(±) *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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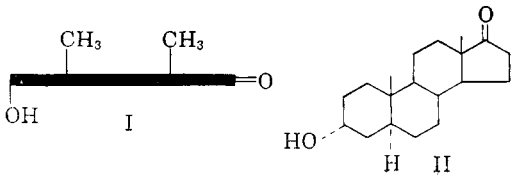
Received March 16, 1961

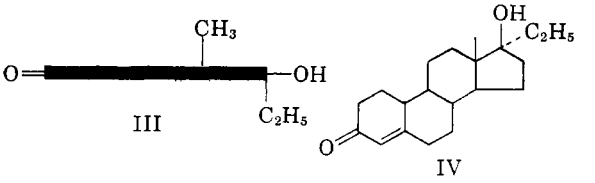
The des-A tricyclic analogs of estrone, 19-nortestosterone, 17α-ethynyl-19-nortestosterone, 17α-ethyl-19-nortestosterone, and the spirolactone of 17α-carboxyethyl-19-nortestosterone were synthesized and submitted for biological testing. The tricyclic analog of estrone was found to be estrogenically active, 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.

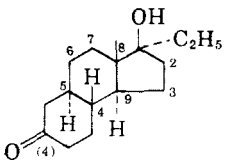


Expression III represents the corresponding cross section of 17α-ethyl-19-nortestosterone (IV).

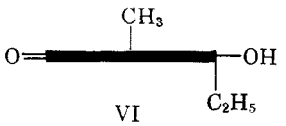


When ring A is missing as in *trans-anti-trans*-1α-ethyl-1β-hydroxy-8β-methyl-4,5-(4-ketoperhydro-

benzo)hydrindane (V), the "template" of the steroid appears to be compressed as shown in VI.



V



VI

Thus, while the objective of this study was to evaluate the influence of the tetracyclic system on the biological activities, the study may also be viewed as an attempt to assess the effect which variation of the interatomic distance between the two oxygen functions at C-3 and C-17 of a steroid would have on the biological properties of the substance.

Although attempts along this line have been made by previous investigators, the analogs, which were selected for many of these studies,[1] had critical limitations in that either they were but a fragment of the steroid molecule or they were of the open chain type. As compounds of the latter type can assume a number of conformations, the interatomic distances may vary with conformational changes. In addition the energetically preferred conformation may not be the one which is analogous to the skeletal arrangement of the steroids. Thus the study of Jeffrey, Koch, and Nyburg[2] suggests that the favored conformation of the potent synthetic estrogens, diethylstilbestrol and o,o′,α,β-tetramethylstilbestrol, bears no resemblance to the ring system of estradiol.

In the des-A analogs of the present study the distance separating the two oxygen functions is rigidly fixed as is evident in VI because of the inflexible nature of the condensed tricyclic ring system. Moreover, since the substituted rings C and D of the analogs are exact replicas of those of the corresponding steroids, they would impart to the analogs an equivalence of the "thickness" that may be a contributory factor toward the biological activities of the steroids.

For the purpose of this study we undertook the synthesis of the following tricyclic compounds in addition to V: *trans*-1-keto-8β-methyl-4,5-(4-hydroxybenzo)hydrindane (IX),[3,4] *anti-trans*-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane (XI),[5] *anti-trans*-1α-ethynyl-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane (XIV), *anti-trans*-1α-ethyl-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane (XVIII), and *anti-trans*-1α-2′-carboxyethyl-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane lactone (XXII).

The starting material for their syntheses was *trans*-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane (VII) prepared according to the procedure of Banerjee, Chatterjee, Pillai, and Bhatt.[3] As a result of the conversion of VII to 19-nortestosterone,[5] the configuration of VII, relative to the two hydrogen atoms and the methyl group at the three centers of asymmetry, has been established as *trans-anti*.

Interestingly *trans*-1-keto-8β-methyl-4,5-(4-hydroxybenzo)hydrindane (IX), the tricyclic analog of estrone, previously had been synthesized by Bachmann and Thomas,[4] and they reported that it was capable of inducing the estrus response in ovariectomized rats at the dose level of 5 mg. We repeated the synthesis of IX from VII[3] and confirmed their biological result.

