[CONTRIBUTION FROM ORMONOTERAPIA RICHTER RESEARCH LABORATORIES]

# 17-Hydroxypregnanes from Androstane Compounds

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The reaction of 3β-acetoxy-17-cyano-5-androstene-17-ol with 2,3-dihydropyran in the presence of an acid catalyst leads to the formation of the epimeric 17-tetrahydropyranyl ethers. One of these has been transformed into 5-pregnene-3β,17α-diol-20-one by a Grignard reaction and hydrolysis. The same reaction sequence, carried out on 3β-acetoxy-5α,6α-epoxy-17-cyano-androstane-17-ol, leads to 6β-methylpregnane-3β,5α,17α-triol-20-one and after oxidation to 6β-methylpregnane-5α,17α-diol-3,20-dione.

The reaction of 2,3-dihydropyran with steroids having an hydroxyl group in position 17, be it secondary or tertiary or in either the α- or β-position, has been described in a preceding paper[1] and has been very useful in the synthesis of testosterone, dihydrotestosterone, 17α-hydroxyprogesterone and their esters.

Given the extreme stability of the tetrahydropyranyl ethers to the metal-organic reagents[2] and moreover to lithium aluminum hydride, to the alkaline metals, and to alkalies in general,[3] we thought to transform the cyanohydrins of the 17-ketones into tetrahydropyranyloxynitriles and then submit them to reaction with methylmagnesium bromide[4] in such a manner as to obtain the 17-hydroxypregnanes. This reaction would not be possible on the unprotected cyanohydrins because the action of the Grignard reagent would lead to the dissociation of the cyanohydrin, thereby regenerating the starting ketone which in turn would react to form the methylcarbinol.

It is now known that the addition of hydrogen cyanide to the 17-ketone leads to a mixture of the epimers 17α-cyano-17β-ol and 17β-cyano-17α-ol with a predominance of the form 17α-cyano-17β-ol.[5] The reaction with 2,3-dihydropyran leads to the 17α-cyano-17β-(2′-tetrahydropyranyloxy) and to the 17β-cyano-17α-(2′-tetrahydropyranyloxy) derivatives,[6] which were separated by crystallization. The percentage of the two epimers at 17 is about 50% each which is somewhat superior to that of the unprotected cyanohydrins.[5] This leads to the supposition that in the course for the formation of the tetrahydropyranyl ether there is a transformation of one epimer into the other.

When 3β-acetoxy-17-cyano-5-androstene-17-ol (I)[5] was treated with 2,3-dihydropyran using *p*-toluenesulfonic acid or phosphorus oxychloride as catalyst an oily product was obtained. Trituration with petroleum ether converted roughly half of the oily residue into a crystalline substance which subsequent reactions demonstrated to be 3β-acetoxy-17α-cyano-17β-(2′-tetrahydropyranyloxy)-5-androstene (II). Thus, on hydrolysis, the 3β-acetoxy-17α-cyano-5-androstene-17β-ol (IV) and successively the 3β-acetoxy-5-androstene-17-one (VI) were obtained. Furthermore treatment of II with methylmagnesium bromide furnished, after hydrolysis of both the 20-ketimine and the tertahydropyranyl ether, the 17-iso-5-pregnene-3β,17β-diol-20-one (IX) which was easily rearranged to 17aβ-methyl-D-homo-3β,17aα-diol-5-androstene-17-one (X).[7-9]

On evaporation of the petroleum ether after trituration of II, an oily residue was obtained which resisted crystallization. It was shown to be the 3β-acetoxy-17β-cyano-17α-(2′-tetrahydropyranyloxy)-5-androstene (III), since hydrolysis furnished the 3β-acetoxy-17β-cyano-5-androstene-17α-ol (V) and successively the 3β-acetoxy-5-androstene-17-one (VII). Treatment of III with methylmagnesium bromide led, after hydrolysis of the unisolated intermediate VIII, to the 5-pregnene-3β,17α-diol-20-one (XI).[10]

The total yield in the form of 17α-hydroxy compound, after making allowance for reconversion of the 17β-epimer to the starting material, was 65–70%.

Recently high progestational activity has been reported for 6α-methyl-17α-acetoxyprogesterone (XVIIIb).[11] We have been able to prepare an important intermediate for the synthesis of this compound from the androstane series by application of the above sequence of reactions.

