1.06, C_2H_5OH); uv max (C_2H_5OH) 220 nm (sh, ε 8000) and 244 (13,300); ir ($CHCl_3$) 1660 (C=CC=O and isoxazole) and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (s, 3, CH_3), 2.15 (s, 3) and 2.28 (s, 3, 2 isoxazole-CH_3), and 3.39 ppm (m, 3, isoxazole-CH_2 and C_{17} H).

Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.88; H, 9.38; N, 3.67.

A solution of 1.159 g (3.0 mmol) of the alkylated enone **15** and 1.10 g of *p*-toluenesulfonic acid monohydrate in 100 ml of benzene was heated at reflux for 1.0 hr. The cooled solution was washed with saturated $NaHCO_3$ solution and saturated brine and dried (Na_2SO_4). Solvent removal gave 1.03 g of yellowish resin which was crystallized from isopropyl ether to give 697 mg (71%) of hydroxy enone **16** as small, white needles: mp 127–127.5°; $[\alpha]^{25}D$ −3.6° (*c* 1.12, $CHCl_3$); uv max (C_2H_5OH) 225 nm (ε 10,200) and 244 (13,600); ir ($CHCl_3$) 3600 and 3400 (OH), 1660 (C=CC=O and isoxazole), and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.90 (s, 3, CH_3), 2.13 (s, 3) and 2.26 (s, 3, 2 isoxazole-CH_3), 3.39 (s, 2, isoxazole-CH_2), and 3.75 ppm (t, 1, $C_{17}H$).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.25; H, 8.49; N, 4.16.

A solution of 415 mg (1.26 mmol) of the hydroxy enone **16** in 25 ml of acetone was cooled in an ice bath as 1.0 ml of Jones reagent[11] was added over 5 min. The mixture was stirred with cooling for 10 min, diluted with $NaHSO_3$ solution, and extracted with benzene. The benzene solutions were washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal gave 430 mg of colorless foam which was crystallized from isopropyl ether to give 280 mg (68%) of enedione **14** as white needles: mp 85.5–87.5°; $[\alpha]^{25}D$ +93.6° (*c* 1.04, $CHCl_3$); uv max (C_2H_5OH) 225 nm (ε 10,600) and 242 (12,700); ir ($CHCl_3$) 1740 ($C_{17}C$=O), 1664 (C=CC=O), 1640 (sh, isoxazole), and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.03 (s, 3, CH_3), 2.15 (s, 3) and 2.28 (s, 3, 2 isoxazole-CH_3), and 3.40 ppm (s, 2, isoxazole-CH_2).

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.67; H, 7.95; N, 4.15.

B. From Mannich Base 2.—To a solution of 1.86 g (5.0 mmol) of optically pure Mannich base **2**, $[\alpha]^{25}D$ −20.36° (*c* 1.26, C_6H_6), in 40 ml of acetone was added 3.0 g of granular anhydrous K_2CO_3 and 5 ml of methyl iodide. The resulting suspension was stirred at room temperature overnight, filtered, and stripped of solvent at reduced pressure to give the Mannich base quaternary salt as a white, semicrystalline mass. To a solution of this material in 75 ml of 4:1 *tert*-butyl alcohol–H_2O was added 1.12 g (10.0 mmol) of 2-methylcyclopentane-1,3-dione[8] and the resulting mixture was degassed, placed under nitrogen, and heated at reflux for 24 hr. The cooled solution was diluted with H_2O and extracted with benzene. The benzene solutions were washed twice with saturated oxalic acid, H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). Solvent removal

(16) The rotations of the Mannich bases are difficult to reproduce exactly and seem to depend to some extent upon the length of time the material is in solution before the determination is made. Presumably these variations in rotation reflect, at least partially, differing concentrations of the acyclic forms **6**.

gave a pale yellow resin which was chromatographed on 100 g of E. Merck 0.05–0.2 mm silica gel. Elution with benzene–ether mixtures (3:2, 2:3, 1:4) gave the mixture of isomeric hemiketals **18** as 1.27 g (70%) of pale yellow resin: ir (film) 3450 (OH), 1740 (cyclopentanone), and 1640 cm^{-1} (isoxazole). To a solution of the hemiketals **18** in 100 ml of benzene was added 100 mg of *p*-toluenesulfonic acid monohydrate and the resulting solution was stirred at 20° for 30 min. An additional 100 mg of acid was added and stirring was continued for another 2.5 hr. The mixture was washed with H_2O, saturated $NaHCO_3$ solution, and saturated brine and dried (Na_2SO_4). The pale yellow resin obtained upon solvent removal was filtered through 100 g of Woelm neutral alumina III with benzene to give 842 mg of cream-white solid. Two crystallizations of this material from isopropyl alcohol–H_2O gave 754 mg (46%, based on Mannich base **2**) of dienol ether **8** as fine, colorless (white) needles, mp 86.5–91.5°, $[\alpha]^{25}D$ −186.5° (*c* 1.19, $CHCl_3$). The melting point and rotation were unchanged by a further recrystallization. The material had ir and uv spectra and tlc behavior identical with those of racemic dienol ether.[1] That the sample contained cis dienol ether **9** was shown by its further conversion (*vide infra*) to a mixture of (±)- and (+)-enediones **14**.