Although we were aware that a high degree of structural specificity was not required for estrogenic activity,[6,1c] we were, nevertheless, encouraged by this observation.

The dihydro alcohol X,[5] obtained by partial reduction of the aromatic ring of VII by means of lithium in liquid ammonia,[7] was converted to the dihydro ketone XII with the application of the Oppenauer oxidation procedure. Treatment of XII with potassium acetylide afforded the dihydroethynylcarbinol XIII, which was hydrolyzed in the presence of mineral acid to give XIV, the des-A analog of 17α-ethynyl-19-nortestosterone, a progestational substance.

The ethynyl group in XIV was postulated as having the α-orientation since the stereochemistry

(1)(a) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **71**, 2388 (1950); A. L. Wilds, C. H. Hoffman, and T. H. Pearson, *J. Am. Chem. Soc.*, **77**, 647 (1955); (b) W. H. Linnell, D. W. Mathieson and G. Williams, *Nature*, **167**, 237 (1951); L. E. Coles, W. H. Linnell, D. W. Mathieson, and A. S. Shoukri, *J. Chem. Soc.*, 2617 (1954); (c) P. Daneberg, *Arzneimittel-Forsch.*, **8**, 339 (1951); (d) K. W. Bentley, *J. Chem. Soc.*, 2398 (1955); K. W. Bentley and W. C. Furth, *J. Chem. Soc.*, 2403 (1955); (e) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).

(2) G. A. Jeffrey, H. P. Koch, and S. C. Nyburg, *J. Chem. Soc.*, 1118 (1948).

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(4) W. E. Bachmann and D. G. Thomas, *J. Am. Chem. Soc.*, **64**, 94 (1942).

(5)(a) L. J. Chinn and H. L. Dryden, Jr., 134th Meeting of the American Chemical Society, Chicago, Ill., September, 1958 (Abstracts of Papers p. 14-O), *J. Org. Chem.*, **26**, 3904 (1961); (b) L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, and A. Pierdet, *Compt. rend.*, **250**, 1084 (1960); L. Velluz, G. Nominé, and J. Mathieu, *Angew. Chem.*, **72**, 725 (1960).

(6) *Cf., inter alia*, E. C. Dodds, *Vitamins and Hormones*, Vol. III, R. S. Harris and K. V. Thimann, ed., Academic Press, Inc., New York, N. Y., 1945, p. 229; A. H. Stuart, A. J. Shukis, R. C. Tallman, C. McCann, and G. R. Treves, *J. Am. Chem. Soc.*, **68**, 729 (1946); R. Courrier, A. Horeau, and J. Jacques, *Compt. rend. soc. biol.*, **141**, 159 (1947); H. Rinderknecht and L. W. Rowe, *Science*, **115**, 292 (1952); R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 871 (1953); R. E. Juday, *J. Am. Chem. Soc.*, **75**, 3008 (1953).

(7) 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).

