STRUCTURE AND PROGESTATIONAL ACTIVITY OF 13-SUBSTITUTED-18-NORPREGN-4-ENE-3,20-DIONES, A PILOT STUDY

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ABSTRACT

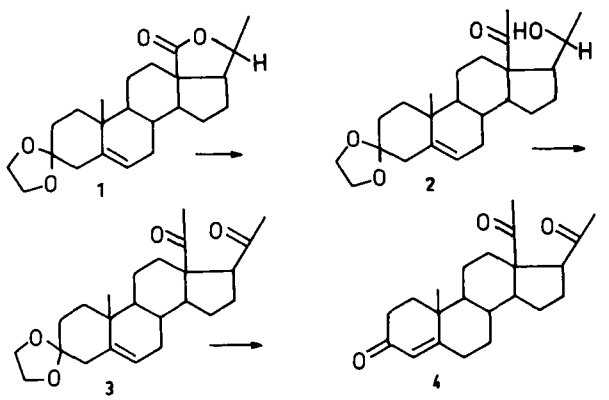
13-Ethyl-18-norpregn-4-ene-3,20-dione (7) and 13-acetyl-18-norpregn-4-ene-3,20-dione (4) were synthesized and tested in the s.c. Clauberg assay. The potencies of these compounds (1x and 1/3 x progesterone, respectively) are compared with those reported for 13-vinyl- and 13-cyanomethyl-18-norpregn-4-ene-3,20-dione. A comparable activity (1/3 x progesterone) was found for 13-acetyl-18-norpregn-4-en-3-one (10) which lacks the 20-carbonyl group.

INTRODUCTION

The relation between structure and progestational activity is ill defined for the 13-substituted-18-norpregn-4-ene-3,20-dione series. Auel, Freerksen and Watt (1) synthesized and tested a series of 18-norpregn-4-ene-3,20-dione derivatives with polar, bulky 13-substituents (CH_2-CN, CH_2COOH, CH_2COOCH_3 and $CH_2CH_2NHCOCH_3$) and found these inactive in the Clauberg test. Kalvoda, Grob and Anner reported that 13-vinyl-18-norpregn-4-ene-3,20-dione is about twice as potent as progesterone in this test (2,3). Baddeley, Carpio and Edwards synthesized 13-ethyl-18-norpregn-4-ene-3,20-dione (7) and 13-acetyl-18-norpregn-4-ene-3,20-dione (4). They discussed the conformation of these compounds but reported no biological data (4).

As a basis for a first more systematic discussion we also synthesized these two derivatives to assess their activities.

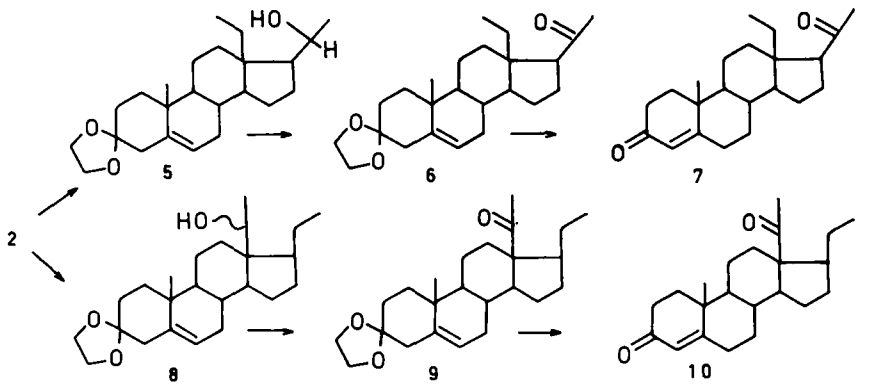
CHEMISTRY



Our synthesis proceeded analogously with that of Baddeley, Carpio and Edwards (4). The lactone 1 (0.04 mol, 15.0 g) (5) in tetrahydrofuran (200 mL) was stirred for 2 hours at room temperature with 0.08 mol CH_3Li in ether (70 mL). Treatment with NH_4Cl, extraction with ether and crystallization from acetone gave compound 2 (0.03 mol, 12.5 g), mp 181-183°C, $[\alpha]_D$-36 (6). This conversion with Ch_3Li is an improvement over the Grignard reaction (4) where severe reaction conditions were necessary.

The alcohol 2 (4.6 mol, 1.8 g) was oxidized with CrO_3 (3.0 g)-pyridine (60 mL) at room temperature to yield, after chromatography on SiO_2 and crystallization from acetone, the diketone 3 (3.6 mmol, 1.4 g), mp 186.5-189°C, $[\alpha]_D$ +1. To remove the acetal group compound 3 was heated for 1 hour under reflux in acetone (40 mL) with p-toluenesulphonic acid (100 mg). Crystallization from methylene chloride-ether gave 13-acetyl-18-norpregn-4-ene-3,20-dione 4 (2.3 mmol, 0.8 g), mp 150-151°C, $[\alpha]_D$ +168 [Cf. 149-151° C, $[\alpha]_D$ +168 (7); 158-159°C, $[\alpha]_D$ +189 (4)].

