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## Steroidal 4-Methylene-2-oxazolidinones

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Farkas and Swallow (1) have recently reported on steroidal carbamic acid  $\gamma$ -lactones in which alkyl isocyanates were allowed to react with steroidal 17 $\alpha$ -ethynyl-17 $\beta$ -ols and the resulting carbamates cyclized to the oxazolidinones. We were also interested in this reaction because of the possibility of pharmacological activity being associated with the products. At the time we began this work, both the five-membered (2) and the six-membered (3) structures had been proposed for the products of the cyclization reaction. Easton (4), working in the aliphatic and alicyclic series, and others (5) have since confirmed the five-membered ring structure. Our own results, using like arguments based on n.m.r. data, agree with this conclusion.

Prior to the report by Farkas (1), however, there were no steroidal examples. Since only the use of alkyl isocyanates was described, we wish to report our data on the use of phenylisocyanate with ethisterone, norethindrone, and ethynyl estradiol-3-methyl ether. The carbanilate esters formed readily from these materials on heating at reflux in toluene or xylene, the higher temperature being required for formation of Ib and Ic. The esters (Ia and Ib) precipitated in high yield from the reaction mixtures. No evidence of the carbaniloyl carbanilates corresponding to Farkas' second product was detected. Cyclization of the carbanilate esters was effected by refluxing in sodium methylate-methanol or sodium ethylate-ethanol. Recrystallization from dimethylsulfoxide also effected the cyclization in the case of Ia. Treatment of Ia with sodium methylate in N-methylpyrrolidone at 90° or brief treatment (5 minutes at 120°) with sodium hydroxide in dimethylsulfoxide gave inferior results.

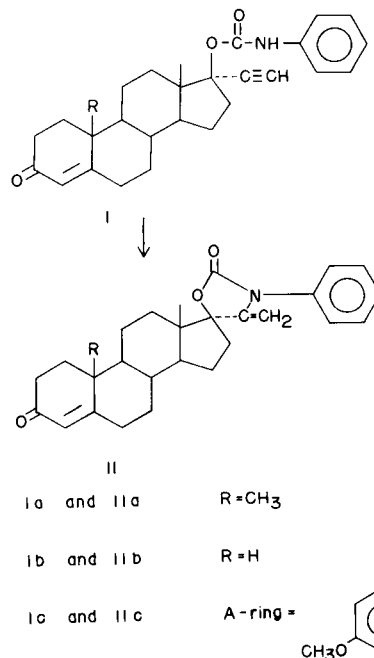
The compounds obtained do not appear to retain significant levels of the pharmacological activities of the parent steroids, nor do they exhibit any antagonism of aldosterone in the salt-loaded rat. The exceptions are remarkably parallel to the alkyl analogs (1). Low estrogenicity was associated with Ic but not with IIc; IIa was very weakly androgenic; while IIb was about one-half as active as progesterone (Clauberg) by subcutaneous injection, but was inactive orally (6).

## EXPERIMENTAL (7)

## Preparation of carbanilate esters.

17 $\alpha$ -Pregn-4-en-20-yn-17 $\beta$ -ol-3-one, carbanilate ester (Ia).

To a mixture of 31.2 g. (0.10 mole) of 17 $\alpha$ -pregn-4-en-20-yn-17 $\beta$ -ol-3-one in two liters of dry toluene was added 23.8 g. (0.20 mole)



of phenylisocyanate and the mixture heated to reflux with stirring for 18 hours. For a brief period after reaching reflux temperature, the mixture was homogeneous, but shortly the product began to separate. At the end of the reflux period, the mixture was cooled in an ice bath and the solid collected by vacuum filtration, washed with benzene and dried in the vacuum oven at 50°. There was obtained 39.6 g. (92%), melting at 295-296° (decomp.);  $[\alpha]_D^{25} = +44^\circ$  (c 0.84, pyridine);  $\lambda$  max 238 m $\mu$  (log  $\epsilon = 4.16$ );  $\nu$  max 3320, 3300, 2120, 1739, 1655, 1603 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>28</sub>H<sub>33</sub>NO<sub>3</sub>: C, 77.93; H, 7.71; N, 3.25. Found: C, 77.47; H, 7.50; N, 3.05.

19-Nor-17 $\alpha$ -pregn-4-en-20-yn-17 $\beta$ -ol-3-one, carbanilate ester (Ib).