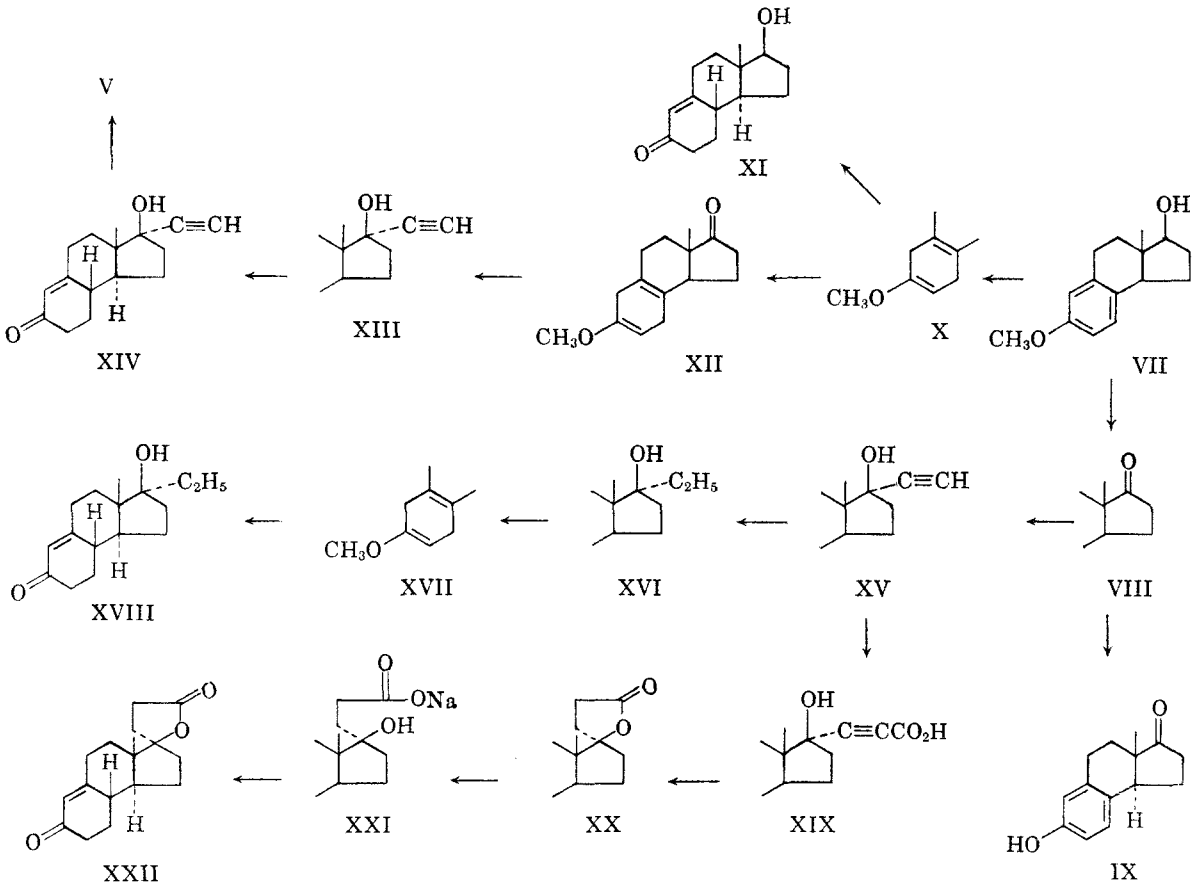
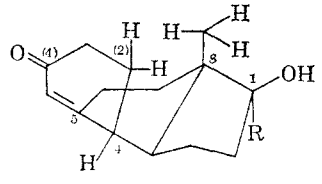


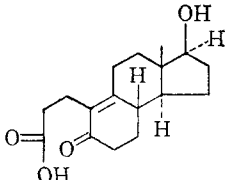
Figure 1

of its addition was strictly analogous to that in the 17-ketosteroid series. The hydrogen atom at C-4 was assigned the β-configuration on the basis that the hydrolysis of XIII would give the thermodynamically more stable *anti-trans* isomer. The *syn-trans* isomer, in which the hydrogen atom at C-4 was α-oriented, was regarded as less stable because of steric compression resulting from the juxtaposition of the C-2 methylene group and the angular methyl group at C-8 (*q.v.* XXIII).

In addition since XI had been prepared in an analogous fashion (*viz.*, acid hydrolysis of the corresponding enol ether) and was converted to 19-nortestosterone,[5] the configuration at C-4 of XIV was firmly established.



XXIII



XXIV

When XIV was hydrogenated in the presence of pyridine over palladium on calcium carbonate in the hope of obtaining the corresponding vinyl compound and thence the ethyl compound XVIII, no break in the hydrogen uptake could be discerned at the stage calculated for the reduction of only the triple bond. The uptake of hydrogen proceeded smoothly until the equivalence of three moles of hydrogen was absorbed. The product obtained after the absorption of the equivalence of three moles of hydrogen proved to be V in which both the triple and double bonds were hydrogenated.

