[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

Studies in the Total Synthesis of Steroids and Their Analogs. I. Synthesis of 19-Nortestosterone[1]

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The total synthesis of 19-nortestosterone from *trans*-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane was achieved in a series of transformations that involved the reduction of this tricyclic substance with lithium in ammonia, conversion of the enol ether to an α,β-unsaturated ketone and condensation of this ketone with methyl acrylate. After saponification the resulting unsaturated acid was reduced either with lithium in ammonia or catalytically to yield the *racemic* seco acid having all six centers of asymmetry oriented as in (+) 19-nortestosterone. Resolution of the racemic seco acid with (+) amphetamine gave the seco acid enantiomorphic with that obtained from (+) 19-nortestosterone. The conversion of the racemic seco acid to racemic 19-nortestosterone followed procedures developed by previous workers for the identical conversion of their optically active counterparts.

The total synthesis of the steroids was undertaken in our laboratory as part of an investigation of the effect of variation of structure on biological activities. It was our hope that in addition to providing for biological testing compounds whose configuration corresponds unmistakably to that of the natural steroids, a successful synthesis could be developed which would obviate the necessity of utilizing estrone as the starting material for the synthesis of the 19-norsteroids.

Of several approaches studied, one which led to 19-nortestosterone (XVb) involved starting with rings B and C and successively constructing rings D and A.

At the time this particular approach was undertaken Banerjee, Chatterjee, Pillai, and Bhatt[2] reported the synthesis of *trans*-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane (I) from 6-methoxytetralone by an adaptation of the sequence of reactions developed by Johnson, Petersen, and Gutsche[3] for the synthesis of equilenin.

The synthesis of Banerjee and his associates was distinguished by the exceptionally high yields obtained in all but one step—*viz.*, that involving the Stobbe condensation.

In repeating their synthesis we were gratified to find that we were able to reproduce their excellent results. Our experience in converting the tricyclic compound I to 19-nortestosterone (XVb)[4] is summarized in this report.

Our original plan called for the partial reduction of the aromatic ring of I to give *anti-trans*-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane (IV). Condensation of IV with methyl vinyl ketone[5] was expected to afford a tetracyclic compound VI or VII which could then be converted to estradiol (VIII) as proof of its structure and configuration.

The reduction of I was accomplished with lithium in liquid ammonia[6] to give the enol ether II, m.p. 87.5–89°, in 65–70% yield. Numerous attempts were made to increase this yield but to no avail. A by-product of the reaction was a deoxy compound to which we have tentatively assigned structure III on the basis of its elemental analysis, infrared, ultraviolet and nuclear magnetic resonance spectra. The NMR spectrum showed an absorption band at 4.67 τ, which is consistent with the presence of an olefinic proton.[7]

When the enol ether II was hydrolyzed with methanolic hydrochloric acid, the expected α,β-unsaturated ketone IV, m.p. 110.5–112°, was obtained in 70% yield. The structure of IV followed from its analysis and infrared and ultraviolet spectra. The ultraviolet absorption maximum at 239 mμ (ϵ 16,600) indicated that the double bond was not in the other possible α,β-position. The ketone IV was formulated as having the *anti-trans* configuration on the basis that the hydrolysis of the enol ether would yield the thermodynamically more stable arrangement about carbons 4,9, and 8. According to the concept of conformational analysis,[8] non-

(1) Presented in part at the 134th Meeting of the American Chemical Society, Chicago, Ill., September, 1958 (Abstracts of Papers, p. 14-O).

(2) D. K. Banerjee, S. Chatterjee, C. N. Pillai, and M. V. Bhatt, *J. Am. Chem. Soc.*, **78**, 3769 (1956).

(3) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *J. Am. Chem. Soc.*, **69**, 2942 (1947).

(4) The stereospecific transformation of the dextrorotatory form of I to (+) 19-nortestosterone has been reported by L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, and A. Pierdet, *Compt. rend.*, **250**, 1084 (1960); also L. Velluz, G. Nominé, and J. Mathieu, *Angew. chem.*, **72**, 725 (1960).

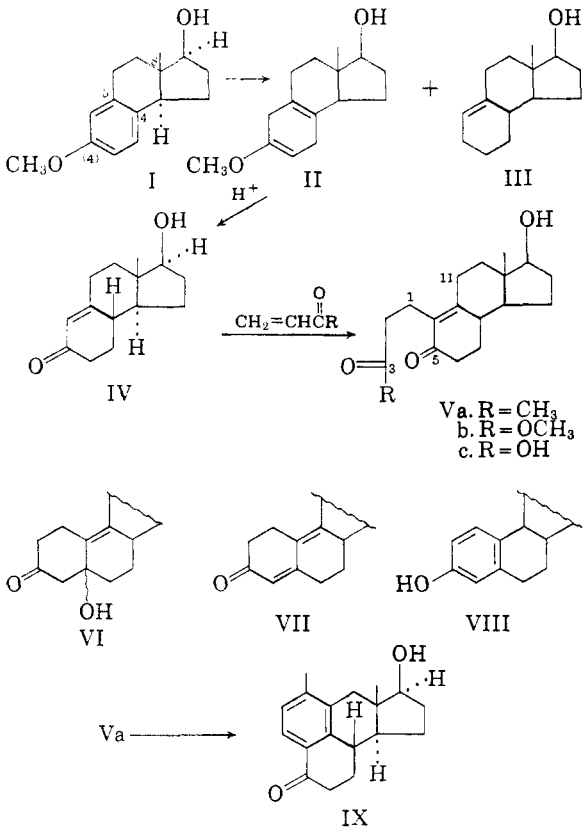
(5) A. L. Wilds, J. W. Ralls, W. C. Wildman, and K. E. McCaleb, *J. Am. Chem. Soc.*, **72**, 5794 (1950); P. Wieland, H. Ueberwasser, G. Anner, and K. Miescher, *Helv. Chim. Acta*, **36**, 1231 (1953); W. S. Johnson, J. Szmuszkovicz, E. R. Rogier, H. I. Hadler, and Hans Wynberg, *J. Am. Chem. Soc.*, **78**, 6285 (1956).

