21-Methoxyprogesterone. Improved Synthesis

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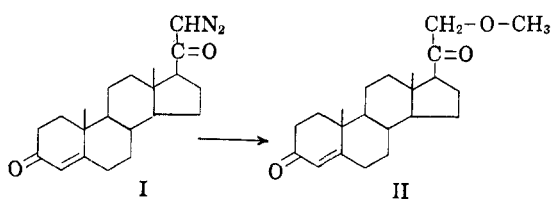
In connection with a current interest in preparing derivatives of adrenocortical hormones which might, possibly, have a modified physiological activity, we became interested, as a first consideration, in securing a quantity of the previously described 21-methoxyprogesterone (II) (21-methyl ether of 11-deoxycorticosterone), prepared by two different routes.[3] The first of these, by Meystre and Wettstein,[3a] was accomplished in eleven steps starting with 3β-hydroxy-Δ⁵-cholenic acid and involved methoxylation at C(21) of 3β-acetoxy-5-chloro-21-bromo-24,24-diphenyl-Δ^{20,23}-choladiene as the key step in the synthesis. The other, a considerably simpler procedure, described by Heusser, *et al.*,[3b] was effected in eight steps starting with 3β-hydroxy-Δ⁵-etiocholenic acid and involved treatment of 21-diazo-Δ⁵-pregnen-3β-ol-20-one in boiling methanol with cupric oxide to give the corresponding 21-methoxy derivative which, on subsequent oxidation, gave 21-methoxyprogesterone (II) in 34% yield.

The method which we wish to describe proceeds *via* 21-diazoprogesterone (I), which may be conveniently prepared from 3β-hydroxy-Δ⁵-etiocholenic acid in five steps.[4] The conversion of I to 21-methoxyprogesterone (II) provides for an extension to



I II

steroid compounds of a reaction described by Newman and Beal,[5] whereby α-diazoketones may be converted directly to α-alkoxyketones in good yield, using boron trifluoride as a catalyst. This reaction, in our case, proved to be virtually quantitative and should apply equally satisfactorily in the case of other steroid 21,20-diazoketones.

EXPERIMENTAL

All melts were performed on the Kofler hot-stage.

21-Methoxyprogesterone (II). To a solution of 34 mg. of 21-diazoprogesterone (I) (m.p. 178–182°) in 2 ml. of anhydrous methanol at 55°, was added 0.1 ml. of boron trifluoride etherate. The reaction was complete in 5 min. as evidenced by cessation of nitrogen evolution. The solution was taken up in ether and extracted first with water, then with dilute sodium bicarbonate. The dried extract was evaporated *in vacuo*, leaving 34 mg. of a white, crystalline residue (m.p. 145–159°). One crystallization from methanol gave pure II, m.p. 159–164° (recrystallization did not improve the melting point), which did not depress the melting point of an authentic specimen.[3a] $[\alpha]_D^{20}$ + 189° ± 4° (*c*, 1.25 $CHCl_3$), λ_{max}^{alc} 240 (4.22).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.34, 76.19; H, 9.69, 9.49.

Bis(2,4-dinitrophenylhydrazone) of II. The method for the preparation of this compound was essentially the same as one previously described.[6] To a solution of 11 mg. of 21-methoxyprogesterone (II) in 1 ml. of absolute ethanol was added a solution of 25 mg. of 2,4-dinitrophenylhydrazine in 3 ml. of the same solvent containing 6 drops of hydrochloric acid. After standing at room temperature overnight, 4 ml. of Benedict's reagent was added, followed by 4 ml. of water. The resulting suspension was heated on a water bath for 10 min. and extracted twice with chloroform. The extract in turn was washed with water, dried, and evaporated, leaving a colored residue which was chromatographed on 3 g. of alumina. Benzene-chloroform (4-1) yielded the desired product. One fraction (8 mg.), selected for its relative purity, was recrystallized twice from chloroform-ethanol, giving 4 mg. of pure 21-methoxyprogesterone bis(2,4-dinitrophenylhydrazone), m.p. 251–253.5°.

Anal. Calcd. for $C_{34}H_{40}O_9N_8$: N, 15.90. Found: N, 14.89.