The hydrogen atom at the new center of asymmetry (C-5) of V was tentatively assigned the α-configuration in analogy to the catalytic reduction of the unsaturated keto acid XXIV, which had been shown earlier to have proceeded from the backside.[5a]

The synthesis of XVIII, the des-A analog of 17α-ethyl-19-nortestosterone (IV) an orally active anabolic agent, was achieved in the following way.

trans-1-Keto-8β-methyl-4,5-(4-methoxybenzo)-hydrindane (VIII) prepared from VII[3] was condensed with potassium acetylide to give the aromatic ethynyl alcohol XV. After the triple bond was reduced catalytically, the resulting product XVI was subjected to reduction with lithium in liquid ammonia.[7] The enol ether XVII so obtained was readily hydrolyzed with hydrochloric acid to give the desired product XVIII.

When the ethynyl alcohol XV was converted to the Grignard derivative with methylmagnesium bromide and then carboxylated with carbon dioxide,

the hydroxyethynyl acid XIX was obtained. The acid XIX was catalytically hydrogenated in the form of its triethylamine salt. Acidification of the reduction mixture gave the aromatic lactone XX in a manner analogous to that described in the steroid series.[8]

The reduction of the aromatic ring of XX to afford XXII, the des-A analog of the aldosterone-blocking spirolactone of 17α-carboxyethyl-19-nortestosterone, was accomplished in several steps.[8]

The lactone XX was first converted to its sodium salt XXI, and the latter was then successively reduced with lithium in liquid ammonia[7] and hydrolyzed with mineral acid to afford XXII.

The configuration of XVIII and XXII was deduced in the same manner as for XIV (*vide supra*).

The biological activities of these tricyclic analogs were determined by our Division of Biological Research and at the Worcester Foundation for Experimental Biology.[9]

Both compounds V and XVIII were found to be devoid of anabolic activity, XI and XIV of androgenic and progestational activities, respectively, while the tricyclic lactone XXII was observed to block the sodium retaining activity of the mineralcorticoids to some extent.

EXPERIMENTAL[10]

trans-1-Keto-8β-methyl-4,5-(4-methoxybenzo)hydrindane (VIII). To a solution of 43.0 g. (0.185 mole) of the tricyclic alcohol VII[3] in 450 ml. of acetone and 10 ml. of water maintained at −9° was added over a period of 30 min. with stirring a solution of 12.3 g. (0.123 mole) of chromium trioxide in 37 ml. of water and 11 ml. of 36*N* sulfuric acid. After the reaction mixture was allowed to warm to −5°, a a solution of 10 ml. of ethanol was added. The reaction mixture was filtered, and the chromium salts were washed with acetone. The combined filtrates were diluted with 200 ml. of water containing 2 g. of sodium bisulfite and concentrated under reduced pressure to remove the acetone. The resulting solid product was collected by filtration and washed well with water. It was then dissolved in a mixture of ethyl acetate and ether. The solution was in turn washed successively with dilute sulfuric acid, water and a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvents by distillation under reduced pressure gave a product, which was crystallized from ethyl acetate–ether to yield 27.1 g. (64%) of the tricyclic ketone VIII, m.p. 110.5–112.5° (reported[3] m.p. 112–113°, yield 40% with pyridine-chromic acid complex as the oxidizing agent). An additional 4.0 g. (9%) of the ketone was obtained from the mother liquor. The infrared spectrum of the residual mother liquor indicated that it was a mixture of ketone and alcohol.

Demethylation of VIII. To 4 g. of pyridine hydrochloride, which had previously been heated to 240° and then cooled, was added 0.500 g. (0.00217 mole) of *trans*-1-keto-8β-methyl-4,5-(4-methoxybenzo)hydrindane (VIII). The reaction vessel was evacuated and filled with nitrogen. After the reaction mixture had stood at 215±5° (bath temp.) for 45 min., it was cooled, diluted with a large volume of water, and chilled in an ice bath. The resulting solid was collected and washed well with water, yield 0.417 g. Two crystallizations from benzene gave 0.311 g. (66%) of *trans*-1-keto-8β-methyl-4,5-(4-hydroxybenzo)hydrindane (IX) as colorless dense crystals, m.p. 211–211.5° (vac.), reported[4] 212–214° (vac.).