(6) A. J. Birch, *Quart. Rev.*, **4**, 69 (1950); A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953); H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(7)(a) L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York, 1959, p. 60. (b) We are indebted to Dr. Neal McNiven and his associates at the Worcester Foundation for Experimental Biology for the NMR spectra.

(8) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

CHART I



bonded interactions in the *anti-trans* form would be at a minimum.

The condensation of IV with methyl vinyl ketone was conducted in the presence of a base. Among the bases studied were potassium *t*-butoxide, sodium ethoxide, sodium methoxide, and potassium hydroxide. In nearly every case the ultraviolet spectrum of the reaction product showed maximal absorption in the region of 246–250 mμ indicating that a condensation had occurred at the desired α-position of the unsaturated carbonyl system. However, in no instance were we able to isolate the tetracyclic dieneone VII or its precursors Va and VI. Heating the crude condensation product with hydrochloric acid in ethanol failed to afford racemic estradiol (VIII) or the corresponding ethyl ether, which would be expected to arise from VII by an acid catalyzed rearrangement of the dieneone system.[9]

A crystalline product, m.p. 198–199.5°, could be isolated from the reaction mixtures. The maximum yield (11%) of this product was obtained when the crude methyl vinyl ketone condensation mixture was heated with ethanolic hydrochloric acid prior to the isolation of the product.

Its infrared spectrum, determined in potassium bromide, displayed peaks at 2.92, 6.03, 6.32, 6.38, and 12.11 μ, and its ultraviolet spectrum showed an absorption maximum at 265.5 mμ (ε 13,900) and a shoulder at 294 mμ (ε 2,430). The spectra and the formation of a red 2,4-dinitrophenylhydrazone suggested the presence of an α-tetralone system. On the basis of these data and of the elemental analysis, which was in accord with the empirical formula $C_{18}H_{22}O_2$, structure IX was assigned to this compound. The correctness of this assignment was subsequently established by nuclear magnetic resonance spectroscopy, which confirmed the presence of the methyl group on the aromatic ring (7.73 τ).[7b,10]

The tetralone IX was envisioned as having risen from Va. The activated methylene group at C-11 (steroid numbering) of Va was assumed to have participated in an aldol condensation with the carbonyl group at C-3. Dehydration of the aldol product followed by air oxidation or disproportionation then gave the aromatic product.

Because of the unpromising results obtained with methyl vinyl ketone,[4,11] we were led to consider the condensation of IV with methyl acrylate. Meakins and Rodig[12] had previously reported the successful condensation of cholest-4-en-3-one with methyl acrylate in the presence of potassium *t*-butoxide to give the acid X. When their conditions were applied to IV, the keto acid Vc, m.p. 196.5–199.5°, was obtained in *ca.* 40% yield. The ultraviolet spectrum of our keto acid showed an absorption maximum at 248 mμ (ε 14,900), which indicated that the condensation had occurred at the desired position.

In a manner analogous to the formation of the tetralone IX, the immediate adduct Vb from the methyl acrylate condensation could have undergone further a Claisen condensation to give a vinylog of a β-diketone, *viz.*, XI, which then could enolize and dehydrogenate to give the hydroxy-α-tetralone XII. In this regard it is pertinent to note that the mother liquor remaining after the isolation of Vc gave an oily product, which dissolved in a solution of potassium hydroxide but not in a solution of potassium bicarbonate and which imparted a violet-gray color to a solution of ferric chloride.

It is not unreasonable to assume, however, that under the conditions employed in the saponification of the total crude reaction product from the methyl acrylate condensation, the major portion of the vinylogous β-diketone XI, which might have been formed as a by-product, would have undergone

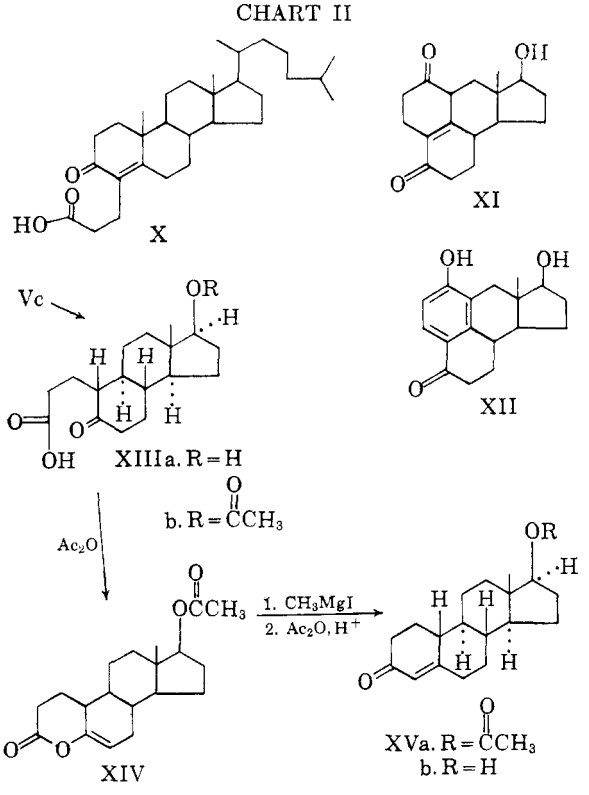
(9) C. Sannié and J. J. Panouse, *Bull. soc. chim. France*, 1435 (1956); C. Sannié, C. Neuville, and J. J. Panouse, *Bull. soc. chim. France*, 635 (1958).