Acknowledgment. The authors are grateful to Dr. A. Wettstein for having his laboratory carry out the mixed melting point. They wish also to thank Dr. E. B. Hershberg of the Schering Corp. for generously supplying the 3β-hydroxy-Δ⁵-etiocholenic acid, and Dr. R. E. Peterson, NIAMD, National Institutes of Health, for the ultraviolet analysis and for having the microchemical laboratory, NIAMD, perform the elemental analyses.

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(3) (a) C. Meystre and A. Wettstein, *Helv. Chim. Acta*, **30**, 1256 (1947). (b) H. Heusser, C. R. Engel, and P. A. Plattner, *Helv. Chim. Acta*, **32**, 2475 (1949).

(4) (a) K. Miescher and A. Wettstein, *Helv. Chim. Acta*, **22**, 1262 (1939). (b) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **70**, 2427 (1948).

(5) M. S. Newman and P. F. Beal III, *J. Am. Chem. Soc.*, **72**, 5161 (1950).

(6) H. Reich, K. F. Crane, and S. J. Sanfilippo, *J. Org. Chem.*, **18**, 822 (1953).

Steroids. LXXXVII.[1] Preparation of Some Estrone-Ethers

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During an investigation of the effect of substitution on physiological activity it became of interest to prepare some substituted estrone and estradiol ethers of glycol and glycolic acid. This communication describes some of the derivatives made.

Condensation of estrone sodium salt with halogenated alcohols[2] in ethanol at elevated temperature

(1) Paper LXXXVI, F. Sondheimer, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 1090 (1957).

(2) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949) have described the preparation of estrone and estradiol glyceryl ethers.

led to the corresponding glycol (I) but in poor yields. Considerably better yields were obtained by refluxing with a higher boiling glycol or by using 2-bromoethyl acetate, preferably in the presence of equimolar quantities of sodium iodide, which afforded the corresponding glycol acetate (II).

The desired carboxylic function was introduced by reacting estrone sodium salt and monochloroacetic acid in aqueous medium,[3] giving in good yields the glycolic acid ether (III) which afforded on esterification the corresponding methyl and ethyl esters (IV and V). Lithium aluminum hydride reduction of the ester led to the corresponding diol (VI).

The glycolic acid ether (III), in the mouse uterine weight increase assay (subcutaneous administration),[4] showed an unexpectedly low estrogenic activity of *ca.* 0.002 that of estrone.[5]

EXPERIMENTAL[6]

Estrone glycol ether acetate (II). Estrone (1.35 g.) was added to a solution of sodium ethoxide (prepared from 0.12 g. of sodium), the excess of alcohol was removed by distillation *in vacuo*, and the resulting sodium salt was well dried in a vacuum desiccator over sulfuric acid.

The dry sodium salt was suspended in 30 ml. of dry toluene, 900 mg. of sodium iodide was added, and the suspension was refluxed with 0.75 ml. of 2-bromoethylacetate added dropwise during the first 2 hr. After 20 hr. refluxing the toluene was removed by distillation under reduced pressure and the solids were suspended in absolute methanol. Acidification of the reaction mixture, removal of the insoluble material, and chromatography of the total crudes on alumina yielded, in the first benzene fractions, 170 mg. of crystalline material, m.p. 118–132°. Crystallization from acetone-ether furnished the pure compound as stout needles, m.p. 135–136°, $[\alpha]_D$ + 126° (methanol), λ_{max} 277 and 286 mμ (log ε 3.28 and 3.25, respectively).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.12; H, 7.92; —$COCH_3$, 12.05. Found: C, 74.27; H, 7.90; —$COCH_3$, 12.32.

Estrone glycol ether (I). (a) *By saponification of the acetate.* The acetate, 80 mg. dissolved in 20 ml. of methanol, was treated with 160 mg. of potassium hydrogen carbonate dissolved in 15 ml. of water and kept at room temperature under nitrogen for 22 hr. Usual isolation procedure and crystallization from hexane-ether produced the free compound as a microcrystalline powder, m.p. 117–118°, $[\alpha]_D$ + 131°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.36; H, 8.36; —$COCH_3$, 0.0.