Oxidation of trans-1β-hydroxy-8β-methyl-4,5-(4-methoxy-2,5-dihydrobenzo)hydrindane (X). To a stirred solution of 6.0 g. (0.0256 mole) of X[5] and 6.0 g. (0.0612 mole) of cyclohexanone in 215 ml. of anhydrous toluene heated under reflux in a nitrogen atmosphere was added over a period of 5 min. a solution of 6.0 g. (0.0294 mole) of aluminum isopropoxide in 80 ml. of anhydrous toluene. The reaction mixture was heated under reflux for an additional hour, cooled to 50°, treated with 45 ml. of a saturated solution of Rochelle salt and steam distilled until the distillate was clear. The residue was cooled and the solid product was collected and dried *in vacuo*, yield 4.8 g. Crystallization from hexane gave 3.45 g. (58%) of *trans-1-keto-8β-methyl-4,5-(4-methoxy-2,5-dihydrobenzo)hydrindane* (XII) as colorless dense crystals, m.p. 97–99°. Its infrared spectrum (potassium bromide) showed the complete absence of the hydroxyl group, the presence of a peak at 5.76 μ (C=O) and the typical enol ether doublet at 5.90 and 6.00 μ. The ultraviolet spectrum revealed the presence of only 0.4% of aromatic contaminant.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.36.

The mother liquor afforded an additional 0.65 g. (11%) of XII, m.p. 90–95°.

trans-1α-Ethynyl-1β-hydroxy-8β-methyl-4,5-(4-methoxy-2,5-dihydrobenzo)-hydrindane (XIII). Under a nitrogen atmosphere 3.4 g. (0.87 g.-atom of potassium was dissolved in 80 ml. of anhydrous *t*-butyl alcohol. The resulting stirred solution was diluted with 20 ml. of anhydrous toluene, cooled in an ice bath, and saturated with acetylene which previously had passed through a solution of 36*N* sulfuric acid. After a solution of 3.4 g. (0.0146 mole) of the ketone XII in 20 ml. of toluene was added, passage of acetylene was resumed for an additional 6 hr. while the stirred reaction mixture was kept cooled in the ice bath. The reaction mixture was diluted with 200 ml. of water and extracted with ether. The ethereal extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness to afford 3.60 g. of the product. Crystallization from hexane gave 2.70 g. (71%) of XIII as colorless dense crystals, m.p. 112–113°. Its infrared spectrum (potassium bromide) displayed peaks at 2.94, 3.03, 4.72, 5.89, and 5.99 μ.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found. C, 79.15; H, 8.65.

An additional 0.3 g. (8%) of XII, m.p. 105–110°, was obtained from the mother liquor.

Acid hydrolysis of XIII. To 1.34 g. (0.00518 mole) of the enol ether XIII was added 8.5 ml. of an aqueous-methanolic solution of hydrochloric acid prepared by mixing 1 ml. of 6*N* hydrochloric acid with 7.5 ml. of methanol. The reaction mixture was stirred at room temperature for 3 hr. in an atmosphere of nitrogen. It was then diluted with a large volume of water. The resulting colorless solid was collected and washed well with water. The combined filtrates were extracted with ethyl acetate. The extracts were in succession washed with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure to afford an oil. The oil was combined with the solid and the mixture was crystallized from acetone after decolorization with charcoal to yield 1.00 g. (79%) of *anti-trans-1α-ethynyl-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane* (XIV), m.p. 182–183.5°. The analytical sample, obtained as colorless dense crystals from benzene, melted at 181.5–184°; infrared (potassium bromide) 2.92, 3.12, 4.75, 6.00, 6.17 μ; $\lambda_{max}^{CH_3OH}$ 238–239 mμ (ε 15,630).

(8) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, 24, 743 (1959).