(10) Ref. 7a, p. 58. Independently, Velluz *et al.* (ref. 4) observed that the condensation of the benzoate of IV with methyl vinyl ketone gave the benzoate of IX.

(11) Subsequently V. I. Maksimov and G. S. Grinenko, *J. Gen. Chem.* (*U.S.S.R.*), 29, 2056 (1959) [*Chem. Abs.*, 54, 8760d (1960)], reported achieving the conversion of IV to VI (but with the secondary hydroxyl and the angular methyl groups missing) by condensing the tricyclic α,β-unsaturated ketone with methyl vinyl ketone, utilizing sodium ethoxide as the condensing agent.

(12) G. D. Meakins and O. R. Rodig, *J. Chem. Soc.*, 4679 (1956).

CHART II



ketone cleavage to give an additional quantity of the desired keto acid Vc rather than proceeding to yield XII.

Reduction of the acid Vc with lithium in liquid ammonia was expected to afford the thermodynamically more stable *anti-trans-anti-trans* saturated keto acid XIIIa as the principle product.[13] The acid obtained from the lithium-ammonia reduction melted at 165–167° and proved to be identical with that obtained by hydrogenation of Vc in aqueous potassium hydroxide solution with palladium on charcoal as the catalyst.[14]

In contrast to catalytic hydrogenation which provided the saturated acid in 71% yield, the reduction with lithium and ammonia gave the same acid in only 16% yield. Consequently the configurations of the two newly created centers of asymmetry could not be definitively assigned without additional evidence.

Since at this stage all six centers of asymmetry were introduced, a comparison was made of the synthetic (±)[15] acid XIIIa with the (+) seco acid, m.p. 158–159.5°, $[\alpha]_D$ +5°, which was obtained from the ozonolysis of (+) 19-nortestosterone.

The infrared spectra of both the (+) and the (±) acids were determined in chloroform solution as well as in the crystalline state (dispersed in potassium bromide). Although the infrared spectra of the (+) and (±) acids showed considerable differences when determined in the crystalline state, they were identical in every respect when the determination was made in chloroform.

The infrared spectrum of the (±) acid, which was determined in potassium bromide, exhibited a single peak at *ca.* 5.85 μ in the carbonyl region. In contrast the corresponding spectrum of the (+) acid displayed two distinct peaks in the same region, *viz.*, at *ca.* 5.78 and 5.88 μ.

In chloroform solution, however, the infrared spectra of both the (+) and the (±) acids showed a single peak at 5.81 μ in the carbonyl region.

Attempts to prepare a crystalline salt of the (+) seco acid with either (−) quinine or (−) brucine were unsuccessful, but with (+) amphetamine, $[\alpha]_D$ + 28.5°, the (+) seco acid afforded the crystalline (+) amphetamine·(+) seco acid salt, m.p. 113–116°, $[\alpha]_D$ + 21°.

When the (±) seco acid, XIII, was treated over a long period of time with the (+) amphetamine base, a small quantity of a salt, m.p. 124–127°, $[\alpha]_D$ *ca.* 0°, was obtained. The physical constants of this salt indicated that it was a diastereomer of the previously prepared (+) amphetamine·(+) seco acid salt. The infrared spectra, determined in potassium bromide, of the two salts were very dissimilar.

Treatment of the (+) seco acid with (−) amphetamine, $[\alpha]_D$ −30°, gave the (−) amphetamine·(+) seco acid salt, m.p. 123.5–127°, $[\alpha]_D$ *ca.* 0°. The infrared spectrum, determined in potassium bromide, of this salt was identical with that of the salt obtained from the resolution of the (±) seco acid with (+) amphetamine. Hence the latter must be the (+) amphetamine·(−) seco acid salt.

The conclusion thus inferred was substantiated by subsequent optical rotatory dispersion studies.[16]

Both the (+) base·(+) acid salt and the (−) base·(+) acid salt displayed negative Cotton effects in methanol, their amplitudes being −8,600 and −7,000, respectively. In contrast the salt obtained from the resolution of the (±) acid, for which the infrared study suggested the assignment (+) base·(−) acid, showed a positive Cotton effect of +9,100.

The acid, m.p. 147–152°, generated from the (+) base·(−) acid salt, in spite of its impurity as evidenced by its broad melting range, proved to be enantiomorphic with the (+) acid obtained from the ozonolysis of (+) 19-nortestosterone. Whereas

(13) F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 2696 (1952); D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954); A. Bowers, H. J. Ringold, and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958).

(14) P. Wieland, H. Ueberwasser, G. Anner, and K. Miescher, *Helv. Chim. Acta*, **36**, 376 (1953).

(15) In this paper the symbols (+) and (−) refer to the dextrorotation and levorotation, respectively, which a particular compound exhibits toward polarized light of 589 mμ. The symbol (±) indicates that the compound is racemic.

(16) We wish to thank Dr. William Klyne and his associates at the Postgraduate Medical School (London) for the rotatory dispersion measurements.

the former acid showed a positive Cotton effect in methanol (a +10,000) and the latter a negative effect (a −10,000), their infrared spectra, determined in *potassium bromide*, were identical in every respect. Thus all six centers of asymmetry of the (±) seco acid were correctly oriented as in (+) 19-nortestosterone.

The transformation of the (−) acetate of the (+) seco acid to (+) 19-nortestosterone acetate-4-C^{14} had previously been achieved in several laboratories.[17] Utilizing the procedures described by Uskokovic and Gut,[17a] we converted the (±) seco acid XIIIa to the androgenically and myotropically active[18] (±) 19-nortestosterone acetate (XVa), m.p. 113–114°, through the intermediate (±) enol lactone acetate XIV, m.p. 114.5–122°. The overall yield for the two steps conversion of the (±) acid to crude (±)-19-nortestosterone acetate was *ca.* 20%.

