

was compared with that of a sample of samogenin isolated at this Laboratory. The spectra were essentially identical, the only significant difference being that the ratio of the absorbances of the 897 and 916 cm^{-1} bands was not so great in the isomerized product as in the authentic samogenin. This probably indicates that conversion was not quite complete and that a small amount of the original normal sapogenin remained unreacted.

Samogenin (22a-Spirostane-2 ξ ,3 β -diol).—A sample of the inflorescent buds of *Yucca carnerosana* was extracted with ethanol as described under markogenin. After standard purification and acid hydrolysis,⁹ the crude sapogenin was chromatographed on activated alumina. A minor fraction was eluted with benzene and was identified as smilagenin in our usual manner.^{9,10} The major component, 75% of the total sapogenin content (which was 0.4% on a moisture-free basis) was eluted with 20% ethanol in benzene. After evaporating the solvent and several recrystallizations from methanol, samogenin, m.p. 203–205, $[\alpha]^{25D} -74^\circ$, diacetate m.p. 198°, $[\alpha]^{25D} -84^\circ$ was isolated. The infrared spectra of our samogenin and that from a sample supplied by Marker were compared at Sloan-Kettering Institute by Dr. Thomas A. Gallagher and were found to be identical.

Effect of Acid Isomerization on Pseudomarkogenin and Pseudosamogenin.—Markogenin diacetate, 1.0 g., was heated in a sealed carius tube with 10 ml. of acetic anhydride for ten hours at 200°. After cooling, a small quantity of solids was removed by filtration. The pseudotriacetate was extracted from the acetic anhydride by repeated extraction with hexane. The hexane solution was washed with sodium bicarbonate solution and distilled water. After drying over anhydrous sodium sulfate, the solvent was evaporated. A yield of 0.92 g. of a viscous, pale yellow oil was obtained. Infrared examination of this product in carbon disulfide indicated that the sapogenin peaks associated with the spiroketal grouping in sapogenins were essentially absent.¹¹ The crude triacetate, (20-(22)-furosten-2 ξ ,3 β ,26-triol triacetate) was refluxed one hour with

a solution of 5% potassium hydroxide in methanol. After dilution with water and ether extraction, 0.6 g. of crude pseudotriol was obtained. A solution consisting of 0.16 g. crude triol, 1 ml. of concentrated hydrochloric acid and 10 ml. of methanol was refluxed one hour. On dilution with water and ether extraction crude markogenin was obtained. The infrared spectrum of the crude product in carbon disulfide was essentially identical with that of an authentic sample of markogenin. The crude markogenin was crystallized once from ether and twice from methanol; m.p. 255–257°. There was no depression of m.p. when mixed with an authentic sample.

Samogenin diacetate, 0.38 g., was converted to the pseudogenin and hydrochloric acid isomerized as described above for markogenin. The infrared spectra of the crude product were essentially identical with those of an authentic sample of samogenin. The crude samogenin was crystallized once from ether and twice from methanol, m.p. 202–203°. There was no depression of m.p. when mixed with an authentic specimen.

Infrared spectra were obtained with a Beckman model IR-3 spectrophotometer, using sodium chloride prisms. Carbon disulfide (A.C.S. grade) was used as received. Chloroform (A.C.S. grade) was purified by filtration through activated alumina and distillation from lithium aluminum hydride.

Acknowledgment.—We gratefully acknowledge the assistance of Mary-Anne Morris, Mary Klumpp Scott and Howard W. Jones with the infrared work. We wish to express our appreciation to Dr. Thomas A. Gallagher, of Sloan-Kettering Institute, for comparing our sample of samogenin with a sample isolated by Marker. We thank Mrs. Ruth B. Kelley for the carbon and hydrogen analyses.

PHILADELPHIA, PA.

[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A., AND THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

Steroids. XLVIII.¹ 19-Norprogesterone, a Potent Progestational Hormone

BY CARL DJERASSI,² L. MIRAMONTES AND G. ROSENKRANZ

RECEIVED APRIL 15, 1953

Reduction of 3-methoxy-17-acetyl-1,3,5-estratriene with lithium in liquid ammonia leads to $\Delta^{2,5(10)}$ -19-nor-3-methoxy-20-hydroxypregnadiene, which upon acid hydrolysis and chromium trioxide oxidation affords 19-norprogesterone. This substance exhibits four to eight times the biological activity of progesterone in rabbits.