A mixture of 6.0 g. of norethindrone (20 mmoles) and 9.5 g. (80 mmoles) of phenylisocyanate in 150 ml. of dry xylene was heated to reflux with stirring for 48 hours. The solid product began to separate after a few minutes. At the end of the reflux time, the mixture was cooled and the product collected, washed thoroughly with benzene and dried in a vacuum oven at 50°. There was obtained 6.2 g. (75%) of an off-white powder, m.p. 308-309°,  $[\alpha]_D^{25} = 0^\circ$  (c sat'd, dioxane);  $\lambda$  max 237 m $\mu$  (log  $\epsilon = 4.55$ );  $\nu$  max 3310, 3270,  $\nu$ (C=C) not discernible, 1738, 1654, 1603, 1545 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>27</sub>H<sub>31</sub>NO<sub>3</sub>: C, 77.67; H, 7.49; N, 3.36. Found: C, 77.52; H, 7.50; N, 3.51.

3-Methoxy-19-nor-17 $\alpha$ -pregna-1,3,5(10)-triene-20-yn-17 $\beta$ -ol, carbanilate ester (Ic).

Ethynyl estradiol-3-methyl ether was prepared by a procedure essentially that described by Wenkert (8). A mixture of 10.0 g. (33.8 mmoles) of ethynyl estradiol, 23.2 g. (5 x 33.8 mmoles) of anhydrous potassium carbonate and 21.2 g. (5 x 33.8 mmoles) of dimethylsulfate in 500 ml. dry acetone was heated to reflux with stirring for 21 hours. The inorganic solids were removed by filtration through a Celite pad and the solvent evaporated. The residue was washed in ether solution with 5% sodium hydroxide and then with water, dried (magnesium sulfate) and the product recovered by evaporation. Crystallization from methanol yielded 9.65 g. (93%), m.p. 148-150°. Two further crystallizations yielded 8.4 g. (81%), m.p. 149-151° containing one molecule of methanol of crystallization. After drying at 100° under reduced pressure, the melting point was 150-152°,  $[\alpha]_D^{25} = +12^\circ$  (c 1.05, CHCl<sub>3</sub>);  $\lambda$  max 219 (log  $\epsilon = 3.98$ ), 278 (log  $\epsilon = 3.32$ ), 287 m $\mu$  (log  $\epsilon = 3.30$ ).

*Anal.* Calcd. for  $C_{21}H_{26}O_2$ : C, 81.25; H, 8.44. Found: C, 81.04; H, 8.74.

A mixture of 3.10 g. (10 mmoles) of ethynyl estradiol-3-methyl ether and 4.8 g. (40 mmoles) of phenylisocyanate in 150 ml. of dry xylene was heated to reflux with stirring for 48 hours. The solvent was removed by distilling at atmospheric pressure and then under reduced pressure. The residue was crystallized by stirring with equal volumes of benzene and methanol to yield 3.05 g. (71%) of colorless crystals, m.p. 182-184°. Two crystallizations from isopropyl alcohol-water (4:1) gave material melting at 186-188°,  $[\alpha]_D^{24} = 0^\circ$  (c 1.15,  $CHCl_3$ );  $\lambda$  max 232 (log  $\epsilon = 4.24$ ), 277 (log  $\epsilon = 3.29$ ), 286  $m\mu$  (log  $\epsilon = 3.17$ );  $\nu$  max 3440, 3300,  $\nu$  (C=C) not discernible, 1740, 1604, 1522  $cm^{-1}$ ; n.m.r.  $\delta = 0.91, 2.62, 3.73, 6.65, 6.72-7.48$ .

*Anal.* Calcd. for  $C_{28}H_{31}NO_3$ : C, 78.29; H, 7.27; N, 3.27. Found: C, 78.02; H, 7.37; N, 3.27.

4'-Methylene-3'-phenylspiro[androst-4-ene-17,5'(1' $\beta$ )-oxazolidine]-2',3-dione (IIa).

