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193. Steroidal Heterocycles 15[1])
4,4-Dialkyl-Δ^5-3-oxosteroids, 1,4′-spiro [cycloalkyl-Δ^5-3-oxo-steroids] and Derivatives

by **H. C. Neumann** and **F. W. Stonner**

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(5. VI. 72)

Summary. Homologs of 17-hydroxy-4,4-17α-trimethyl-3-oxo-androst-5-ene-2α-carbonitrile (**6d**), such as the 4,4-diethyl-(**6a**), 4,4-cyclopentyl-(**6c**) and 4,4-cyclohexyl-(**6b**) analogs were synthesized.

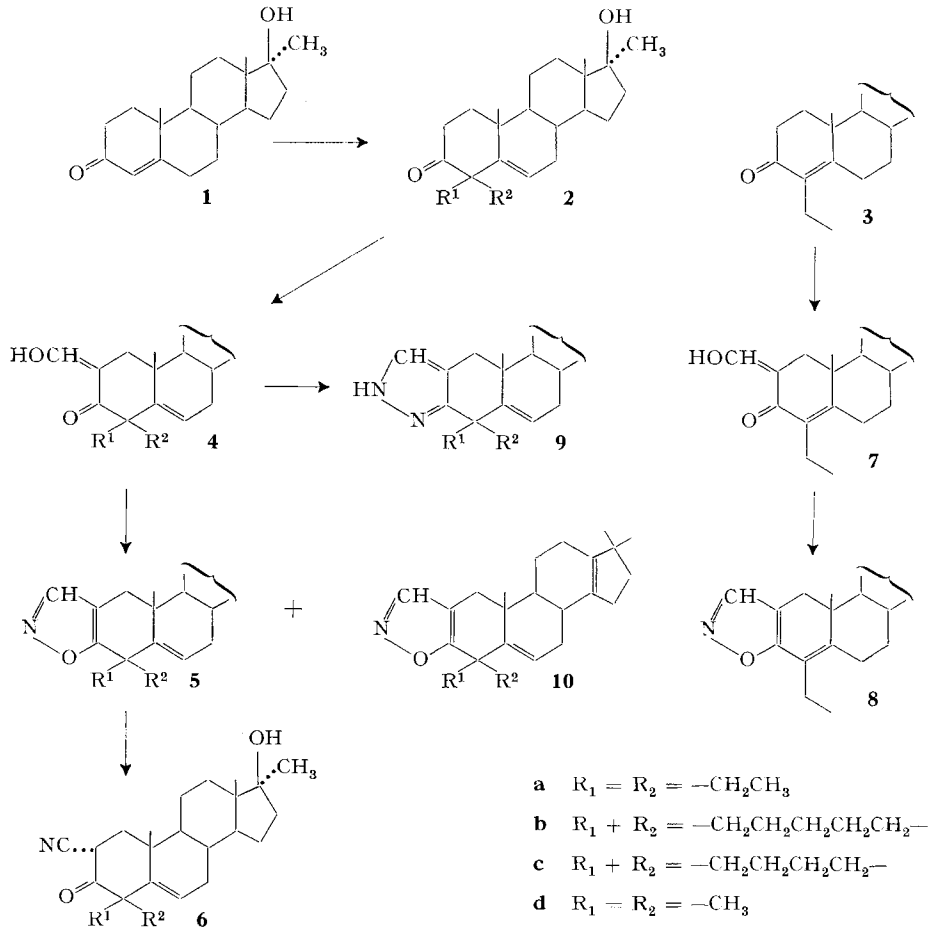
The interesting biological activity exhibited by 17β-hydroxy-4,4, 17-trimethyl-3-oxoandrost-5-ene-2α-carbonitrile [2] [3] [4] (**6d**), prompted the sythesis of the 4,4-diethyl homolog **6a** and 1,4′-spiro-cyclohexyl- and 1,4′-spiro-cyclopentyl-analogs **6b** and **6c**. Known procedures [5] [6] were employed for alkylation at the C(4) position.