(9) We are indebted to Drs. Victor A. Drill, Richard A. Edgren, Richard L. Elton, Charles M. Kagawa, Gregory Pincus, Francis J. Saunders, and their associates for performing the biological assays.

(10) Melting points were determined on a Fisher-Johns block.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.83; H, 8.16.

trans-anti-trans-1α-Ethyl-1β-hydroxy-8β-methyl-4,5-(4-ketoperhydrobenzo)hydrindane (V). To a prereduced mixture of 10 ml. of purified dioxane, 2 ml. of pyridine and 400 mg. of 5% palladium on calcium carbonate was added a solution of 0.466 g. (0.0019 mole) of XIV in 20 ml. of purified dioxane. Over a period of 3 hr. the reaction mixture absorbed smoothly at 1 atm. a total of 154 ml. of hydrogen after which no further uptake of hydrogen was observed (calculated for 0.0057 mole of hydrogen: 141 ml.). The catalyst was removed by filtration and washed with acetone. The combined filtrates were distilled to dryness to afford a semisolid residue. The semisolid was washed with a mixture of ether and pentane, yielding a colorless crystalline product, m.p. 129–132.5°. Three crystallizations from ether gave 0.132 g. (28%) of V as colorless dense crystals, m.p. 132–133°; infrared (potassium bromide) 2.88, 5.89 μ. Its ultraviolet spectrum showed no absorption.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.70; H, 10.39.

The combined mother liquors and ether-pentane wash gave an additional 0.182 g. (38%) of V, m.p. 132.5–133.5°.

trans-1α-Ethynyl-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane (XV). A solution of potassium *t*-butoxide was prepared by dissolving 22 g. (0.563 g.-atom) of potassium in 500 ml. of anhydrous *t*-butyl alcohol. After dilution with 100 ml. of anhydrous toluene, the stirred solution was cooled in an ice bath. The solution was saturated with acetylene and then to it was added a solution of 22.5 g. (0.0976 mole) of the tricyclic ketone VIII in 400 ml. of anhydrous toluene. After the addition was complete, passage of acetylene was resumed for an additional 7 hr. while the reaction mixture was stirred and kept cooled in the ice bath. After standing overnight in the refrigerator, the reaction mixture was poured into 1 l. of ice water. The product was extracted with ether. The ethereal extracts were concentrated to a small volume by distillation under reduced pressure. The residue was diluted with pentane and allowed to crystallize whereupon it afforded 15.0 g. (60%) of XV, m.p. 125.5–127.5°. From the mother liquor there was obtained an additional 4.55 g. (18%) of XV, m.p. 122–126°. The analytical sample was crystallized from ethyl acetate-pentane, m.p. 127.5–128.5°; infrared (chloroform) 2.73, 3.00, 6.18, 6.23 μ.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.61; H, 8.09.

trans-1α-Ethyl-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane (XVI). A solution of 8.58 g. (0.0334 mole) of the ethynyl compound XV in 250 ml. of 95% ethanol was hydrogenated at 3 atm. over 0.8 g. of 5% palladium on charcoal. After the absorption of hydrogen had ceased, the catalyst and solvent were removed from the reduction mixture. The residue was crystallized from ether-pentane to afford 7.53 g. (87%) of XVI, m.p. 91–92°; infrared (potassium bromide) 2.94, 6.22, 6.38 μ. An additional 0.58 g. g. (7%) of XVI was obtained from the mother liquor.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.22; H, 9.01.

trans-1α-Ethyl-1β-hydroxy-8β-methyl-4,5-(4-methoxy-2,5-dihydrobenzo)hydrindane (XVII) and *anti-trans-1α-Ethyl-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane* (XVIII). To a stirred solution of 4.07 g. (0.0156 mole) of XVI, 100 ml. of liquid ammonia, 50 ml. of tetrahydrofuran, and 50 ml. of *t*-butyl alcohol was added 1.3 g. (0.188 g.-atom) of lithium wire. After 3.5 hr. the excess lithium was destroyed by the careful addition of 25 ml. of methanol to the reaction mixture. The ammonia was allowed to evaporate at room temperature. The residue was diluted with 100 ml. of water and concentrated under reduced pressure at 30° to remove the tetrahydrofuran. The product was extracted with ether. The ethereal extracts were washed with water and dried over anhydrous potassium carbonate. After the solvent was removed by distillation under reduced pressure, the residue was crystallized from ether-pentane to afford 2.61 g. (64%) of XVII, m.p. 92–96°. An additional 0.31 g. (8%) of XVII m.p. 86–93°, was obtained from the mother liquor.