The series of reactions converting the dienol ether mixture **8** and **9** to the crude enedione **14** is essentially that previously described for the racemic series.[1] Thus, 654 mg (2.0 mmol) of the mixed dienol ethers, $[\alpha]^{25}D$ −186.5°, was reduced with lithium aluminum hydride in tetrahydrofuran to give the 17-hydroxy dienol ether **10** as a pale yellow resin. Hydrogenation over palladium on carbon in tetrahydrofuran gave the enol ether **11** as a pale yellow glass: ir (film) 3480 (OH), 1675 (C=CO–), and 1640 cm^{-1} (isoxazole). Hydration of the enol ether with 1 *N* H_2SO_4 in acetone, followed by Jones oxidation[11] of the hemiketal **12**, gave the trione **13** as a pale yellow oil. Cyclization with KOH in methanol gave the crude enedione **14**, which was chromatographed on 50 g of Woelm neutral alumina III. Elution with benzene and 95:5 benzene–ether gave 410 mg (63%) of pale yellow resin, $[\alpha]^{25}D$ +74.0° (*c* 4.05, $CHCl_3$). This material was triturated with 12 ml of ether and cooled to −20°. The mother liquors were decanted and the process was repeated to give 39 mg of (±)-19-(3,5-dimethyl-4-isoxazolyl)-de*A*-androst-9-ene-5,17-dione:[1] mp 141–144°; mixture melting point with an authentic sample[1] undepressed; ir, uv, and nmr spectra identical with those of the authentic sample; $[\alpha]^{25}D$ 0° (*c* 1.10, $CHCl_3$).

The mother liquors from the trituration of the racemic material were stripped of solvent to give 340 mg of yellowish resin. Crystallization of this material from 20 ml of isopropyl ether gave 203 mg (31%) of (+)-enedione **14** as long, white prisms, mp 85.5–88.5°. Recrystallization from ether–hexane gave fine white needles: mp 85.5–89°; mixture melting point with material from part A undepressed; $[\alpha]^{25}D$ +93.82° (*c* 1.0, $CHCl_3$); ir, uv, and nmr spectra identical with those of the sample prepared in part A.

(+)-Estr-4-ene-3,17-dione (23). A. From (+)-17β-Hydroxyestr-4-en-3-one.—To a cold (ice bath) solution of 558 mg (2.0 mmol) of 17β-hydroxyestr-4-en-3-one[14] in 25 ml of acetone was added 2.0 ml of Jones reagent.[11] The mixture was stirred with cooling for 10 min, diluted with $NaHSO_3$ solution, and extracted with benzene. The benzene solutions were washed with saturated brine and dried (Na_2SO_4). Solvent removal gave a white solid which was crystallized from acetone–hexane to give the dione **23** as 475 mg (85%) of shiny platelets, mp 173–174°, $[\alpha]^{25}D$ +139.2° (*c* 1.20, $CHCl_3$) (lit.[3] mp 170–171°, $[\alpha]^{25}D$ +147 ± 1°).

B. From (+)-Enedione 14.—The procedure employed in this preparation is that described previously[1] for the preparation of (±)-estr-4-ene-3,17-dione. Thus, hydrogenation of 6.55 g (20 mmol) of the (+)-enedione **14** over palladium on carbon in 3:1 ethanol–triethylamine gave the dione **19** as an off-white glass. A purified sample was obtained as white needles: mp 107–110.5° from isopropyl ether; $[\alpha]^{25}D$ −0.76° (*c* 1.45, $CHCl_3$); uv max (C_2H_5OH) 223 nm (ε 4500); ir ($CHCl_3$) 1739 (cyclopentanone), 1713 (cyclohexanone), and 1639 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.99 (s, 3, CH_3), 2.26 (s, 3), and 2.40 ppm (s, 3, 2 isoxazole-CH_3).

Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.01; H, 8.20; N, 4.04.

Ketalization of the crude dione **19** gave the diketal **20** as a colorless oil. A purified sample was obtained as white rods: mp 148–150° from methylene chloride–isopropyl ether; $[\alpha]^{25}D$ +3.5° (*c* 1.05, $CHCl_3$); uv max (C_2H_5OH) 224 nm (ε 4600); ir ($CHCl_3$) 1638 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 0.82 (s, 3, CH_3), 2.25 (s, 3) and 2.32 (s, 3, 2 isoxazole-CH_3), and 3.92 ppm (m, 8, 2 $-OCH_2CH_2O-$).

Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.04; H, 8.45; N, 3.35. Found: C, 68.91; H, 8.52; N, 3.22.

The crude diketal was hydrogenated over 5% palladium on carbon in 4% ethanolic NaOH solution. The vinylogous amide **21** was cleaved with aqueous base to give the keto diketal **22** as a light yellow oil. A purified sample was obtained as irregular white prisms: mp 83.5–86.5° from ether–hexane; $[\alpha]^{25}D$ −16.0° (*c* 1.17, C_6H_6); no uv absorption; ir ($CHCl_3$) 1710 cm^{-1} (CO-CH_3); nmr ($CDCl_3$) δ 0.88 (s, 3, CH_3), 2.14 (s, 3, $COCH_3$), and 3.92 ppm (d, 8, 2 $-OCH_2CH_2O-$).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.74; H, 9.10.

The crude keto diketal was treated with methanolic HCl to give the crude steroid **23** as 5.85 g of light yellow solid. Chromatography of this material on 500 g of E. Merck 0.05–0.2 mm silica gel (elution with 85:15 benzene–ether) gave 4.28 g of pale yellow solid. Crystallization from 15 ml of acetone and 100 ml of hexane gave 3.34 g (61%) of shiny, colorless plates: mp 172–173°; mixture melting point with material from part A undepressed; $[\alpha]^{25}D$ +139.5° (*c* 0.95, $CHCl_3$). An additional 328 mg (5%) of material, mp 165–171°, was obtained by concentration of the mother liquors.

Registry No.—**2**, 33276-61-8; **2** oxalate, 34770-09-7; **3**, 34770-10-0; **8**, 34770-11-1; **14**, 34770-12-2; **15**, 34770-13-3; **16**, 34770-14-4; **19**, 34770-15-5; **20**, 34770-16-6; **22**, 34770-17-7; **23**, 734-32-7.

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