(b) *By reaction with 2-bromoethanol.* The dry sodium salt of estrone (made from 10.0 g. of estrone) was suspended in 75 ml. of freshly distilled ethylene glycol and heated to 140° for 4 hr. with 6.6 ml. of 2-bromoethanol added dropwise during the first 2 hr. The mixture was cooled, diluted with 300 ml. of ice water and made acidic with dilute hydrochloric acid. The resulting gummy material was extracted with ethyl acetate, the extract was washed with aqueous sodium hydrogen carbonate and water, and the oily material obtained after removal of the solvent was chromatographed on alumina. Elution of the column with benzene ether (2:1), followed by crystallization from acetone-ether furnished 2.9 g. of crystalline material, m.p. 112–114°. The identity of this compound with the glycol ether already described was established by mixture melting point and infrared comparison.

Estrone glycolic acid ether (III). Estrone, 1.0 g., suspended in 3.5 ml. of 33% aqueous sodium hydroxide solution, was brought into solution by the addition of 1 ml. of methanol. Two and one-half ml. of 50% aqueous monochloroacetic acid was added and the solution was heated on the steam bath for 0.5 hr. Heating was then continued for 2 hr. while alternate portions of monochloroacetic acid (1 ml.) and sodium hydroxide solution (1.5 ml.) were added at 20 min. intervals. The crude solid product, obtained after acidification of the cold reaction mixture, was purified by extracting the acidic material (76% yield) from an organic phase with aqueous sodium hydrogen carbonate. Crystallization from ethanol produced the analytical sample as needles, m.p. 213–214°, $[\alpha]_D$ + 132°, λ_{max} 277 and 286 mμ (log ε 3.34 and 3.33, respectively).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37; M/NE, 328. Found: C, 73.10; H, 7.32; M, 322; NE, 309.

The *methyl ester* (IV) was obtained by esterification of the above compound with absolute methanol and dry hydrogen chloride in almost quantitative yield; crystallization from methanol gave needles, m.p. 128–129°, $[\alpha]_D$ + 117°.

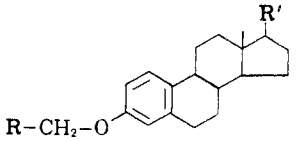
Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.09; H, 7.65.

The *ethyl ester* (V) was obtained in similar manner and crystallized from ether in stout prisms, m.p. 100–102°, $[\alpha]_D$ + 126°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.14; H, 7.92. Found: C, 74.00; H, 7.75.

Estradiol 3-glycol ether (VI). The ethyl ester, 1.0 g., was reduced with lithium aluminum hydride by the Soxhlet technique in tetrahydrofuran by refluxing for 1 hr. The resulting oily material, obtained after removal of the solvent, was triturated with ether to produce the desired estradiol glycol ether, 520 mg., as needles, m.p. 142–148°. The analytical sample crystallized from ether-acetone, m.p. 155–156°, $[\alpha]_D$ + 74°, + 65° (methanol).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 9.13. Found: C, 75.91; H, 8.92.



I. R = —CH_2OH, R′ = =O
II. R = —CH_2OAc, R′ = =O
III. R = —COOH, R′ = =O
IV. R = —COOMe, R′ = =O
V. R = —COOEt, R′ = =O
VI. R = —CH_2OH, R′ = —OH

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(3) C. F. Koelsch, *J. Am. Chem. Soc.*, **53**, 304 (1931).

(4) We wish to thank Dr. Ralph I. Dorfman, The Worcester Foundation for Experimental Biology for bioassay determination.

(5) R. Courrier, L. Velluz, J. J. Alloiteau, and G. Rousseau, *Compt. rend. Soc. biol.*, **139**, 128 (1945) reported only slightly lower activity for estrone 3-ethyl ether as compared to the parent compound.

(6) All melting points were taken on the Kofler block; rotations were measured in chloroform unless otherwise stated. The ultraviolet absorption spectra were measured in 96% ethanol with a Beckmann Model DU spectrophotometer. We wish to thank Mr. E. Avila for the physical measurements. Thanks are also due to Miss J. Lisci for able technical assistance.