A solution of 2.50 g. (0.00954 mole) of XVII, 15 ml. of methanol, 1 ml. of 12*N* hydrochloric acid, and 1 ml. of water was allowed to stand at room temperature for 4 hr. It was then diluted with water and concentrated under reduced pressure to remove the methanol. The residue was extracted with ether. The ethereal extracts were washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and distilled to dryness under reduced pressure. The product was crystallized from acetone-pentane to afford 1.64 g. (70%) of XVIII, m.p. 114–117° with preliminary melting and resolidifying in the range of 46–56°. Several recrystallizations from acetone-pentane followed by sublimation at 100°, 0.3 mm., gave the analytical sample, m.p. 118–118.5°; infrared (potassium bromide) 2.91, 6.07, 6.22 μ; $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 17.150).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.78; H, 9.97.

trans-1α-Carboxyethynyl-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane (XIX). To a stirred solution of 4.9 g. (0.0188 mole) of XV in 100 ml. of tetrahydrofuran freshly distilled from methylmagnesium bromide was added 40 ml. of a 3*M* solution of methylmagnesium bromide in diethyl ether. The reaction mixture was stirred and heated under reflux for 24 hr. after which period it still gave a positive Michler's ketone test. After it had cooled to room temperature, carbon dioxide was passed into the reaction mixture during a period of 24 hr. with rapid stirring. The reaction mixture was then poured into 600 ml. of 1.0*N* sulfuric acid and extracted with ether. The ethereal extracts were washed with water and evaporated to dryness to afford 6.0 g. of a glass. The glass was dissolved in 150 ml. of boiling ether to which was then added 80 ml. of carbon tetrachloride. The ether–carbon tetrachloride solution was concentrated by distillation whereupon crystallization of the acid began. The residual suspension of crystals was allowed to stand in the refrigerator for 24 hr. to yield 4.48 g. (78%) of XIX as a colorless powder, m.p. 170–175°. Recrystallization from acetonitrile raised the m.p. to 173–175°; infrared (potassium bromide): 2.91, 4.48, 5.88, 6.21, 6.32 μ.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.08; H, 7.13.

trans-1α-2'-Carboxyethyl-1β-hydroxy-8β-methyl-4,5-(4-methoxybenzo)hydrindane lactone (XX). A solution of 4.25 g. (0.0142 mole) of the ethynyl acid XIX and 1.8 g. (0.0197 mole) of triethylamine in 50 ml. of absolute ethanol was hydrogenated at 1 atm. over 1.0 g. of 5% palladium on charcoal. After the calculated amount of hydrogen was absorbed, the catalyst was removed by filtration and washed with ethanol. The combined filtrates were evaporated to a volume of 40 ml. and while lukewarm treated with 10 ml. of 6*N* hydrochloric acid. After 5 min. the reaction mixture was diluted with 500 ml. of water. The colorless granular solid was collected by filtration, washed with water and dried, yield 3.85 g. (97%). For analysis a sample of the crude lactone XX was crystallized from a mixture of ethyl acetate and isopropyl ether (1:2), m.p. 115°. Its infrared spectrum (potassium bromide) showed the characteristic lactone peak at 5.65 μ.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75. Found: C, 75.25; H, 7.56.

anti-trans-1α-2'-Carboxyethyl-1β-hydroxy-8β-methyl-4,5-(4-keto-1,2,3,4-tetrahydrobenzo)hydrindane lactone (XXII). A 3.75-g. (0.0133 mole) sample of the crude lactone XX was dissolved in 75 ml. of methanol containing 0.572 g. (0.0143 mole) of sodium hydroxide and 10 ml. of water. The reaction mixture was concentrated to one-third its initial volume on the steam bath and then evaporated to dryness under reduced pressure. The resulting colorless sodium salt XXI was further dried at 80°, 10 mm., for 2 hr.