Progestational activity is extremely specific and is limited to the natural hormone, progesterone, and a few of its dehydro derivatives.³ As a result, it appeared very surprising that a substance, believed to be 19-norprogesterone, exhibited progestational activity⁴ equal to that of the parent hormone. This 19-norprogesterone was obtained⁵ as a resin in 0.07% yield by a twelve-step degradation from strophanthidin, and was clearly a mixture of stereoisomers with the "abnormal" configuration at C-14 (β) and C-17 (α),^{6,7} and of unknown con-

figuration at C-10. Since 17-isoprogesterone⁸ and 14-iso-17-isoprogesterone⁶ show no progestational activity, there remains the intriguing alternative that removal of the angular methyl group confers high biological potency. That this does not necessarily follow, at least in the androgen series, is demonstrated by the fact that 19-nortestosterone,^{9,10} which possesses the "natural" configuration at all asymmetric centers,^{10,11} exhibits only ca. one-third the androgenic activity of testosterone.^{10–12} Since the mechanism of androgenic and progestational activity is not necessarily comparable, it appeared of very considerable interest to synthesize 19-norprogesterone with the "natural"

physical constants of this isomer are quite different from those of the presently described 19-norprogesterone (IIIc).

(8) A. Butenandt, J. Schmidt-Thomé and H. Paul, *Ber.*, **72**, 1112 (1939).

(9) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(10) A. L. Wilds and N. A. Nelson, *THIS JOURNAL*, in press.

(11) A. J. Birch and H. Smith, *J. Chem. Soc.*, 1882 (1951).

(12) A. J. Birch, *Ann. Repts. Prog. Chem. (Chem. Soc. London)*, **47**, 210 (1950).

(1) Paper XLVII, *THIS JOURNAL*, **75**, in press (1953).

(2) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(3) Cf. M. Ehrenstein, *Chem. Revs.*, **42**, 457 (1948).

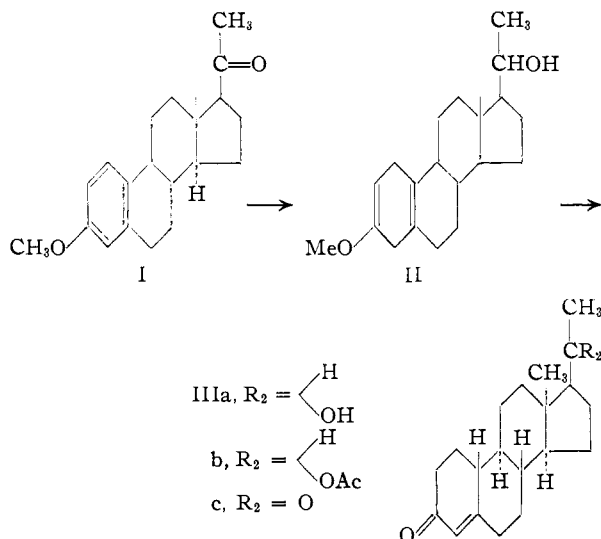
(4) W. M. Allen and M. Ehrenstein, *Science*, **100**, 251 (1944).

(5) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944).

(6) P. A. Plattner, H. Heusser and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(7) M. Ehrenstein, G. W. Barber and M. W. Gordon, *J. Org. Chem.*, **16**, 355 (1951). Recently, Ehrenstein (*Chimica*, **6**, 287 (1952)), reported the isolation of a crystalline 19-nor-14-iso-17-isoprogesterone (with unknown configuration at C-10) from strophanthidin. Its biological activity has not yet been recorded, but, as was expected, the

configuration at all asymmetric centers and which would differ from progesterone only by the absence of the angular methyl group at C-10. A preliminary account of this work has already been published¹³ and the present communication is concerned with a description of the experimental details.