The infrared spectrum of (±)-19-nortestosterone acetate (XVa) was completely identical with that of (+) 19-nortestosterone acetate; both spectra were determined in chloroform.

The infrared spectrum, determined in chloroform, of the (±) enol lactone acetate XIV was nearly identical with that of the (−) enol lactone acetate.[17b,c] The minor differences could be attributed to the presence of impurities in the (±) product, which would also explain the wide range over which this substance melted. In the course of treating the (±) enol lactone acetate XIV with methylmagnesium bromide, we obtained a by-product[17c] which proved to be the acetate of the (±) seco acid, XIIIb, m.p. 151–152.5°. The (−) acetate,[17b] m.p. 111.5–113°, of the (+) seco acid was prepared for comparison, and it was found that the infrared spectra of the two acetates, determined in chloroform, were identical.

Hydrolysis of (±) 19-nortestosterone acetate gave (±) 19-nortestosterone (XVb) as an oil. Efforts to obtain it crystalline were unsuccessful.

We had thought of resolving (±) 19-nortestosterone into its optical antipodes with (−) menthoxyacetyl chloride, but this attempt was abandoned in favor of the resolution of the (±) seco acid XIIIa when we found that the corresponding menthoxyacetate of (+) 19-nortestosterone was an oil.

EXPERIMENTAL[19]

trans-1β-Hydroxy-8β-methyl-4,5-(4-methoxy-2,5-dihydrobenzo)hydrindane (II). To a stirred solution of 500 ml. of distilled liquid ammonia, 10.0 g. (0.043 mole) of *trans*-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane (I), 200 ml. of anhydrous ether, and 200 ml. of *t*-butyl alcohol was added 6 g. (0.865 g.-atom) of lithium wire in small portions. After the blue reaction mixture was stirred for 5 hr., it was carefully treated with 30 ml. of methanol whereupon the blue color was discharged. The ammonia was allowed to evaporate. Then the reaction mixture was diluted with water and concentrated under reduced pressure until the alcohol was removed. After the oil solidified, the solid was collected by filtration, washed well with water and dried.

Crystallization of the solid from hexane gave 6.7 g. (66.5%) of the enol ether, m.p. 84.5–90°. The analytical sample was obtained as colorless dense crystals after recrystallization from hexane, m.p. 87.5–89°; infrared (potassium bromide) 3.00, 5.91, 6.02 μ. The ultraviolet spectrum showed no significant absorption.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.06; H, 9.50.

anti-trans-1β-Hydroxy-8β-methyl(1,2,3,4-tetrahydrobenzo)-hydrindane (III). The combined mother liquors of the enol ether II were dissolved in 30 ml. of methanol and treated with 1.2 ml. of 4*N* hydrochloric acid. After the reaction mixture had stood at room temperature for 2 hr., it was neutralized with a 5% solution of sodium bicarbonate and then concentrated under reduced pressure to remove the methanol. The residue was saturated with sodium chloride and extracted with ether. The ethereal solution in turn was extracted with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure to afford an orange viscous oil. The oil was chromatographed on 300 g. of silica gel, and the column was eluted with a mixture of benzene and ethyl acetate of varying proportions. The solid product obtained with 10% ethyl acetate in benzene amounted to 1.4 g. It was crystallized from pentane to afford 0.82 g. (9.2%) of III, m.p. 93–97°. Recrystallization of III from pentane gave colorless plates, m.p. 96–98.5°; $\lambda_{max}^{CH_3OH}$ 190 mμ (ε 6,230); infrared (potassium bromide) 3.02 μ. Its NMR spectrum showed absorption at 4.67, 6.37, 8.34, and 9.17 τ.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.71; H, 10.86.

anti-trans-1β-Hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane (IV). To a solution of 23.2 g. (0.099 mole) of the enol ether II in 100 ml. of methanol was added 14 ml. of 6*N* hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 4 hr. It was then diluted with water and concentrated under reduced pressure to remove all the alcohol. The residue was extracted with a mixture of ether-pentane (3:1). The organic extract in turn was washed with water, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure. The oil remaining was crystallized from ether-pentane to afford 15.4 g. (70.6%) of the α,β-unsaturated ketone IV, m.p. 109–115°. An additional 1.4 g. (6.4%) of IV, m.p. 97–108° was obtained from the mother liquor.

The analytical sample of IV was obtained as colorless dense crystals after several crystallizations from ether, m.p. 110.5–112°; $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 16,600); infrared (potassium bromide) 2.92, 6.08, 6.28 μ.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.14; H, 9.33.

Condensation of IV *with methyl vinyl ketone.* To a chilled solution of sodium ethoxide prepared from 55 mg. (0.00238 g.-atom) of sodium and 20 ml. of absolute ethanol, which was freshly distilled from sodium, was added in several portions 500 mg. (0.00227 mole) of the α,β-unsaturated ketone IV. The homogeneous reaction mixture was stirred and cooled in an ice bath for 20 min. To it was then added 0.2 ml. (0.00247 mole) of anhydrous methyl vinyl ketone. The reaction mixture was stirred and allowed to come to room temperature over a period of 17 hr. After 2 ml. of glacial acetic acid was added, the reaction mixture was concentrated to a small volume under reduced pressure at 30°.

(17)(a) M. Uskokovic and M. Gut, *J. Org. Chem.*, **22**, 996 (1957); (b) J. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956); (c) S. Kushinsky, *J. Biol. Chem.*, **230**, 31 (1958).

(18) We are indebted to Dr. Victor A. Drill and Mr. Ehard F. Nutting and their associates for performing the biological assay.

(19) Melting points were determined on a Fisher-Johns melting block. Optical rotations were determined at 23°.

