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SYNTHESIS OF HOMO-DINORDRIN, ALLENYL A-NOR AND DINOR-STEROIDS[1]

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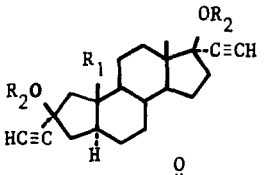
A recent report by Chinese investigators[2] about the unusual fertility inhibitor properties of Anordrin (1a) has induced us to prepare and evaluate biologically Dinordrin, as the free alcohol (1b), as well as the corresponding diacetate (1c) and dipropionate (1d)[1].

We now wish to report the synthesis of the 18-homo analogue of Dinordrin as well as allenyl derivatives of A-nor and A,19-dinor-steroids.

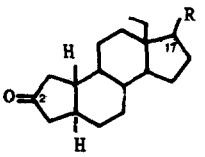
Birch reduction of the Δ^4-double bond of 17β-hydroxy 13β-ethyl 4-gonen-3-one[3], acetylation at C-17, chromic acid oxidation and pyrolysis by usual procedures[1], followed by alkaline hydrolysis afforded the 18-homo-dinor steroid (2a) [m.p. 186-187° ; $[\alpha]_D$ +185° ; IR ν_{max} 3500 (OH), 1735 cm^{-1} (ketone) ; m/e 276 (M^+)]. The alcohol group of compound (2a) was oxidized to the corresponding 2,17-diketone (2b) [m.p. 102-104° ; $[\alpha]_D$ +211° ; IR ν_{max} 1740 cm^{-1} (broad) ; m/e 274 (M^+)]. Alkylation of compound (2b) by treatment with BuLi in THF at -78°, followed by bubbling a stream of acetylene through the solution[4], provided regioselectively the mono-ethynyl steroids (3a) [m.p. 242° ; $[\alpha]_D$ +93° ; NMR δ 2.52 ppm (s, C≡C<u>H</u>) ; m/e 300 (M^+)] and (3b) [m.p. 216-217° ; $[\alpha]_D$ +42° ; NMR δ 2.57 ppm (s, C≡C<u>H</u>) ; m/e 300 (M^+)] as a 1:1 mixture, which could be separated easily by preparative TLC.

Ethynylation of the keto-group at position 17 in each isomer was then achieved by addition of lithium acetylide-ethylenediamine complex in DMSO-THF solution[5], thus affording the bis-ethynyl steroids (4a) [m.p. 147° ; $[\alpha]_D$ -17°; IR ν_{max} 3500 (OH), 3300 cm^{-1} (C≡C<u>H</u>) ; NMR δ 2.43, 2.52 ppm (2s, C≡C<u>H</u>) ; m/e 326 (M^+)] and (5a) [m.p. 72-74° ; $[\alpha]_D$ -59° ; IR ν_{max} 3500 (OH), 3300 cm^{-1} (C≡C<u>H</u>) ; NMR δ 2.45, 2.53 ppm (2s, C≡C<u>H</u>) ; m/e 326 (M^+)], respectively.

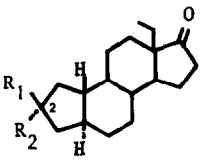
Esterification of diols (4a) and (5a) with acetic anhydride and propionic anhydride, in pyridine solution at 80° for 5 days, yielded the corresponding diesters (4b) and (4c) (18-Homo-Dinordrin), as well as (5b) and (5c).



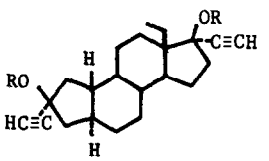
1 a, R_1 = Me, R_2 = $-\overset{O}{\overset{\|}{C}}-Et$
b, R_1 = R_2 = H
c, R_1 = H, R_2 = Ac
d, R_1 = H, R_2 = $-\overset{O}{\overset{\|}{C}}-Et$



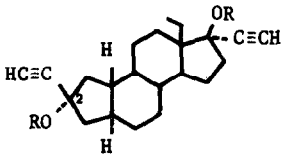
2 a, R = β-OH
b, R = ketone



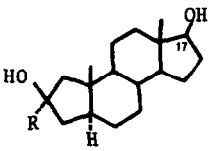
3 a, R_1 = OH, R_2 = C≡CH
b, R_1 = C≡CH, R_2 = OH



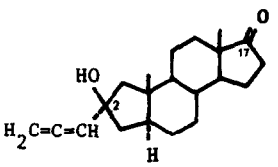
4 a, R = H
b, R = Ac
c, R = $-\overset{O}{\overset{\|}{C}}-Et$



5 a, R = H
b, R = Ac
c, R = $-\overset{O}{\overset{\|}{C}}-Et$



6 a, R = C≡CH
b, R = $C\equiv C-CH_2-N(iPr)_2$
c, R = $C\equiv C-CH_2-\overset{+}{N}(iPr)_2$ (Me) I^-
d, R = $CH=C=CH_2$



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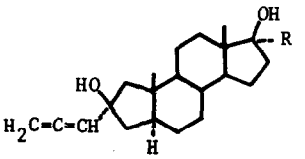
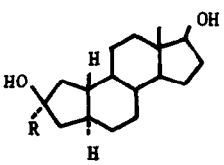
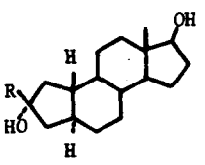


8 a, R = C≡CH
b, R = $CH=C=CH_2$



9 a, R = C≡CH
b, R = $C\equiv C-CH_2-N(iPr)_2$
c, R = $CH=C=CH_2$



10 a, R = C≡CH
b, R = $C\equiv C-CH_2-N(iPr)_2$
c, R = $CH=C=CH_2$

Parallel to our effort aimed at the preparation of 18-Homo-Dinordrin, we have also introduced an allene functionality in the nor-steroid skeleton at positions 2 and 17.