A synthesis of the desired 19-norprogesterone (IIIc) with stereochemical control appeared possible by applying the Birch reduction¹⁴ to the recently described^{15,16} 3-methoxy-17-acetyl-1,3,5-estratriene. The standard Birch reduction of aromatic steroids requires the use of glyceryl ethers^{9,17} and does not proceed in good yield. However, Wilds and Nelson¹⁰ have recently developed an improved procedure¹⁸ for the conversion of estradiol methyl ether to 19-nortestosterone employing lithium metal in liquid ammonia, and a modification of their procedure was employed for the reduction of the methyl ether I. The resulting enol ether II showed no selective absorption in the ultraviolet, but did exhibit a strong infrared hydroxyl band due to reduction of the 20-keto group. Hydrolysis of the enol ether with ethanolic hydrochloric acid proceeded satisfactorily with concomitant rearrangement of the 5-10 double bond to the 4,5-position as was confirmed by ultraviolet and infrared spectroscopy. Although 19-nor- Δ^4 -pregnen-3-one-20-ol (IIIa) as well as its 20-acetate (IIIb) were obtained in crystalline form, they probably represent a mixture of C-20 epimers. The synthesis was completed by chromium trioxide oxidation of IIIa which yielded 19-norprogesterone (IIIc) in 55% over-all yield (based on I). The spectral data of this crystalline substance were fully consistent with the assigned structure, since there was observed an ultraviolet absorption maximum at 240 $m\mu$ and infrared carbonyl bands at 1706

cm^{-1} (20-ketone) and 1674 cm^{-1} (Δ^4 -3-ketone).¹⁹ Similarly, the ultraviolet spectrum of the 3,20-bis-2,4-dinitrophenylhydrazone was nearly identical with that of progesterone bis-dinitrophenylhydrazone.²⁰ Biological tests²¹ in rabbits indicate that the presently described 19-norprogesterone (IIIc) has approximately four to eight times the activity of progesterone and thus appears to be the most potent progestational hormone known at the present time.²²

The mode of synthesis automatically establishes the "normal" configuration at all asymmetric centers with the exception at C-10. As pointed out earlier,^{10,11,13,23} the Δ^4 -3-keto moiety is generated under conditions which permit entrance of the proton at C-10 from the more favored β -side to produce the *anti* back-bone and it is quite likely, therefore, that the configuration at C-10 is the same as that in the parent hormone. The exceptionally high biological activity of 19-norprogesterone raises the question as to the importance of the angular methyl group in the cortical hormones and the synthesis of such 19-norcortical hormones, recently completed in this Laboratory, will be reported in a future communication.^{23a}

Experimental²⁴

$\Delta^{2,5(10)}$ -19-Nor-3-methoxy-20-hydroxypregnene (II).—To a solution of 8 g. of lithium metal (wire) in 1 l. of liquid ammonia in a dewar flask was added with mechanical stirring over a period of *ca.* 15 minutes dropwise a solution of 1.0 g. of 3-methoxy-17-acetyl-1,3,5-estratriene (I)¹⁶ in 40 cc. of absolute ethanol and 200 cc. of dry ethyl ether. At the end of the addition, there were added 30 cc. of ethanol and finally, after disappearance of the blue color, 50 cc. of water. The ammonia was allowed to evaporate at room temperature overnight, the residue was extracted with a mixture of ether and ethyl acetate, washed with water until neutral, dried and evaporated. A small amount of the resulting pale yellow oil (0.86 g.) was crystallized from acetone to give colorless crystals of the enol ether II with m.p. 135–138°, $[\alpha]^{20D} +88^\circ$, no selective absorption in the ultraviolet, free hydroxyl band in the infrared.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.33; H, 10.47.

Δ^4 -19-Norpregnen-20-ol-3-one (IIIa).—The above oily enol ether (0.86 g.) was refluxed for one hour with 25 cc. of methanol and 15 cc. of 4 *N* hydrochloric acid, then poured into 250 cc. of saturated salt solution, extracted four times with ethyl acetate, washed until neutral, dried and evaporated. The semi-solid residue (0.77 g.) was passed through a short column of alumina and eluted with benzene-ether (1:1) whereupon there was obtained 0.65 g. of colorless crystals with m.p. 160–168°, $[\alpha]^{20D} +44^\circ$, ultraviolet absorption maximum at 240 $m\mu$ ($\log \epsilon$ 4.26), which were satisfactory for the next step; the material apparently represents a mixture of 20-hydroxy epimers. The analytical sample, obtained from hexane-ethyl acetate, showed m.p. 174–177°,

(19) R. N. Jones, P. Humphries and K. Dobriner, *THIS JOURNAL*, **72**, 956 (1950).