The semisolid residue was diluted with a large volume of water. The heavy viscous oil, which formed, was separated and triturated with several fresh portions of water. After drying at 68°, 1.0 mm., for 2 hr., it turned to a yellow amorphous powder, $\lambda_{max}^{CH_3OH}$ 246–250 and 325 mμ; λ_{min} 233–234 and 280–282 mμ; infrared (potassium bromide) 2.93, 5.82, 6.05, 6.28, and 6.45 μ.

The amorphous powder was dissolved in 5 ml. of absolute ethanol and to this solution was added a solution of 1 ml. of 12*N* hydrochloric acid and 5 ml. of absolute ethanol. The reaction mixture was heated under reflux in an atmosphere of nitrogen for 24 hr. It was then cooled and made neutral with a solution of 1.4*N* sodium hydroxide. The alcohol was removed by distillation under reduced pressure. The residue was extracted with ether. The ethereal extracts in turn were washed with a solution of 5% sodium hydroxide, which on acidification afforded no precipitate, and then with water, dried over anhydrous sodium sulfate and evaporated to dryness to yield 475 mg. of a brown semicrystalline product. This product was chromatographed on 10 g. of silica gel. The column was eluted with varying proportions of benzene–ethyl acetate. Elution with 15% ethyl acetate in benzene gave 148 mg. (24.1%) of a crystalline product. Successive crystallizations first from ether and then from benzene gave 68 mg. (11.1%) of *3-keto-8β-hydroxy-6,7aβ-dimethyl - 1,2,3,7,7a,8,9,10,10aα,10bβ - decahydrocyclopenta[e]phenalene* (IX), m.p. 196.5–196.5°. The analytical sample was obtained as colorless dense crystals, m.p. 198–199.5°, after another crystallization from benzene; $\lambda_{max}^{CH_3OH}$ 265.5 mμ (ε 13,900), $\lambda_{shoulder}$ 294 mμ (2,430), λ_{min} 233 (1,410); infrared (potassium bromide) 2.92, 6.03, 6.32, 6.38 μ; NMR 2.13, 2.25, 7.73, 9.18 τ. It afforded a red precipitate with the 2,4-dinitrophenylhydrazine reagent.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.68; H, 8.34.

No additional product could be identified in the remaining chromatography fractions.

(±) *17β-Hydroxy-5-keto-3,5-seco-4-norestr-9-an-3-oic acid* (Vc). To a solution of potassium *t*-butoxide prepared from 3.6 g. (0.092 g.-atom) of potassium and 80 ml. of anhydrous *t*-butyl alcohol was added in succession 80 ml. of anhydrous ether and 4.0 g. (0.0182 mole) of the unsaturated tricyclic ketone IV. The reaction mixture was stirred at room temperature for 30 min. It was then cooled in an ice bath, and a solution of 2.4 ml. (0.0266 mole) of redistilled methyl acrylate in 40 ml. of anhydrous ether was added over a period of 20 min. The reaction mixture was stirred with cooling in the ice bath for 1.5 hr. The ice bath was removed, and the reaction mixture was stirred at room temperature for an additional 3 hr. After 25 ml. of water was added, the reaction mixture was distilled under reduced pressure to remove the alcohol. A solution of 20 g. of potassium hydroxide, 20 ml. of water, and 20 ml. of methanol was added to the residue, and the mixture was heated under reflux in an atmosphere of nitrogen for 1.25 hr.

The reaction mixture was concentrated under reduced pressure to remove the alcohol, and the residue was diluted with water and extracted with ether. The ethereal extracts were washed with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness to afford a viscous oil. Crystallization of the oil from ether-pentane gave 0.21 g. (5.3%) of the starting material, m.p. 99.5–107.5°.

The aqueous alkaline solution was acidified by pouring into a mixture of ice and 12*N* hydrochloric acid. The turbid mixture was saturated with sodium chloride and extracted with ethyl acetate. The combined ethyl acetate extracts were washed successively with water and a saturated solution of sodium chloride, then dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure. The semisolid residue was crystallized from acetone to afford 2.01 g. (37.8%) of the unsaturated acid Vc, m.p. 194.5–199.5°. Concentration of the mother liquor gave two additional crops of the acid, one melting at 190–195.5° (yield 0.52 g., 9.8%) and the other at 186–191° (yield 0.10 g., 1.9%).

The analytical sample was obtained as colorless dense crystals from acetone-benzene, m.p. 196.5–199.5°; $\lambda_{max}^{CH_3OH}$ 248 mμ (ε 14,900); infrared (potassium bromide) 2.88, 5.73, 5.84, 6.15, 6.25 μ.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.85; H, 8.42.

In one run the oily product, obtained by evaporating to dryness the residual mother liquor, was partitioned between ethyl acetate and a 5% solution of sodium bicarbonate. The ethyl acetate phase was evaporated to dryness and the residue was observed to impart a violet-gray color to a solution of ferric chloride.

(±) *17β-Hydroxy-5-keto-3,5-seco-4-norestran-3-oic acid* (XIIIa). (a) *By lithium and ammonia reduction of* Vc. A mixture of 50 ml. of liquid ammonia, 25 ml. of tetrahydrofuran, and 0.5 g. of lithium was stirred until the blue color had disappeared. To the mixture was then added 0.62 g. (0.00212 mole) of the unsaturated keto acid Vc, and the reaction mixture was stirred for 15 min. Upon the addition of 0.2 g. (0.0288 g.-atom) of lithium the reaction mixture turned blue almost instantaneously. The reaction mixture was stirred for an additional 5 min. Solid ammonium chloride was added to destroy the excess lithium, and after evaporation of the ammonia water was added to the residue. The tetrahydrofuran was removed by distillation under reduced pressure, and the residue was acidified with 12*N* hydrochloric acid. The acidified mixture was saturated with sodium chloride and then extracted with ethyl acetate. The ethyl acetate solution in turn was extracted with a 5% solution of potassium bicarbonate, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure to afford a moderate amount of a neutral substance, which could not be induced to crystallize and which was not investigated further.