The insertion of a propadiene moiety was performed by a Mannich type condensation, followed by reductive treatment[6]. More specifically, reaction of the acetylenic steroid (6a)[7] with formaldehyde and diisopropylamine in the presence of cuprous bromide as a catalyst (0,03 equiv.) for 1 hr. 45 min., in refluxing dioxane, afforded the amino-steroid (6b), converted to its crystalline quaternary salt (6c) [m.p. 160° (dec.) ; $[\alpha]_D$ +28° ; m/e 415 (M^+-CH_3I)], by reaction with methyl iodide in acetone. Treatment of the salt (6c) in pyridine solution with lithium aluminium hydride for 2 hr. at 50°[6,8], provided the corresponding allenyl-steroid (6d) [m.p. 118° ; $[\alpha]_D$ +41° ; IR ν_{max} 3600 (OH), 1950 cm^{-1} (allene) ; NMR δ 4.87 (d, C=C=C$\underline{H}_2$, J = 6.5 Hz), 5.37 ppm (dd, C$\underline{H}$=C=CH_2, J = 6.5 Hz) ; m/e 316 (M^+)].

Various attempts to oxidize the 17-alcohol function of the 2-allenyl-steroid (6d) into the keto-steroid (7) by different procedures failed, only decomposition products were obtained. However, the 17-hydroxyl group of the allenyl-steroid (6d) could be converted smoothly to the corresponding ketone (7) [m.p. 152-153°; $[\alpha]_D$ +78° ; IR ν_{max} 1950 (allene), 1735 cm^{-1} (ketone) ; m/e 314 (M^+)] in 99% yield, by treatment with manganese dioxide[9] one hour in refluxing pentane solution. Clearly, these mild conditions did not affect the propadiene moiety in contrast to other oxidation techniques.

Ethynylation at C-17 was then performed by the lithium acetylide-ethylenediamine complex procedure[5], thus affording the 17α-ethynyl 2α-propadienyl A-nor steroid (8a) [m.p. 78-79° ; $[\alpha]_D$ -13° ; IR ν_{max} 3580, 3400, 1945 cm^{-1} ; NMR δ 4.83 (d, C=C=C$\underline{H}_2$, J = 6.5 Hz), 5.36 (dd, C$\underline{H}$=C=CH_2, J = 6.5 Hz), 2.54 ppm (s, C≡C$\underline{H}$) ; m/e 340 (M^+)], without affecting the mono-substituted propadiene located at position 2.

A-nor-androstane-2,17-dione[7] was also converted to the bis-allenyl steroid (8b) [m.p. 70-73° ; $[\alpha]_D$ -38° ; IR ν_{max} 3600 (OH), 1960 cm^{-1} (allene) ; NMR δ 4.75 (d, C=C=C$\underline{H}_2$, J = 6.5 Hz), 5.25 ppm (dd, C$\underline{H}$=C=CH_2, J = 6.5 Hz) ; m/e 354 (M^+)], by the above sequence of reactions.

The dinor-allenyl steroid (9c) and its 2-epimer (10c) were prepared from 17β-hydroxy-A-nor-oestran-2-one[10]. The introduction of acetylene at position 2 by the BuLi procedure[4] furnished a ca. 1:1 mixture of isomeric 2-ethynyl derivatives (9a) and (10a), which were separated by preparative TLC. Each isomer was submitted to a Mannich reaction to provide the amino-derivatives (9b) and (10b), respectively. These amino-steroids were then transformed into the corresponding allenyl dinor-steroids (9c) [m.p. 158° ; $[\alpha]_D$ +67° ; IR ν_{max} 3400 (OH), 1950 cm^{-1} (allene) ; NMR δ4.78 (d, C=C=C$\underline{H}_2$, J = 6.5 Hz), 5.30 ppm (dd, C$\underline{H}$=C=CH_2, J = 6.5 Hz) ; m/e 302 (M^+)] and (10c) [m.p. 48-52° ; $[\alpha]_D$ +1° ; IR ν_{max} 3400 (OH), 1950 cm^{-1} (allene) ; NMR δ 4.77 (d, C=C=C$\underline{H}_2$), J = 6.5 Hz), 5.28 ppm (dd,

$C\underline{H}=C=CH_2$, J = 6.5 Hz) ; m/e 302 (M^+)], through their quaternary salt[11], followed by reductive treatment.

During the Mannich reaction with the ethynyl steroid (9a), under the above conditions, we observed the direct formation of up to 31% of allenyl steroid (9c). The nature of this substance was established on the basis of its characteristic spectroscopic properties, in addition to the fact that this material was shown to be identical with an authentic sample of steroid (9c). A careful investigation of the reaction conditions indicated that treatment of the acetylenic compound (9a) with formaldehyde, diisopropyl amine and an excess (0,1 equiv.) of copper bromide, at reflux temperature in dioxane solution for 7 hr. allowed to isolate exclusively the expected allenyl steroid (9c). The scope and the mechanism of this unusual one-step conversion of an acetylene group into an allene functionality are currently being investigated.

A detailed report on the biological properties of these novel nor-steroids, some of which show a high binding affinity for receptor sites and thus exhibit potentially useful antifertility properties, will appear elsewhere.

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11. Satisfactory elemental analyses, mass spectra, NMR and other spectroscopic properties, obtained for all new compounds and consistent with their formulation, will be mentioned in the full paper.

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