The spiro-cyclopentyl derivative **2c** proved to be unstable when subjected to elevated temperatures, possibly due to rearrangement of the spiro-system resulting from the release of steric compression between the rigid cyclopentyl ring and the hydrogen atom at C(6).

The hydroxymethylene derivatives **4** and the corresponding pyrazoles **9**, isoxazoles **5** and cyanoketones **6** were prepared using procedures similar to those previously

[1]) 14th communication, see [1].

published [2] [7]. Rearrangement at C(17) occured readily under the acidic conditions of the isoxazole formation to give the 17,17-dimethyl compounds **10**, but could be avoided with sodium acetate buffering [2].



Experimental Part

General. Melting points (cor) were determined in a *Hershberg*-type apparatus; optical rotations were determined in $CHCl_3$ at 25°, $C \sim 1$; UV. spectra were determined in 95% EtOH (*Cary* 15); IR. spectra were determined in KBr discs (*Perkin Elmer* 21); NMR. spectra were determined in $CDCl_3$ with TMS as internal standard (*Varian* A60). Spectra were determined by Dr. *R. K. Kullnig* and staff; microanalyses were performed by Mr. *K. D. Fleischer* and staff.

The following example is representative of the alkylation procedure employed:

4,4-Diethyl-17-hydroxy-17α-methylandrost-5-en-3-one (**2a**) and *4-Ethyl-17-hydroxy-17α-methylandrost-4-en-3-one* (**3**). To a stirred solution of potassium *t*-butoxide (7g) in *t*-BuOH (450 ml) under N_2 was added methyltestosterone (20 g) in *t*-BuOH (200 ml); the solution was cooled to 20° and EtBr (65.4 g) was added dropwise. When addition was complete, the solution was stirred 1 hour and was allowed to stand 3 h at room temperature. Ice/H_2O (100 ml) containing $NaHCO_3$ (10 g) was added with stirring. *t*-BuOH was evaporated under reduced pressure, C_6H_6 (200 ml) was added and solution was warmed until 2 layers formed; C_6H_6 layer was separated, washed with

H_2O, dried, concentrated and MeOH (100 ml) added. Precipitate (9 g) recrystallized from EtOH to give **2a** (6 g): m.p. 185–190°; $[\alpha]_D^{25} = -30°$.

$C_{24}H_{38}O_2$ (358.5) Calc. C 80.39 H 10.68% Found C 80.41 H 10.44%

Additional **2a** (6 g) was obtained from mother liquors on chromatography (1500 g SiO_2, 3–5% EtOAc/C_6H_6); EtOAc/C_6H_6 (10%) eluted **3** (2.5 g): m.p. 116.5–118°; $[\alpha]_D^{25} = 88.3°$; UV. max 251 (ε 15400).

$C_{22}H_{34}O_2$ (330.5) Calc. C 79.95 H 10.37% Found C 80.07 H 10.35%

Recovered **1** (5 g) (20% EtOAc/C_6H_6). IR. and NMR. spectra were consistent with these structures as well as for all of the following compounds.

1,4'-Spiro[cyclohexane-17'-hydroxy-17'α-methylandrost-5'-en-3'-one] (**2b**) – from methyltestosterone (**1**) and 1,5-diiodopentane. Yield 46%: m.p. 196–198° (EtOAc); $[\alpha]_D^{25} = 17.2°$.

$C_{25}H_{38}O_2$ (370.6) Calc. C 81.03 H 10.34% Found C 81.28 H 10.46%

1,4'-Spiro[cyclopentane-17'-hydroxy-17'α-methylandrost-5'-en-3'-one] (**2c**) – from methyltestosterone (**1**) and 1,4-dibromobutane. Yield 60% (heat unstable): m.p. 180.5–181.5°; $[\alpha]_D^{25} = -54.5°$.