The bicarbonate extracts were in succession acidified with 12*N* hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure. The residue was crystallized from acetone-hexane to yield 0.10 g. (16%) of (±) XIIIa, m.p. 160.5–162.5°. No additional product could be obtained from the mother liquor. The analytical sample melted at 165–167° after repeated crystallizations from acetone-hexane; infrared (potassium bromide) 2.98, *ca.* 5.85 μ; infrared (chloroform) 2.68, 5.81 μ. The infrared spectrum, determined in chloroform, was identical with the corresponding spectrum of the (+) acid obtained from the ozonolysis of (+) 19-nortestosterone (*vide infra*).

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.00; H, 8.51.

(b) *By catalytic hydrogenation of* Vc. A solution of 5.55 g. (0.019 mole) of the unsaturated acid Vc and 1.8 g. (0.0273 mole) of 85% potassium hydroxide pellets in 125 ml. of water was hydrogenated over 1.0 g. of 5% palladium on charcoal. The hydrogenation was carried out at room temperature and at three atmospheres. After 10 min. the calculated amount of hydrogen was absorbed. The reduction mixture was freed of the catalyst by filtration and acidified with cold 12*N* hydrochloric acid. After the acidified mixture was saturated with sodium chloride, it was extracted with ethyl acetate. The ethyl acetate extracts were in turn washed with several portions of a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure. The crystalline residue was recrystallized from acetone-hexane to afford 3.25 g. (58.6% of (±) XIIIa, m.p. 160–162.5°. An additional 0.7 g. (12.6%) of (±) XIIIa, m.p. 158–160°, was obtained from the mother liquor. The infrared spectra, determined in chloroform and potassium bromide, of the acid, m.p. 160–162.5°, were identical with the corresponding spectra of the acid prepared according to procedure (a).

(+) *17β-Hydroxy-5-keto-3,5-seco-4-norestran-3-oic acid* (XIIIa). A solution of 4.9 g. (0.018 mole) of (+) 19-nortestosterone in 100 ml. of methylene chloride and 20 ml. of absolute methanol was colled in an acetone–Dry Ice bath. Ozone was passed into the reaction mixture over a period of 23 min. during which time the calculated amount of ozone was absorbed. A solution of 1.5 ml. of 30% hydrogen peroxide and 3 ml. of water was added, and the reaction mixture was allowed to stand at room temperature with occasional swirling for 15 hr. After water was added to the reaction mixture, the methylene chloride phase was separated. The methylene chloride solution was washed with water and then extracted with a saturated solution of sodium bicarbonate. The combined sodium bicarbonate extracts were acidified with a mixture of ice and 12*N* hydrochloric acid. After nitrogen was bubbled into the acidified mixture, a colorless crystalline product formed. The solid was collected, washed well with water and dried, m.p. 155–156.5°, yield 2.29 g. (43.6%). After three crystallizations from acetone-hexane the (+) seco acid XIIIa was obtained as colorless dense crystals, m.p. 158–159.5°; $[\alpha]_D$ + 5° (1% dioxane); trough, λ 310 mμ, $[M]_{310}$ − 4,500, peak, λ 265 mμ, $[M]_{265}$ + 5,500, *a* −10,000 (methanol); infrared (potassium bromide) 2.93, 2.98, *ca.* 5.78, 5.88 μ; infrared (chloroform) 2.68, 5.81 μ.

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.17; H, 8.80.

(+) *Amphetamine·(+) 17β-Hydroxy-5-keto-3,5-seco-4-norestran-3-oic acid salt.* A solution of 0.058 g. (0.00043 mole) of (+)amphetamine ($[\alpha]_D$ + 28.5° in dioxane) in 0.4 ml. of ethyl acetate was added to a warm solution of 0.100 g. (0.00034 mole) of (+) XIIIa in 4 ml. of ethyl acetate. Upon cooling to room temperature, the reaction mixture deposited a colorless crystalline product. The solid was collected by filtration and crystallized twice from ethyl acetate to afford 0.16 g. (79.4%) of the (+) base·(+) acid salt, m.p. 113–116° $[\alpha]_D$ + 21° (1% water); trough, λ 308 mμ $[M]_{308}$ − 2,800, peak, λ 270 mμ, $[M]_{270}$ + 5,800, *a* −8,600 (methanol); infrared (potassium bromide) 3.05, 5.84, 6.13 μ.

Anal. Calcd. for $C_{26}H_{39}O_4N$: C, 72.69; H, 9.15. Found: C, 72.76; H, 8.83.

(−) *Amphetamine·(+) 17β-Hydroxy-5-keto-3,5-seco-4-norestran-3-oic acid salt.* To a warm solution of 0.300 g. (0.00102 mole) of (+) XIIIa in 8 ml. of ethyl acetate was added a solution of 0.188 g. (0.00139 mole) of (−) amphetamine ($[\alpha]_D$ −30° in ethanol) in 3 ml. of ethyl acetate. The reaction mixture on standing at room temperature deposited a colorless crystalline product. The mixture was then cooled to 5°. The solid was collected, yield 0.432 g. (98.6%), m.p. 123–126°. Two crystallizations from ethyl acetate gave 0.314 g. of the (−) base·(+) acid salt, m.p. 123.5–127°; $[\alpha]_D$ −0.5 ±1.0° (1% water); trough, λ 308 mμ, $[M]_{308}$ −3,000, peak, λ 270 mμ, $[M]_{270}$ + 4,000, *a* −7,000(methanol); infrared (potassium bromide) 3.02, 5.84, 6.08 μ. The infrared spectrum differed vastly from that of the (+) base·(+) acid salt.

