PRELIMINARY COMMUNICATIONS

Steroids-XC*

11α-Methyl-11β-hydroxy storoids

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WE WISH to record the synthesis of several 11α -methyl- 11β -hydroxy steroid hormone analogs derived by the addition of metallo-organic reagents to the C-11 position of 11-keto steroids.¹[†] Reaction of androstan-3 β -ol-11,17-dione (I) § (m.p. 169–171°, [α]_D + 125°.¹ Anal. Found for C₁₈H_{as}O_a: C, 74.56; H, 8.98) with methylmagnesium bromide in benzene-ether solution at 25° gave, in addition to the expected 17a-methylandrostane-3 β , 17 β -diol-11-one (m.p. 218-221°, [a]_D ± 0°), a 30 per cent vield of a more polar by-product (II) (m.p. 164–166°, $[\alpha]_D - 5^\circ$. Anal. Found for $C_{11}H_{3e}O_3$: C, 75-32; H, 10.91) to which we assign the 11α , 17α -dimethylandrostane-3 β , 11β , 17β -triol structure, since it exhibited no carbonyl absorption in the infrared and differed from 17a-methylandrostane-3, 11β , 17β -triol.** Substitution of methyllithium in ether for methylmagnesium bromide gave an 80 per cent yield of the same 11,17-dimethyl compound.

Pyridinium-chromate oxidation of (II) smoothly led to the 3-keto compound, 11α , 17α -dimethylandrostane-11 β ,17 β -diol-3-one (III) (m.p. 202-205°, $[\alpha]_D + 6^\circ$. Anal. Calcd. for $C_{21}H_{24}O_3$: C. 75.40; H, 10.24. Found C, 75.03; H, 10.08).

Confirmation and extension of 11-methyl addition was provided by the reaction with methyllithium of mono-functional 11-keto compounds, such as pregnan-11-one^a and allopregnan-11-one,^a which yielded ketone-free products, resistant to chromic acid oxidation, e.g. 11a-methyl-allopregnan- 11β -ol (m.p. 112–113°, $[\alpha]_{\rm D}$ + 23°. Anal. Found for C₃₂H₃₈O: C, 83·17; H, 11·77; O, 4·89).

Although a number of more complex molecules failed to react at C-11 with methyllithium, 11 α -methyl-11 β -hydroxytestosterone (IV) was readily derived by the following reaction sequence. Adrenosterone 3,17-biscycloethylene ketal³ was converted to 11a-methyl-3,17-dicycloethylenedioxy- Δ^{s} -androsten-11 β -ol (V) (m.p. 192-194°, [α]_D - 94° (pyr.). Anal. Found for C₂₄H₃₈O₅: C, 70-90; H, 9.01) by reaction with methyllithium in ether-tetrahydrofuran solution. Hydrolysis of the ketal moieties of (V) in 70 per cent acetic acid gave 11α -methyl- Δ^4 -androsten- 11β -ol-3,17-dione (VI) (m.p. 151–152°, $[\alpha]_{D}$ + 162°, $\lambda_{max.}^{EtOH}$ 243 m μ , log ε 4·19. Anal. Found for C₂₀H₂₅O₃: C, 75·61;

* Paper LXXXIX, A. Bowers, H. J. Ringold and R. I. Dorfman J. Amer. Chem. Soc. 79, 4556 (1957). † Ruzicka et al. reported the addition of methylmagnesium iodide to the triterpene, 11-keto-β-amyrin, but it should be noted that they were dealing with an α,β -unsaturated carbonyl function.

[‡] The addition of methylmagnesium bromide to a steroidal C-11 carbonyl function was reported in the case of the ring A unsubstituted androstane-11,17-dione in a talk given at the Dallas Meeting of the American Chemical Society, April 1956, by Dr. John C. Babcock of The Upjohn Company.

§ Prepared by sodium bismuthate cleavage of allopregnane 3β , 17α , 21-triol-11, 20-dione. || All melting points are uncorrected and rotations were determined at 20° in chloroform. We are grateful to Mrs. E. Necoechea, Miss G. Monroy and Miss J. Lisci for their valuable technical assistance and to Mr. E. Avila for determination of rotations and spectra.

Carbanion addition would be expected to follow the stereochemical course of hydride attack and thus yield the 11α -methyl compound.

** This compound, prepared by the addition of methylmagnesium bromide to androstane- 3β , 11β -diol-17-one, melts at 247-251°, $[\alpha]_D + 12°$. Anal. Found for $C_{30}H_{34}O_3$: C, 74·14; H, 10·52. While reduction of hindered ketones with methyl Grignard reagents has not been described nor would such reduction appear to be mechanistically feasible, in contrast to the corresponding ethyl reagent, we did not wish to discount this possibility a priori.