On treatment of 3β-acetoxy-5α,6α-epoxyandrostane-17-one (XII)[12] with acetone cyanohydrin,[13] 3β-acetoxy-5α,6α-epoxy-17-cyanoandrostane-17-ol (XIII) (mixture of the epimers) was obtained and this was transformed with 2,3-dihydropyran into 17-tetrahydropyranyloxynitrile epimers (XIV).[14] Subsequent treatment with methylmagnesium bromide led to XV by attack on both the nitrile and the epoxide. After the customary hydrolysis it was possible to isolate 6β-methylpregnan-3β,5α,17α-triol-20-one (XVI). This was oxidized with pyridine–chromic acid complex[15] to the

(1) P. de Ruggieri and G. A. De Ferrari, *Ann. Chim. (Rome)*, **48**, 1048 (1958).

(2) I. Elphimoff-Felkin, *Compt. rend.*, **236**, 387 (1953).

(3) For a more detailed review of the subject see note 1.

(4) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **71**, 1487 (1938).

(5) H. Heusser, P. Th. Herzig, A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

(6) Epimers arising from isomerism at the 2-position of the tetrahydropyranyl group are, of course, also probable. Such an effect may lower the yield of the isolated crystalline tetrahydropyranyl ether.

(7) H. E. Stavely, THIS JOURNAL, **63**, 3127 (1941); C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 201 (1943).

(8) H. E. Stavely, THIS JOURNAL, **62**, 489 (1940).

(9) R. B. Turner, M. Perelman and K. T. Park, Jr., *ibid.*, **79**, 1108 (1957).

(10) P. L. Julian, E. W. Meyer and I. Ryden, *ibid.*, **72**, 367 (1950).

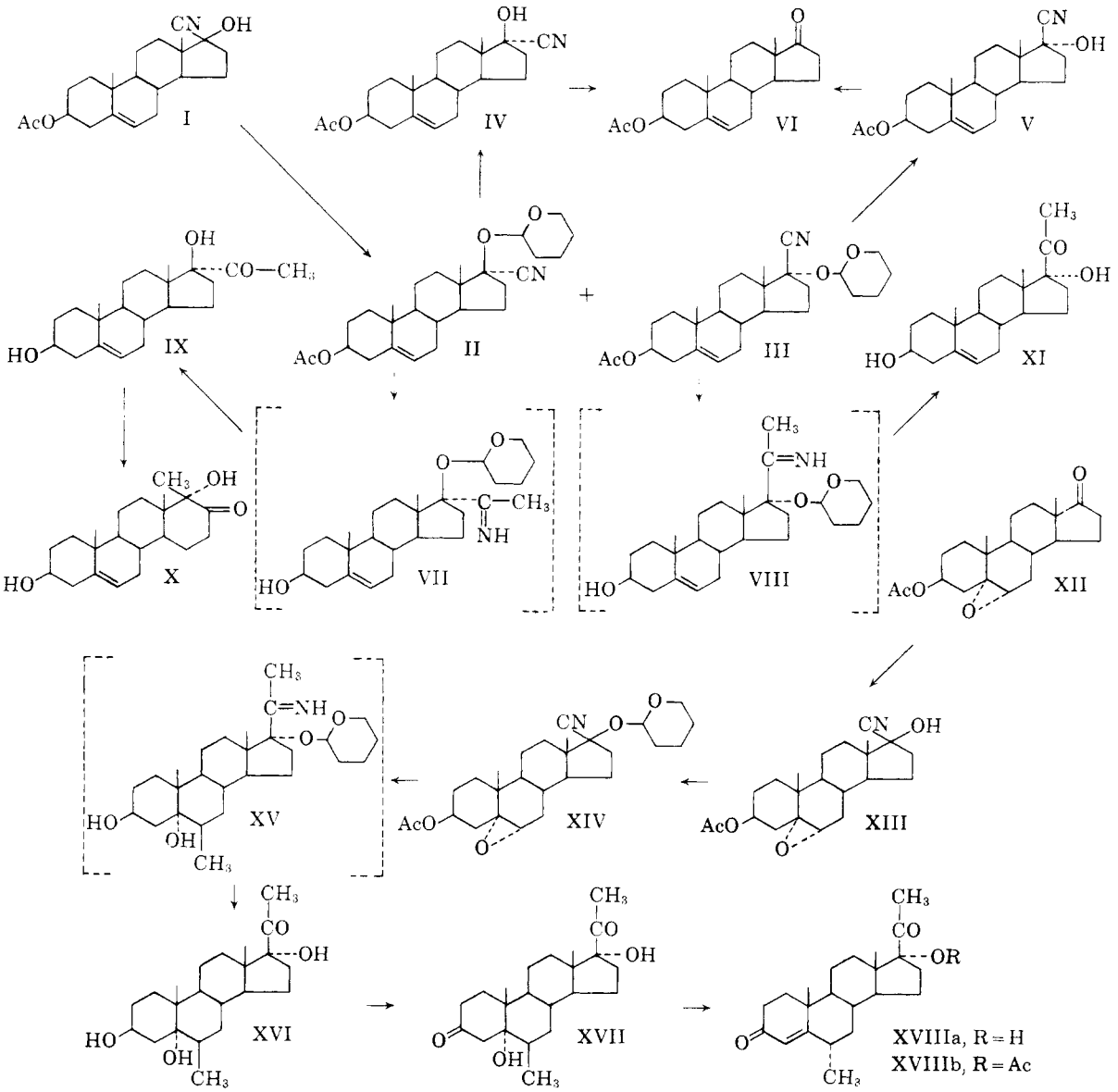
(11) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucky, L. E. Barnes and W. E. Dulin, *ibid.*, **80**, 2904 (1958).