Anal. Calcd. for $C_{26}H_{39}O_4N$: C, 72.69; H, 9.15. Found: C, 72.94; H, 9.03.

Resolution of (±) *17β-hydroxy-5-keto-3,5-seco-4-norestran-3-oic acid* (XIIIa) with (+) *amphetamine.* To a warm solution of 0.898 g. (0.00305 mole) of (±) XIIIa in 15 ml. of ethyl acetate was added a solution of 0.182 g. (0.00135 mole) of (+) amphetamine in 1 ml. of ethyl acetate. On cooling to room temperature, the reaction mixture deposited an oil. The solution was decanted, and on further standing at room temperature it afforded a colorless crystalline product. The product was collected, yield 0.109 g. (18.8% based on amphetamine used), m.p. 114.5–119°. Repeated crystallizations from ethyl acetate gave the (+) *amphetamine·(−) acid salt,* m.p. 124–127°; $[\alpha]_D$ + 0.5 ± 1.0° (1% water), peak, λ 308 mμ, $[M]_{308}$ + 3,800, trough, λ 270 mμ, $[M]_{270}$ −5,300, *a* +9,100 (methanol); infrared (potassium bromide) 3.02, 5.84, 6.08 μ. Its infrared spectrum was identical with that of the (−) amphetamine·(+) acid salt and differed considerably from that of the (+) amphetamine·(+) acid salt.

Anal. Calcd. for $C_{26}H_{39}O_4N$: C, 72.69; H, 9.15. Found: C, 72.65; H, 8.78.

A sample of the (+) amphetamine·(−) acid salt, m.p. 116–119°, was acidified with 6*N* hydrochloric acid. The mixture was extracted with ethyl acetate, and the combined ethyl acetate extracts were washed with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness to afford a brown oil. The oil was crystallized from acetone-ether-hexane to afford colorless dense crystals, m.p. 147–152°; peak, λ 310 mμ, $[M]_{310}$ + 3,500, trough, λ 265 mμ, $[M]_{265}$ −6,500, *a* +10,000 (methanol); infrared (potassium bromide) 2.93, 2.98, *ca.* 5.78, 5.88 μ. The infrared spectrum was found to be identical with the corresponding spectrum, determined in potassium bromide, of (+) XIIIa.

(−) *17β-Acetoxy-5-keto-3,5-seco-4-norestran-3-oic acid* (XIIIb). A solution of 200 mg. (0.00068 mole) of the (+) seco acid XIIIa, 1 ml. (0.016 mole) of acetic anhydride and 1 ml. of pyridine was allowed to stand at room temperature for 17 hr. The reaction mixture was then treated with ice and water to afford a wax-like substance. The wax was collected by filtration and washed well with water. Since it could not be induced to crystallize, it was dissolved in a mixture of ether and a 5% solution of sodium bicarbonate. The bicarbonate phase was separated and then acidified by pouring into a mixture of ice and 12*N* hydrochloric acid. The resulting solid was collected, washed well with water, and dried, yield 88 mg. (38.4%), m.p. 111.5–113.5°. Three crystallizations from ether-pentane gave the (−) acetoxy acid XIIIb as colorless dense crystals, m.p. 111.5–113°; infrared (potassium bromide) 5.80, 5.87, 7.95, 8.07 μ; infrared (chloroform) 2.84, 5.78, *ca.* 5.8, 7.94 μ (reported[16b] m.p. 113–115°; $[\alpha]_D$ −4.08° (chloroform)).

(−) *17β-Acetoxy-5-keto-3,5-seco-4-norestran-3-oic acid enol lactone* (XIV). A solution of 270 mg. (0.000918 mole) of the (−) seco acid XIIIa and 1.5 ml. (0.0159 mole) of acetic anhydride was heated under reflux for 1.5 hr. in an atmosphere of nitrogen. After 10 mg. (0.000122 mole) of anhydrous sodium acetate was added, the reaction mixture was heated under reflux for an additional 3 hr. in an atmosphere of nitrogen. The reaction mixture was then distilled to dryness under reduced pressure, and the residue was diluted with ether. The mixture was filtered and the filtrate was concentrated to a small volume by evaporation in a stream of nitrogen. The residue was diluted with hexane whereupon the (−) enol lactone acetate XIV began to crystallize. The crystalline product amounted to 195 mg. (66.8%), m.p. 114–120°. Successive crystallizations first from 95% ethanol and then from ethane-pentane gave XIV as colorless plates, m.p. 114.5–116°; infrared (chloroform) 5.73, 5.77, 5.92, *ca.* 7.90 μ (reported m.p. 129–130°, $[\alpha]_D^{25}$ −37.9° (chloroform)[16b]; m.p. 121–125°[16c]).

(±) *17β-Acetoxy-5-keto-3,5-seco-4-norestran-3-oic acid enol lactone* (XIV). A solution of 240 mg. (0.000815 mole) of the (±) seco acid XIIIa and 1.5 ml. (0.015 mole) of redistilled acetic anhydride was heated under reflux in an atmosphere of nitrogen for 1.5 hr. After 10 mg. (0.000122 mole) of anhydrous sodium acetate was added to the reaction mixture, heating was continued in the nitrogen atmosphere for an additional 4 hr. The reaction mixture was concentrated to a very small volume by distillation under reduced pressure. The residue was diluted with a mixture of ether and benzene. The solid was removed by filtration. The filtrate was evaporated to dryness to afford viscous residue, which was crystallized from ether-hexane to yield 150 mg. (58%) of the (±) enol lactone acetate, m.p. 114.5–119.5°. Two crystallizations from ether-hexane gave (±) XIV as colorless dense crystals, m.p. 114.5–122°; infrared (chloroform) 5.72, 5.77, 5.92, *ca.* 7.90 μ. Its infrared spectrum was very nearly identical with that of (−) XIV.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.44; H, 8.28.