Ia, 4.3 g. (10 mmoles), was added to a solution of 0.23 g. (10 mmoles) of sodium in 250 ml. of absolute ethanol and the mixture heated to reflux overnight (20 hours). Acidification with glacial acetic acid and evaporation yielded a solid product which was charcoal-treated in methylene chloride-methanol solution and crystallized from methanol to yield 3.6 g. (84%) of pale yellow leaflets, m.p. 280-282°. The analytical sample was crystallized from acetonitrile, m.p. 281-283°,  $[\alpha]_D^{24} = 0^\circ$  (c 0.96,  $CHCl_3$ );  $\lambda$  max 232  $m\mu$  (log  $\epsilon = 4.32$ );  $\nu$  max 1772, 1676, 1635, 1612, 1600, 1390  $cm^{-1}$ ; n.m.r. ( $CCl_4$ )  $\delta = 1.08, 1.22, 4.20$  (AB pattern,  $\Delta\delta = 9.5$  c.p.s.,  $J_{AB} = 3$  c.p.s.), 5.75, 7.38.

*Anal.* Calcd. for  $C_{28}H_{31}NO_3$ : C, 77.93; H, 7.71; N, 3.25. Found: C, 77.83; H, 7.68; N, 3.33.

4'-Methylene-3'-phenylspiro[estra-4-ene-17,5'(1' $\beta$ )-oxazolidine]-2',3-dione (IIb).

To a solution of 0.70 g. (30 mmoles) of sodium in 250 ml. of anhydrous methanol was added 4.2 g. (10 mmoles) of IIa. The mixture was stirred and heated to reflux for 12 hours. The mixture was worked up as was the previous example and the product crystallized from acetonitrile, 3.1 g. (74%), m.p. 267-270°. The analytical sample, from acetonitrile, melted at 269-272°,  $\lambda$  max 231  $m\mu$  (log  $\epsilon = 4.37$ );  $\nu$  max ( $CHCl_3$ ) 1764, 1666, 1622, 1600, 1397  $cm^{-1}$ ; n.m.r.  $\delta = 1.10, 4.19$  (AB pattern,  $\Delta\delta = 10.5$  c.p.s.,  $J_{AB} = 2.5$  c.p.s.), 5.87, 7.4.

*Anal.* Calcd. for  $C_{27}H_{31}NO_3$ : C, 77.67; H, 7.49; N, 3.35. Found: C, 77.71; H, 7.58; N, 3.45.

4'-Methylene-3'-phenylspiro[3-methoxy-estra-1,3,5(10)-triene-17,5'(1' $\beta$ )-oxazolidine]-2'-one (IIc).

To a solution of 1.1 g. (45.6 mmoles) of sodium in 500 ml. of anhydrous methanol was added 9.80 g. (22.8 mmoles) of Ic. The mixture was heated to reflux with stirring for 12 hours and then acidified and worked up as in the previous examples. The product was recrystallized from dilute ethanol to yield 7.9 g. (81%), m.p. 175-177°. The analytical sample, from ethanol, melted at 176-177.5°,  $[\alpha]_D^{25} = -82^\circ$  (c 1.14,  $CHCl_3$ );  $\lambda$  max 220 (log  $\epsilon = 4.33$ ), 277 (log  $\epsilon = 3.33$ ), 287  $m\mu$  (log  $\epsilon = 3.29$ );  $\nu$  max 1765, 1682, 1610, 1577, 1505, 1400  $cm^{-1}$ ; n.m.r.  $\delta = 1.08, 3.75, 4.25$  (AB pattern,  $\Delta\delta = 11$  c.p.s.,  $J_{AB} = 3$  c.p.s.), 6.64-7.41.

*Anal.* Calcd. for  $C_{28}H_{31}NO_3$ : C, 78.29; H, 7.27; N, 3.27. Found: C, 78.05; H, 7.45; N, 3.44.

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- (6) We are indebted to Drs. O. D. Bird, L. T. Blouin and M. R. Callantine of these laboratories for the pharmacological data.
- (7) The melting points were determined in a Thomas-Hoover melting point apparatus and are corrected. The infrared spectra were recorded in KBr discs or in solution, if indicated, with a Beckman IR-7 spectrophotometer. The n.m.r. spectra were recorded in deuteriochloroform solution or in carbon tetrachloride, if indicated, using a Varian A-60 spectrometer with resonances reported as parts per million downfield from tetramethylsilane used as an internal reference. The ultraviolet spectra were recorded in methanol solution using a Cary Model 14 spectrophotometer. Microanalyses are by Mr. C. E. Childs and the staff of our Microanalytical Laboratory. The physical chemical data were obtained by Dr. J. M. Vandenberg and the staff of our Physical Chemistry Laboratory.
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