(12) L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta*, **27**, 503 (1944).

(13) A. Ercoli and P. de Ruggieri, THIS JOURNAL, **75**, 650 (1953).

(14) The separation of the 17-cyano-17-(2′-tetrahydropyranyloxy) forms with successive reactions on the two epimers is still in progress. At this time we report the reactions on the mixture with $CH_3MgBr$ at the end of which the desired 17α-hydroxy product is easily separated.

(15) G. I. Poos, G. E. Arth, R. H. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).




already known[11] 6β-methylpregnane-5α,17α-diol-3,20-dione (XVII) which, by dehydration and inversion with alcoholic HCl, yielded the 6α-methyl-17α-hydroxyprogesterone (XVIIIa).

And thus this is a method of general character which, for the first time, permits the 17-hydroxypregnanes to be obtained from the cyanohydrins of the 17-ketones of the androstane series.

## Experimental[16]

**3β-Acetoxy-17α-cyano-17β-(2′-tetrahydropyranyloxy)-5-androstene (II) and 3β-Acetoxy-17β-cyano-17α-(2′-tetrahydropyranyloxy)-5-androstene (III).**—A solution of 10.0 g. of 3β-acetoxy-17-cyano-5-androstene-17-ol (I) in 40 ml. of 2,3-dihydropyran was treated at the boiling point with 0.2 ml. of phosphorus oxychloride for 1.5 hours. The solution was then diluted with ether, washed with an aqueous sodium carbonate solution followed by water, dried over sodium sulfate and distilled under reduced pressure. The oily residue was crystallized from petroleum ether to give 6.7 g. of product, m.p. 127–130°, $(\alpha)_D$ −92° (diox.) which was shown to be the 3β-acetoxy-17α-cyano-17β-(2′-tetrahydropyranyloxy)-5-androstene (II).

*Anal.* Calcd. for $C_{27}H_{39}O_4N$: C, 73.43; H, 8.90; N, 3.17. Found: C, 73.48; H, 8.88; N, 3.15.

The petroleum ethereal mother liquors when evaporated to dryness yielded an oily residue of 7.1 g. which resisted crystallization attempts. Subsequent reactions demonstrated it to be the 3β-acetoxy-17β-cyano-17α-(2′-tetrahydropyranyloxy)-5-androstene (III).

**3β-Acetoxy-17α-cyano-5-androstene-17β-ol (IV).**—A solution of 1.0 g. of 3β-acetoxy-17α-cyano-17β-(2′-tetrahydropyranyloxy)-5-androstene (II) in 10 ml. of acetone was heated at reflux for 15 minutes with a few drops of concd. HCl. It was then diluted with water and, after cooling, the crystalline product was filtered and washed well with water. In this manner there was obtained 0.8 g. of material, m.p. 195–200° dec., $(\alpha)_D$ −121° (diox.); lit.[5] m.p. 195–205° dec., $(\alpha)_D$ −126° (diox.).