(±) *19-Nortestosterone acetate* (XVa). A solution of magnesium iodide in 200 ml. of anhydrous ether was prepared from 11.2 g. (0.078 mole) of methyl iodide and 2.0 g. (0.0824 g.-atom) of magnesium. The Grignard solution was cooled in an ice bath, and to it was added over a period of 15 min. a solution of 7.87 g. (0.0247 mole) of the (±) enol lactone acetate XIV in 200 ml. of anhydrous ether. The reaction mixture was stirred and maintained at 5–7° for 3 hr. Then it was treated with 200 ml. of water and acidified with 1.2*N* hydrochloric acid. The ethereal phase was separated, washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure. The residue was treated with a small volume of ether whereupon it afforded 0.36 g. (5%) of a crystalline product, which proved to be (±) 17β-hydroxy-5-keto-3,5-seco-4-norestran-3-oic acid (XIIIa). The ethereal solution was evaporated to dryness, and the residual gum was dissolved in a mixture of 50 ml. (0.53 mole) of acetic anhydride and 5 ml. of 12*N* hydrochloric acid. After the reaction mixture had stood at room temperature for 13 hr., it was poured into a solution of 6 g. of potassium carbonate in 200 ml. of water. The mixture was concentrated under reduced pressure and then extracted with ether. The combined ether extracts were in turn extracted with a 5% solution of potassium carbonate, dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure. The residual oil was chromatographed on 250 g. of silica gel. Elution of the column with benzene gave 2.09 g. of an unidentified oil, which showed carbonyl absorption only at 5.80 μ in chloroform solution. Further elution with 15% ethyl acetate in benzene gave 2.65 g. (33.9%) of crude (±) 19-nortestosterone acetate (XVa), which exhibited polymorphism. The first crystallization from ether-pentane gave 1.65 g. (21.1%) of massive, colorless rhombs, m.p. 95–96°. A second crystallization from the same solvent pair afforded (±) XVa as colorless rods, m.p. 113–114°, unchanged on further crystallization; $\lambda_{max}^{CH_3OH}$ 239.5 mμ (ε 17,600); infrared (chloroform) 5.75, 5.97, 6.15, 7.90 μ. Its infrared spectrum was identical with that of (+) 19-nortestosterone acetate.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.16; H, 8.86.

The potassium carbonate extracts were acidified with 12*N* hydrochloric acid to afford 1.03 g. (12.4%) of (±) *17β-acetoxy-5-keto-3,5-seco-4-norestran-3-oic acid* (XIIIb). Repeated crystallizations from ether-pentane afforded (±) XIIIb as colorless, densely packed crystals, m.p. 151–152.5°; infrared (potassium bromide) *ca.* 5.8, 5.84, *ca.* 8.0 μ; infrared (chloroform) 2.84, 5.78, ca. 5.8, 7.94 μ. Its infrared spectrum, determined in chloroform, was identical with the corresponding spectrum of (−) XIIIb (*vide supra*).

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.65; H, 8.22.

(±) *19-Nortestosterone* (XVb). A 0.21-g. (0.000765 mole) sample of (±) 19-nortestosterone acetate was dissolved in a solution of 1 g. (0.025 mole) of sodium hydroxide in 2 ml. of water and 18 ml. of methanol. The reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 1 hr. Then it was chilled in an ice bath and diluted with a large volume of water. The oil which resulted could not be induced to solidify. The mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were washed successively with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and evaporated to dryness. The residual oil was chromatographed on 4 g. of silica gel. Elution of the column with varying proportions of benzene–ethyl acetate afforded no crystalline product.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

Studies in the Total Synthesis of Steroids and Their Analogs. II. Des-A Analogs of Clinically Active Steroids

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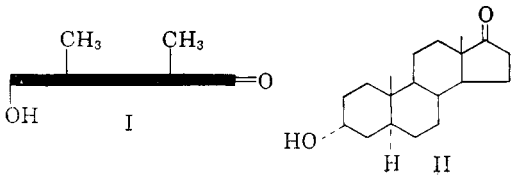
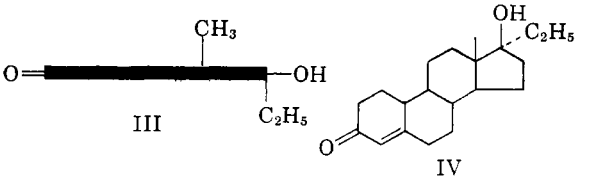
The des-A tricyclic analogs of estrone, 19-nortestosterone, 17α-ethynyl-19-nortestosterone, 17α-ethyl-19-nortestosterone, and the spirolactone of 17α-carboxyethyl-19-nortestosterone were synthesized and submitted for biological testing. The tricyclic analog of estrone was found to be estrogenically active, confirming the result of previous workers. With the exception of the tricyclic spirolactone none of the other compounds possessed the principal biological activities of their steroid counterparts.

The clinical usefulness of a number of steroids has been amply demonstrated. In an attempt to determine the extent to which the tetracyclic ring system contributes to biological activities, we have synthesized and submitted for biological testing the des-A analogs of several steroids which have attained therapeutic importance.

The ring system of these steroids is nearly planar. This is delineated in I, the cross section of androsterone (II) taken through C-3, 10, 13, and 17 with the projection of the ring hydrogen atoms being omitted.



Expression III represents the corresponding cross section of 17α-ethyl-19-nortestosterone (IV).



When ring A is missing as in *trans-anti-trans*-1α-ethyl-1β-hydroxy-8β-methyl-4,5-(4-ketoperhydro-