(20) C. Djerassi, *Anal. Chem.*, **20**, 880 (1948).

(21) W. W. Tullner and R. Hertz, *J. Clin. Endocrinology & Metab.*, **12**, 916 (1952).

(22) It is interesting to note that the aromatic progesterone analog I (as the free alcohol, *cf.* ref. 16) is devoid of progestational activity.

(23) W. Klyne, *J. Chem. Soc.*, 2923 (1952).

(23a) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *THIS JOURNAL*, **75**, 4117 (1953).

(24) Melting points are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements and for the infrared spectra which were determined on a Perkin-Elmer model 12C single beam spectrophotometer. Thanks are due to Srta. Amparo Barba and staff for the microanalyses.

(13) L. Miramontes, G. Rosenkranz and C. Djerassi, *THIS JOURNAL*, **73**, 3540 (1951).

(14) *Cf.* A. J. Birch, *Quart. Rev.*, **4**, 69 (1950).

(15) L. Velluz and G. Muller, *Bull. soc. chim. France*, 166 (1950).

(16) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Romo and J. Berlin, *THIS JOURNAL*, **73**, 1523 (1951).

(17) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(18) We are greatly indebted to Prof. A. L. Wilds of the University of Wisconsin for informing us of this procedure prior to publication (ref. 10).

$[\alpha]^{20D} +42^\circ$, $\lambda_{\max}^{EiOH} 240 \text{ m}\mu$, $\log \epsilon 4.25$, $\lambda_{\max}^{CS_2} 3617$ and 1678 cm.^{-1} .

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.45; H, 10.24.

The acetate IIIb was recrystallized from ethyl acetate, whereupon it exhibited m.p. $178-179^\circ$, $\lambda_{\max}^{EiOH} 240 \text{ m}\mu$, $\log \epsilon 4.25$, $\lambda_{\max}^{CS_2} 1736$ and 1674 cm.^{-1} .

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.95; H, 9.37.

Δ^4 -19-Norpregnene-3,20-dione (19-Norprogesterone) (IIIc).—The above crude 20-alcohol IIIa (0.65 g.) in 15 cc. of glacial acetic acid was treated at 20° dropwise with a solution of 0.15 g. of chromium trioxide in 1 cc. of water and 5 cc. of acetic acid. After 90 minutes at room temperature, the excess reagent was decomposed with methanol and the solution was evaporated to dryness *in vacuo*. The product

was extracted with ether, washed with sodium carbonate solution and water, dried, evaporated and crystallized from methanol; yield 0.54 g., m.p. $142-145^\circ$, $[\alpha]^{20D} +154^\circ$. The analytical sample showed m.p. $144-145^\circ$, $[\alpha]^{20D} +147^\circ$, $\lambda_{\max}^{EiOH} 240 \text{ m}\mu$, $\log \epsilon 4.24$, $\lambda_{\max}^{CS_2} 1706$ and 1674 cm.^{-1} .

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.07; H, 9.28.

The 3,20-bis-dinitrophenylhydrazone was prepared in methanol containing a small amount of concentrated hydrochloric acid and was obtained as dark orange crystals (after recrystallization from chloroform-methanol) with m.p. $278-279^\circ$, $\lambda_{\max}^{CHCl_3} 380 \text{ m}\mu$, $\log \epsilon 4.78$.

Anal. Calcd. for $C_{32}H_{38}O_8N_8$: C, 58.17; H, 5.49; N, 16.95. Found: C, 58.28; H, 5.37; N, 16.57.

MEXICO CITY, D. F.

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Veratrine Alkaloids. XXXVII. The Structure of Isorubijervine. Conversion to Solanidine

BY S. W. PELLETIER AND WALTER A. JACOBS

RECEIVED APRIL 10, 1953

The structure of isorubijervine has been established as a hydroxy-solanidine by conversion to solanidine. Tosylation of isorubijervine gave a unique, quaternary-type monotosylate IX which was converted to a quaternary iodide XII by the action of sodium iodide. Reductive cleavage of either the tosylate or the iodide with sodium in ethanol afforded solanidine (XV) and a new isomeric base designated as pseudosolanidine (XIV). The data at hand confirm the structure originally proposed for isorubijervine, *viz.*, Δ^5 -solanidene-3 β ,18-diol (I).

