STEROIDS AND RELATED PRODUCTS. XLVI*.

THE REGIOSPECIFIC α-HYDROXYMETHYLATION OF SATURATED CARBONYL COMPOUNDS VIA PREFORMED ENOLATE IONS. AN IMPROVED SYNTHESIS OF 17-HYDROXYMETHYL 20-KETO STEROIDS**

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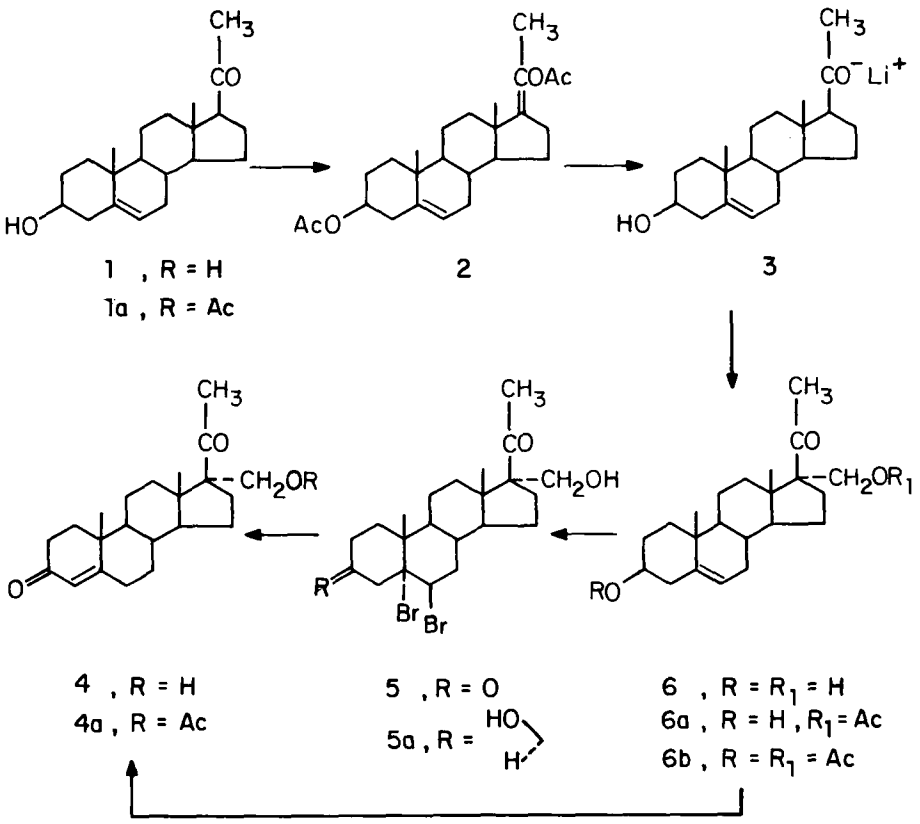
Received: 7-9-79

As demonstrated for pregnenolone, saturated ketones are conveniently α-hydroxymethylated by their transformation into a lithium enolate and by the reaction of the latter with formaldehyde. The 17-hydroxymethylpregnenolone prepared by this method in very good yield was readily converted to 17-hydroxymethylprogesterone; either by selective acetylation in position 17[1] and subsequent Jones oxidation, followed by hydrolysis, or by conversion to the 4,5-dibromo 3-ketone - by bis(tri-n-butyltin)oxide-bromine oxidation or by dibromination and oxidation with N-bromoacetamide - and debromination with zinc and acetic acid.

As we have shown (2, cf. also 3), saturated ketones may be α-alkoxycarbonylated by the reaction of their lithium enolates with a dialkyl carbonate. We thus prepared 17-methoxycarbonylated 20-keto steroids and showed that these products could be readily transformed, by ketalization of the 20-keto group, lithium aluminum hydride reduction of the etio ester function, and by liberation of the 20-ketone, into 17-hydroxymethyl 20-keto steroids (2, 3). We have also shown that lithium 17,20-enolates undergo a number of useful reactions (cf. 4), affording a series of 17-substituted 20-keto steroids. Among successful reactions of lithium enolates derived from saturated ketones which we investigated so far, were direct hydroxymethylations with formaldehyde which lead in the case of lithium 17,20-enolates in a single step to 17-hydroxymethyl 20-ketones. We intended to publish these



findings together with results involving reactions of a number of ketones, but a recent paper by Wieland (5) which relates the synthesis of a 17-hydroxymethyl 20-ketone by the transformation of a 16-unsaturated 20-ketone, via a trimethylsilyl 17,20-enol ether, into its lithium enolate and the reaction of the latter with formaldehyde, prompts us to record here our own results.

