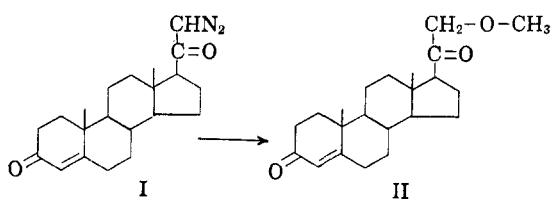
21-Methoxyprogesterone. Improved Synthesis

W. WERNER ZORBACH[1] AND C. RICHARD TAMORRIA[2]

Received March 1, 1957

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.

DEPARTMENT OF CHEMISTRY, THE COLLEGE
GEORGETOWN UNIVERSITY
WASHINGTON, D. C.

(1) Present address: NIAMD, National Institutes of Health, Bethesda, Md.

(2) Taken from the M.S. thesis of C.R.T.

(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

F. A. KINCL, H. J. RINGOLD, AND G. ROSENKRANZ

Received March 7, 1957

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.