Isorubijervine, an alkaloid of *Veratrum album* and *Veratrum viride*, first isolated and characterized in this Laboratory,^{1,2} has been shown to be a tertiary steroidal base of 3-hydroxy- Δ^5 -stenol character. This was supported by its formulation, $C_{27}H_{43}NO_2$, by hydrogenation to a dihydro derivative,³ by formation of a digitonide,^{2,3} and by oxidation to a Δ^4 -3-ketone (II), which in turn was reduced to a mixture of epimeric Δ^4 -stenols (III).² That the non-nitrogenous portion of isorubijervine possesses a normal steroid ring system was given support by the isolation of 1,2-cyclopentenophenanthrene (VII) as a product of its selenium dehydrogenation.² Also isolated from the dehydrogenation mixture was the characteristic 2-ethyl-5-methylpyridine (VIII) obtained from other veratrine alkaloids and from the potato base, solanidine.^{1,2,4} Such data suggested that isorubijervine, like rubijervine,⁵ is a solanidine derivative. The primary character of the second hydroxyl group was shown by oxidation of dihydroisorubijervine (IV) to a keto acid, $C_{27}H_{41}NO_3$ (V), which could be reconverted to dihydroisorubijervine by reduction of the methyl ester VI with lithium aluminum hydride. The resistance of this ester to saponification together with certain other data indicated that this primary hydroxyl group is located on an angular methyl group. The data at hand were best explained by assuming for isorubijervine the structure of Δ^5 -solanidene-3 β ,18-diol (I).⁶ This assumed relationship to solanidine

has since been confirmed by a direct conversion of isorubijervine to solanidine (Δ^5 -solanidene-3 β -ol) itself. A preliminary account of this work was outlined in our Communication to the Editor,^{7,8} and it is the purpose of this paper to disclose the details of this conversion and to discuss the structure of isorubijervine.

The route originally considered for this conversion involved the preparation of a tosyl ester of the primary hydroxyl group of isorubijervine, followed by replacement of this tosyl group with hydrogen. Treatment of isorubijervine (I) with a slight excess of one equivalent of *p*-toluenesulfonyl chloride in pyridine gave an excellent yield of a monotosylate which in reality is a quaternary salt as discussed below. That the secondary hydroxyl group at carbon 3 was not involved in the formation of this monotosylate was shown by oxidation of the latter with aluminum *t*-butoxide to a Δ^4 -3-ketone (XI) which was in all respects identical with the compound formed by the tosylation of Δ^4 -isorubijervone-3 (II). This Δ^4 -3-ketone was further characterized by the oxime. Treatment of isorubijervine or of its monotosylate with an excess of *p*-toluenesulfonyl chloride yielded a neutral ditosylate (X).

Normal structures for isorubijervine monotosylate and Δ^4 -isorubijervone-3 tosylate were first assumed by us.⁷ However, an attempt to reduce the monotosylate of isorubijervine to solanidine by boiling for 90 hours in ether with lithium aluminum hydride was unsuccessful. The tosylate was therefore

(1) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **148**, 41 (1943).

(2) W. A. Jacobs and L. C. Craig, *ibid.*, **159**, 617 (1945).

(3) L. C. Craig and W. A. Jacobs, *ibid.*, **149**, 451 (1947).

(4) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **129**, 79 (1939); *ibid.*, **139**, 263 (1948); *ibid.*, **148**, 57 (1943); *Science*, **97**, 122 (1943); V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **125**, 1306 (1942).

(5) Y. Sato and W. A. Jacobs, *J. Biol. Chem.*, **179**, 623 (1949).

(6) Y. Sato and W. A. Jacobs, *ibid.*, **191**, 63 (1951).

(7) S. W. Pelletier and W. A. Jacobs, *THIS JOURNAL*, **74**, 4218 (1952).

(8) While our Communication was in press, a preliminary report by Burn and Rigby (*Chemistry and Industry*, **37**, 668 (1952)) appeared which described the conversion of dihydroisorubijervine to solanidan-3 β -ol. An article by Weisenborn and Burn⁹ appeared later in which similar methods were used to convert isorubijervine to solanidan and solanidan-3 β -ol.