The Wolff-Kishner reaction, used to remove the keto group of compound 2, proved difficult as had been noted in analogous cases by other authors (4,7). The Huang-Minlon procedure is accompanied by rearrangement. Thus, when compound 2 (5.1 mmol, 2.0 g) was heated first for 1.5 hours under reflux with hydrazine hydrate (20 mL), ethanol (20 mL) and diethylene glycol (60 mL), then, after the addition of powdered KOH (10 g), for 1.5 hour under reflux and finally, under distillation of alcohol and water, for 3.5 hours at 180-185°C, a mixture of epimeric alcohols 8 was obtained. Oxidation with CrO_3 (3.3 g)-pyridine (60 mL), chromatographic purification (SiO_2) and crystallization from methylene chloride-methanol gave the 13-acetyl derivative 9 (1.6 mmol, 0.6 g), mp 167-168°C, $[\alpha]_D$-34.



This rearrangement could be avoided by preparing the hydrazone first under acid catalysis. When ketone 2 (26 mmol, 10.0 g) was heated first for 1.5 hours under reflux with hydrazine hydrate (100 mL), diethylene glycol (250 mL), ethanol (100 mL) and conc. hydrochloric acid (90 mL), then, after the addition of powdered KOH (100 g) and diethylene glycol (800 mL), under distillation of alcohol and water for 3.5 hours at 200°C, compound 5 was obtained after chromatographic purification (7.4 mmol, 2.75 g), mp 159-161.5°C. This product was oxidized with CrO_3(3.0 g)-pyridine (55 mL) and crystallized from methylene chloride-methanol to give the 20- ketone 6 (6 mmol, 2.2 g), mp 153-154 °C, $[\alpha]_D$+32.

To remove the ketal protecting group compound 6 (0.7 mmol, 0.25 g) was heated under reflux in acetone (10 mL) with p-toluenesulphonic acid (50 mg) for 1 hour. Crystallization from aqueous acetone gave 13-ethyl-18-norpregn-4-ene-3,20-dione 7 (0.6 mmol, 0.20 g), mp 165-165.5°C, $[\alpha]_D$ +210 [Cf. 169-171°C, $[\alpha]_D$ + 204 (4)].

Compound 9, when treated similarly, yielded 13-acetyl-18-norpregn-4-en-3-one 10, mp 176.5-178°C, $[\alpha]_D$ + 138, UV λ_{max} 241 nm, ε_{mol} = 16700. The 17β-configuration in compounds 8, 9 and 10 is based on the molecular rotations of the dione 10, which shows the expected value by comparison with related compounds (7).

BIOLOGICAL ACTIVITY

Compounds 4, 7 and 10 were evaluated for their progestational activity in the Clauberg-McPhail test (8) after s.c. administration. 13-Ethyl-18-norpregn-4-ene-3,20-dione 7 was about as potent as progesterone. This

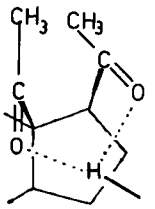
corresponds reasonably well with the reported potency (1/4 x progesterone) of racemic 7 (9). The potencies found for 13-acetyl-18-norpregn-4-ene-3,20-dione 4 and 13-acetyl-18-norpregn-4-en-3-one 10 were 1/3 and 1/4 of the potency of progesterone, respectively.

DISCUSSION

To facilitate the discussion, we have calculated the lipophilicity of the 13-substituents from the Rekker fragmental constants (10). These are: C_2H_5 1.23, $CH{=}CH_2$ 0.93, CH_3 0.70, CH_2CN -0.14 and $COCH_3$ -0.53. In view of the small difference in potency between the most lipophilic compound, 13-ethyl-18-norpregn-4-ene-3,20-dione 7, and the least lipophilic compound, 13-acetyl-18-norpregn-4-ene-3,20-dione 4, the low potency (< 1/40 of progesterone) reported for 13-cyanomethyl-18-norpregn-4-ene-3,20-dione (1) can not be explained by the polar nature of the 13-substituent. A steric effect is more likely. The 18-substituent may, for example, distort the receptor protein when it binds with the progestogen. To verify this assumption, we carried out a Hansch type analysis using the data for the 13-methyl, vinyl, ethyl, acetyl and cyanomethyl derivatives (11) and found the following relation: log potency = $0.40\Sigma f - 0.87L + 2.04$ (Σf = sum of the Rekker fragmental constants for the 13-substituent, and L is Verloops L parameter (12) for the 18-substituent). The regression coefficient $r = 0.87$, $r^2 = 0.76$ is acceptable and the coefficient which correlates potency with lipophilicity (0.40) is in the

expected range for a drug-receptor interaction (13). This shows that the explanation given is a possible one. Data on more compounds with a spread of potencies are needed to put this hypothesis on firm grounds.

It is of interest to note that 13-acetyl-18-norpregn-4-en-3-one, which lacks the 20-carbonyl group of progesterone, is still an active compound. This suggests that the carbonyl group of the 13-acetyl group may, in binding with the receptor, take over the function of hydrogen bond acceptor. This is possible when both carbonyl groups bind in their preferred conformation and the hydrogen bond donor of the receptor is located over ring D in the vicinity of C-15.



NOTES AND REFERENCES

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