¹ L. Ruzicka, G. Müller and H. Schellenberg Helv. Chim. Acta 22, 767 (1939).

² F. Sondheimer, E. Batres and G. Rosenkranz J. Org. Chem. 22, 1090 (1957)

⁸ S. Bernstein, R. Littell and J. H. Williams J. Amer. Chem. Soc. 75, 1481 (1953).

H, 8.89) which was converted to the testosterone analog (IV) (m.p. 255-256°, $[\alpha]_D + 111°$, λ_{max}^{EtOH} 244 mµ, log s 4-18. Anal. Found for C₂₀H₂₀O₃: C, 75-24; H, 9-62) by selective reduction⁴ with sodium borohydride in methanol at 0°. Alternately, reaction of the 3,17-dione (VI) with pyrrolidine in methanol gave the 3-enamine,⁵ (11 α -methyl-3-(N-pyrrolidyl)- $\Delta^{s,s}$ -androstadien-11 β -ol-17-one (VII) (m.p. 249-250°, [a]D - 140° (pyr.), $\lambda_{max.}^{\text{Bther}}$ 281 mµ, log e 4.35. Anal. Found for C₁₄H₃₄NO₂: C, 77.87; H, 9.43; N, 3.85) which, after lithium aluminum hydride reduction followed by hydrolysis, gave authentic (IV).

We shall report at a later date on further interconversions in this interesting series, as well as on the dehydration products of 11α -methyl- 11β -hydroxy steroids.

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H. J. RINGOLD E. BATRES J. A. ZDERIC

⁴ J. K. Norymberski and G. F. Woods J. Chem. Soc. 3426 (1955).

J. Johnson, M. Herr, J. Babcock, A. Fonken, J. Stafford and F. Heyl J. Amer. Chem. Soc. 78, 430 (1956).

Steroids-XCI *

Microbiological oxidations of 19-norprogesterone

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THE clinical importance of 19-nor steroids such as 19-nor-17a-methyltestosterone,¹ 19-nor-17aethinyltestosterone (Norlutin)¹ and of the latter's $\Delta^{s(10)}$ -isomer² is now well recognized[†] and these substances are all prepared on an industrial scale by modified Birch reductions³ of aromatic precursors. The synthesis of the more complicated 19-nor analogs of 11-oxygenated adrenal hormones, on the other hand, has been carried out only by adrenal incubation of 19-norpregnenes or by starting with 11-oxygenated aromatic precursors⁵ amenable to Birch reduction.³ The much more attractive and direct route of attempting 11-oxygenation in the 19-nor series by microbiological means has so far only been accomplished with 19-nortestosterone⁴ and is thus of no direct utility for the facile synthesis of 19-nor cortical hormones.⁴ We should now like to report that 19-norprogesterone (I)' reacts readily with a variety of micro-organisms and that the way is now open to the synthesis of a large number of 11-oxygenated-19-nor as well as 11-oxygenated aromatic analogs of steroidal hormones of the pregnane series.

Incubation of (I) for 24 hr at 28° with Rhizopus nigricans (ATCC no. 6227b) in a medium containing peptone and corn molasses, furnished in ca. 70 per cent yield 11a-hydroxy-19-norprogesterone (II) (m.p. 171-173°, $[\alpha]_D$ + 62° (CHCl_a), $\ddagger \lambda_{max}^{\text{BtOH}}$ 242 mµ, log ε 4.22; Anal. Found for

* Paper XC. H. J. Ringold, E. Batres and J. A. Zderic Tetrahedron. 2, 164 (1958).

† New York Academy of Sciences Conference on New Steroid Compounds with Progestational Activity, New York City, October 7-8, 1957.

 \ddagger The 11a-hydroxy assignment is also consistent with molecular rotation data: ΔM_D 11a-hydroxy-19norprogesterone \rightarrow 19-norprogesterone + 245 as compared to ΔM_D 11 α -hydroxy-19-nortestosterone \rightarrow 19nortestosterone +284.*

¹ C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer J. Amer. Chem. Soc. 76, 4092 (1954); Abstracts, Milwaukee A.C.S. Meeting p. 18J, April, 1952; U.S. patents 2,744,122 and 2,774,777.

* F. B. Colton U.S. patent 2,725,389.

 A. J. Birch Quart. Rev. Chem. Soc. Lond. 4, 69 (1950); J. Chem. Soc. 367 (1950).
A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi J. Amer. Chem. Soc. 76, 6210 (1954).

 ⁶ B. J. Magerlein and J. A. Hogg J. Amer. Chem. Soc. 79, 1508 (1957).
⁶ R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke and D. H. Peterson J. Amer. Chem. Soc. 78, 1512 (1956).

7 C. Djerassi, L. Miramontes and G. Rosenkranz J. Amer. Chem. Soc. 75, 4440 (1953).