$C_{24}H_{36}O_2$ (356.5) Calc. C 80.85 H 10.18% Found C 80.62 H 9.96%

The following 2-hydroxymethylene compounds (**4**), [2,3-*d*]isoxazoles (**5**), carbonitriles **6** and [3,2-*c*]pyrazoles (**9**) were prepared using previously published procedures [2] [7].

4,4-Diethyl-17-hydroxy-2-(hydroxymethylene)-17α-methyl-androst-5-en-3-one (**4a**). – Yield 95%; m.p. 177–178° (EtOAc); $[\alpha]_D^{25} = -40.3°$; UV. max 281 (ε 7810).

$C_{25}H_{38}O_3$ (386.6) Calc. C 77.67 H 9.91% Found C 77.64 H 9.76%

1,4'-Spiro[cyclohexane-17'-hydroxy-2'-(hydroxymethylene)-17'α-methylandrost-5'-en-3'-one] (**4b**). – Yield 72%; m.p. 186–191° (EtOAc); $[\alpha]_D^{25} = -17.0°$; UV. max. 270 (ε 7980).

$C_{26}H_{38}O_3$ (398.6) Calc. C 78.35 H 9.61% Found C 78.25 H 9.54%

1,4'-Spiro[cyclopentane-17'-hydroxy-2'-(hydroxymethylene)-17'α-methylandrost-5'-en-3'-one] (**4c**). – Yield 87%; m.p. 186.5–190° (EtOAc); $[\alpha]_D^{25} = -89.0°$; UV. max 277 (ε 7620).

$C_{25}H_{36}O_3$ (384.5) Calc. C 78.08 H 9.44% Found C 78.24 H 9.69%

*4-Ethyl-17α-methylandrost-4-eno[2,3-*d*]isoxazol-17-ol* (**8**) – from uncharacterized resinous 4-ethyl-17-hydroxy-2-(hydroxymethylene)-17α-methylandrost-4-en-3-one (**7**). Overall yield 52%; m.p. 110–113°, resolidified and remelted 153–155°; $[\alpha]_D^{25} = 73.9°$; UV. max. 288 (ε 11400).

$C_{23}H_{33}NO_2$ (355.5) Calc. C 77.70 H 9.36 N 3.94% Found C 77.64 H 9.13 N 3.89%

*4,4-Diethyl-17α-methylandrost-5-eno[2,3-*d*]isoxazol-17-ol* (**5a**). – Yield 78% from **4a**; m.p. 138–140° (MeOH); $[\alpha]_D^{25} = -54.1°$; UV. max 230 (ε 6080).

$C_{25}H_{37}NO_2$ (383.6) Calc. C 78.28 H 9.72 N 3.65% Found C 78.44 H 9.48 N 3.54%

*1,4'-Spiro[cyclohexane-17',17'-dimethyl-18'-norandrosta-5',13'-dieno(2',3'-*d*)isoxazole]* (**10b**) and *1,4'-Spiro[cyclohexane-17'α-methylandrost-5'-eno(2',3'-*d*)isoxazol-17'-ol]* (**5b**) – from **4b**. Chromatography on silica gel yielded 20% of **10b** (C_6H_6) and 31% **5b**. (10% Et_2O in C_6H_6).

Compound **5b**: m.p. 225–229° (EtOH); $[\alpha]_D^{25} = -92.5°$; UV. max 231 (ε 5800).

$C_{26}H_{37}NO_2$ (395.6) Calc. C 78.94 H 9.43 N 3.54% Found C 78.78 H 9.51 N 3.55%

Compound **10b**: m.p. 172–174° (EtOH); $[\alpha]_{25}^{D} = -196.3°$; UV. max 228 ($\varepsilon$ 6330).

$C_{26}H_{35}NO$ (377.5) Calc. C 82.71 H 9.34 N 3.71% Found C 82.44 H 9.34 N 3.61%

*1,4'-Spiro[cyclopentane-17'α-methylandrost-5'-eno(2',3'-*d*)-isoxazol-17'-ol]* (**5c**) – from **4c**. Yield 90% when mild acidic conditions were employed (NaOAc buffering); m.p. 210–214° (EtOAc); $[\alpha]_D^{25} = -89.8°$; UV. max 231 (ε 6490).