*Anal.* Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.91. Found: C, 73.85; H, 8.75; N, 3.85.

**3β-Acetoxy-17β-cyano-5-androstene-17α-ol (V).**—Hydrolysis of 1.0 g. of the oily residue III according to the above conditions yielded 0.78 g. of material, m.p. 207–210° dec., $(\alpha)_D$ −56° (diox.); lit.[5] m.p. 210–211°, $(\alpha)_D$ −53° (diox.).

(16) The melting points are uncorrected; all rotations were taken in chloroform at 20° unless otherwise noted. The analyses were done by Mr. Aug. Peisker-Ritter, Microanalytisches Laboratorium, Brugg (Switzerland), whom we thank.

*Anal.* Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.91. Found: C, 73.78; H, 8.81; N, 3.91.

**3β-Acetoxy-5-androstene-17-one (VI).**—Either IV or V (0.2 g.) was heated at reflux for an hour with 3 ml. of 80% aqueous pyridine. The reaction mixture was diluted with a large excess of water and the crystalline product filtered which yielded, after drying, 0.16 g. of product, m.p. 167–170°. The mixed melting point with an authentic sample remained unaltered.

**17-Iso-5-pregnene-3β,17β-diol-20-one (IX).**—A solution of 4.5 g. of 3β-acetoxy-17α-cyano-17β-(2′-tetrahydropyranyloxy)-5-androstene (II) in 75 ml. of anisole was treated with 130 ml. of an ethereal solution of methylmagnesium bromide (obtained from 9 g. of magnesium). The ether was removed and the reaction mixture held at 95° for 18 hours. After decomposition with 180 ml. of acetic and 140 ml. of water, the mixture was heated at reflux for 15 minutes and the solvent was removed by steam distillation. The aqueous suspension was filtered and the product recrystallized from methanol to yield 2.65 g. of material, m.p. 175–177°, $(\alpha)_D$ −58°.[7]

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.81; H, 9.68.

**17aβ-Methyl-D-homo-5-androstene-3β,17aα-diol-17-one (X)** was obtained from the preceding substance IX by treatment with KOH; m.p. 275°, $(\alpha)_D$ −108° (diox.).[8,9]

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.78; H, 9.73.

**5-Pregnene-3β,17α-diol-20-one (XI).**—To a solution of 4.5 g. of the oily 3β-acetoxy-17β-cyano-17α-(2′-tetrahydropyranyloxy)-5-androstene (III) in 75 ml. of anisole was added 130 ml. of an ethereal solution of methylmagnesium bromide (from 9 g. of magnesium). The ether was removed and the reaction mixture held at 95° for 18 hours. After decomposition with 180 ml. of acetic acid and 140 ml. of water, the mixture was refluxed for 15 minutes and then the solvent removed by steam distillation. The residual aqueous suspension was filtered and the product, crystallized from acetone, yielded 2.5 g. of 5-pregnene-3α,17α-diol-20-one (XI) with m.p. 265–267°, $(\alpha)_D$ −36° (diox.)[10]; the melting point remained unchanged when mixed with an authentic sample.

**3β-Acetoxy-5α,6α-epoxy-17-cyanoandrostane-17-ol (XIII).**—In 40 ml. of freshly prepared acetone cyanohydrin[17] was dissolved 10.0 g. of 3β-acetoxy-5α,6α-epoxy-androstane-17-one (XII)[12] while stirring and heating lightly. After allowing the reaction to stand for 2 hours, the product, partially crystallized, was completely precipitated by dilution with water, filtered and dried in vacuum. In this manner was obtained 10.58 g. of compound, m.p. 178–180° dec., $(\alpha)_D$ −61°.

(17) *Org. Syntheses*, **20**, 43 (1940).

*Anal.* Calcd. for $C_{22}H_{31}O_4N$: C, 70.75; H, 8.36; N, 3.75. Found: C, 70.82; H, 8.35; N, 3.78.