The powdered sodium salt was suspended in 75 ml. of anhydrous *t*-butyl alcohol and 75 ml. of anhydrous tetra-

hydrofuran. Upon the addition of 175 ml. of liquid ammonia, a clear solution resulted. To the stirred solution was then added over a period of 5 min. 2.3 g. (0.332 g.-atom) of lithium wire. After 3 hr. the bronze and deep blue colors of the reaction mixture discharged spontaneously. Twenty milliliters of methanol was then carefully added, and the ammonia was evaporated under a stream of nitrogen. The residue was diluted with 100 ml. of water and then distilled under reduced pressure until 125 ml. of distillate was collected. The residual gel was diluted with an additional 500 ml. of water and acidified with 40 ml. of glacial acetic acid. The finely divided, colorless precipitate was collected by filtration, washed well with water, and dried.

The crude enol ether was hydrolyzed by dissolving in 200 ml. of methanol containing 18 ml. of 12*N* hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 4 hr. and then poured into 1 l. of water. The product was extracted with chloroform. The chloroform solution was evaporated to dryness to afford 3.5 g. of a pale yellow oil, which crystallized when treated with ether. The crystalline product was collected and recrystallized twice from ethyl acetate after treatment with charcoal to yield 0.700 g. (19%) of XXII as colorless dense crystals, m.p. 155°; infrared (potassium bromide) 5.63, 6.01, and 6.20 μ; $\lambda_{max}^{CH_3OH}$ 238 mμ (ϵ 17,000).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.49; H, 7.80.

An additional 0.405 g. (11%) of XXII, m.p. 152–153°, was recovered from the mother liquors.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of Certain 7α-Alkylthio and 7α-Acylthio Steroid Hormone Derivatives

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Received April 6, 1961

7α-Alkylthio and/or 7α-acylthio derivatives of cortisone, 9α-fluorohydrocortisone, progesterone, deoxycorticosterone and testosterone have been prepared by condensation of the corresponding 6-dehydro derivatives with sulfur nucleophiles. 7α-Methylthiotestosterone acetate (XVI) and 7α-mercaptotesterone acetate (XIX) showed anabolic activity (levator ani assay). Various additional derivatives of testosterone containing the 7α-methylthio and/or the 7α-acetylthio group have been synthesized.

As part of our steroid analog program[1] it was of interest to prepare various structures containing a substituent at C-7. At the start of this investigation we were aware of no fully elaborated steroid hormone substituted at this position. However, since then several such analogs have been reported. These analogs include the 7α-hydroxy derivatives[2a] of cortisone and prednisone, the 7α- and 7β-hydroxy derivatives[2b] of progesterone and deoxycorticosterone, the 7α-acylthio derivatives[3a] of testosterone, progesterone, deoxycorticosterone, cortisone, and hydrocortisone,[3b] and the 7α- and 7β-methyl derivatives of hydrocortisone,[4] testosterone,[4a,c] and progesterone.[4c,5,6] For our program, convenient entry into the C-7 position appeared possible *via* the 1,6-addition of various nucleophiles with the known and readily available 6-dehydro derivatives of appropriate Δ^4-3-keto steroids. Although at the start of this study, such a condensation had not been reported in the literature, similar reactions with the analogous $\Delta^{3,5}$-7-keto system were on record.[7] However, during the course of our investigation Dodson and Tweit[3a] reported the reaction of thio acids with several $\Delta^{4,6}$-3-ketones to give a series of 7α-acylthio derivatives, certain of which were closely related to or identical with some of the compounds already prepared in our laboratory.

Our initial studies were carried out with 6-dehydrocortisone acetate (I).[8] Treatment of this compound with various sulfur nucleophiles (methyl mercaptan, ethyl mercaptan, thioacetic acid and

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