$C_{25}H_{35}NO_2$ (381.5) Calc. C 78.68 H 9.25 N 3.67% Found C 78.65 H 9.06 N 3.67%

*1,4'-Spiro[cyclopentane-17',17'-dimethyl-18'-norandrosta-5',13'-dieno(2',3'-*d*)isoxazole]* (**10c**) – from **4c** when NaOAc buffering was not employed. Yield 72%; m.p. 134–136° (EtOAc); $[\alpha]_D^{25} = -196.7°$; UV. max 229 ($\varepsilon$ 6500).

$C_{25}H_{33}NO$ (363.5) Calc. C 82.60 H 9.15 N 3.85% Found C 82.50 H 9.12 N 3.81%

4,4-Diethyl-17-hydroxy-17α-methyl-3-oxoandrost-5-ene-2α-carbonitrile (**6a**) – from **5a**. Yield 69%; m.p. 135–140° (C_6H_6); $[\alpha]_D^{25} = -33.8°$; UV. max 240 (ε 7930).

$C_{25}H_{37}NO_2$ (383.6) Calc. C 78.28 H 9.72 N 3.65% Found C 78.47 H 9.83 N 3.81%

1,4'-Spiro[cyclopentane-17'-hydroxy-17'α-methyl-3'-oxoandrost-5'-ene-2'α-carbonitrile] (**6c**) – from **5c**. Yield 65%; m.p. 150–152° (EtOAc); $[\alpha]_D^{25} = -20.0°$; UV. max 239 (ε 5810).

$C_{25}H_{35}NO_2$ (381.5) Calc. C 78.68 H 9.25 N 3.67% Found C 78.42 H 8.99 N 3.59%

4,4-Diethyl-17α-methylandrost-5-eno[3,2-c]pyrazol-17-ol (**9a**) – from **4a**. Yield 80%; m.p. 229–233° (EtOH); $[\alpha]_D^{25} = -50.9°$; UV. max 224 (ε 5690).

$C_{25}H_{38}N_2O$ (382.6) Calc. C 78.48 H 10.01 N 7.32% Found C 78.42 H 9.76 N 7.31%

1,4'-Spiro[cyclohexane-17'α-methylandrost-5'-eno(3',2'-c)-pyrazol-17'-ol] (**9b**) – from **4b**. Yield 93%; m.p. 278–280° (EtOAc); $[\alpha]_D^{25} = -62.8°$; UV. max 223 (ε 5340).

$C_{26}H_{38}N_2O$ (394.6) Calc. C 79.14 H 9.17 H 7.10% Found C 79.20 H 9.12 N 7.33%

1,4'-Spiro[cyclopentane-17'α-methylandrost-5'-eno-(3',2'-c)-pyrazol-17'-ol] (**9c**) – from **4c**. Yield 88%; m.p. 266–270° (EtOH); $[\alpha]_D^{25} = -67.9°$; UV. max 224 (ε 5820).

$C_{25}H_{36}N_2O$ (380.6) Calc. C 78.90 H 9.54 N 7.36 Found C 78.64 H 9.36 N 7.07%

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194. Heuristic Programming as an Ion Generator in Mass Spectrometry

I. Generation of Primary Ions with Charge Localization

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(3 V 72)

Résumé. Un programme connu sous le nom de *ION GENERATOR* a été élaboré. Pour le moment ce programme est capable de créer, à partir de n'importe quelle molécule organique, les ions primaires résultant de la fragmentation de l'ion moléculaire et de proposer des mécanismes de fragmentation pour expliquer la formation des ions.

In this paper we present a heuristic program we have devised to simulate the formation of ions in the ion source of a mass spectrometer. Our program, the *ION GENERATOR*, acts in much the same way as the chemist who is trying to rationalize ion formations with the help of paper and pencil; it is based on the well known method