**3β-Acetoxy-5α,6α-epoxy-17-cyano-17-(2′-tetrahydropyranyloxyandrostane) (XIV).**—Ten grams of 3β-acetoxy-5α,6α-epoxy-17-cyano-androstane-17-ol (XIII) was treated with 40 ml. of 2,3-dihydropyran and 200 mg. of *p*-toluenesulfonic acid for 2.5 hours at the boiling point. The solution was diluted with ether, washed with aqueous solution of sodium carbonate, water, and the solvent removed by vacuum distillation. The residue, crystallized with ether, gave 8.9 g. of material, m.p. 183–186°, $(\alpha)_D$ −48°.[14]

*Anal.* Calcd. for $C_{27}H_{39}O_5N$: C, 70.86; H, 8.59; N, 3.06. Found: C, 71.01; H, 8.55; N, 3.11.

**6β-Methylpregnane-3β,5α,17α-triol-20-one (XVI).**—A solution of 3 g. of 3β-acetoxy-5α,6α-epoxy-17-cyano-17-(2′-tetrahydropyranyloxy)-androstane (XIV) (mixture of α- and β-epimers) in 70 ml. of anisole was treated with 150 ml. of an ethereal solution of methylmagnesium bromide (from 10 g. of magnesium) for 2 days at room temperature. After the ether was evaporated, the mixture was heated at 95° for 18 hours. The reaction mixture was decomposed with 200 ml. of acetic acid and 160 ml. of water and refluxed for 15 minutes, after which the solvent was removed by steam distillation. The aqueous suspension was filtered and the product crystallized several times from acetone yielding 0.97 g. of material, m.p. 247–249°, $(\alpha)_D$ −34°.

*Anal.* Calcd. for $C_{22}H_{36}O_4$: C, 72.48; H, 9.95. Found: C, 72.51; H, 9.98.

**6β-Methylpregnane-5α,17α-diol-3,20-dione (XVII).**—A solution of 0.5 g. of 6β-methylpregnane-3β,5α,17α-triol-20-one (XVI) in 5 ml. of pyridine was added at room temperature to the pyridine–chromic acid complex obtained from 0.5 g. of chromic acid in 5 ml. of pyridine[15] and left at the same temperature overnight. After dilution with water and filtration, the product was crystallized from methylene chloride–acetone and 0.39 g. was obtained with m.p. 270–273°, $(\alpha)_D$ −6°[11]; the melting point remained unaltered in mixture with an authentic sample obtained by other means.

**6α-Methyl-17α-hydroxyprogesterone (XVIIIa).**—A suspension of 0.3 g. of 6β-methylpregnane-5α,17α-diol-3,20-dione in 24 ml. of ethanol was brought to the boiling point and 0.3 ml. of concd. HCl added, with continued boiling. After about 20 minutes, the insoluble product went into solution and the heating was prolonged for one hour in total. The reaction mixture was then concentrated under vacuum to one-third its volume and subsequently diluted with water. The crystalline product was filtered and dried to yield 0.23 g. of 6α-methyl-17α-hydroxyprogesterone (XVIIIa), m.p. 218–222°, $(\alpha)_D$ −73°, $\lambda_{max}^{EtOH}$ 241 mμ (16,000).[11]

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

# Conformational Analysis. III. Applications to Some Medium Ring Compounds[1,2]

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A simple potential function derived from the rotational barrier of ethane has been assumed to hold in cyclic compounds. Using this function, together with values for the dihedral angles as obtained from direct measurements on scale models, the enthalpies of various conformations have been calculated for the flexible ("boat") form of cyclohexane, for cycloheptane, cyclooctane, the corresponding ketones and a few selected related compounds. The preferred conformation in each case is predicted, and the agreement with the experimental heats of combustion and other data is in all cases reasonable.

## Introduction

Although the conformational analysis of cyclohexane rings has been quite extensively pursued,[3] no similar detailed studies have been made in rings of other sizes. The chair form of cyclohexane is unique in that the dihedral angles of the substituents are an optimum 60°. There is also good reason to believe that the six-membered chair also differs from most other simple rings in being rigid,

(1) This work was supported by a research grant from the National Science Foundation.

(2) Paper II, N. L. Allinger and J. Allinger, THIS JOURNAL, **80**, 5476 (1958).

(3) For recent reviews see the following: (a) W. G. Dauben and K. S. Pitzer in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 1; (b) W. Klyne, in "Progress in Stereochemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1954, p. 36; (c) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).