Pregnenolone (3β-hydroxy-5-pregnen-20-one) (1) was transformed as described before (2, 3), via the mixture of its 20-isomeric enol acetates (2) (2, 6-8) into the analogous lithium enolates (3) (cf. 2). At -10° and in the presence of zinc chloride (cf. 9), this mixture was now

subjected, in the medium in which it had been formed, to the action of formaldehyde, generated from paraformaldehyde. Thus, 17-hydroxymethylpregnenolone (6) was obtained in 65% yield from the mixture of the enol acetates 2, and over 10% of pregnenolone (1) was recuperated. Taking this recovery of starting material into account, the total yield of 17-hydroxymethylpregnenolone (6) from the enol acetates 2 amounted to 72%. The 3β,17[1]-diol 6 was further characterized as its diacetate 6b, also described by Wieland (5), and could be selectively acetylated to the 17[1]-monoacetate 6a, in over 80% yield, by reaction with 1.1 equivalents of acetic anhydride in pyridine at 0°.

The free 17-hydroxymethylpregnenolone (6) was converted readily to 17-hydroxymethylprogesterone (4) (2, 3, 10) by oxidizing selectively the secondary alcohol function with bis(tri-n-butyltin)-oxide and bromine at 0° (cf. 11, 12) and by debrominating the resulting 5α,6β-dibromo 3-ketone 5 with zinc and acetic acid. Even better yields (approximately 60%) were obtained by bromination of the keto diol 6 to the dibromide 5a, by oxidation of the latter with N-bromoacetamide, and by debromination of the resulting dibromo hydroxy ketone 5. The most attractive route consists, however, in Jones oxidation, under conditions which we described previously (13), of the 17[1]-monoacetate 6a; this affords in 85% yield 17-acetoxymethylprogesterone (4a), the hydrolysis of which to 17-hydroxymethylprogesterone (4) - in 99% yield - we have already reported (10).

We have thus prepared 17-hydroxymethylprogesterone (4) in very good yields and by very short routes, from the enol acetates 2 of pregnenolone acetate. This pathway to 17-hydroxymethylated 20-keto

steroids is simpler and more efficient than the sequence of reactions proceeding from 16-unsaturated 20-ketones and involving as intermediates trimethylsilyl enol ethers (5); apart from giving significantly better yields, our hydroxymethylation is regiospecific (no 21-hydroxymethylated adduct is obtained), and the formation of a tertiary 20-methylated 20-hydroxy steroid (cf. 5) is avoided.

EXPERIMENTAL

The melting points were taken in evacuated capillaries and the temperatures were corrected. For thin-layer chromatography, Merck-Darmstadt silica gel G was used. The infrared spectra were recorded on a Beckman IR-12 spectrometer, the ultraviolet spectra on a Beckman DK-1A instrument, the n.m.r. spectra on a Brucker HFX-90 spectrometer, with tetramethylsilane as internal standard, in deuteriochloroform. The microanalyses were performed by Ayerst Laboratories, Montreal, Canada (under the direction of Dr. G. Schilling) and by Dr. C. Daesslé, Montreal. We thank the management and staff of these laboratories for their excellent collaboration.

3β-Hydroxy-17-hydroxymethyl-5-pregnen-20-one (6). - An ethereal solution of the lithium enolates 3 was prepared, as described previously (2), from 4 g of the geometrically isomeric mixture of the enol acetates 2 (2, 6-8), m.p. 135-140°, dissolved in 100 ml of absolute ether, and from 25 ml of a 1.6 M ethereal methyllithium solution. There was added, at room temperature, a solution of 1.35 g of freshly fused zinc chloride in 25 ml of absolute ether. Gaseous formaldehyde, generated by heating 360 mg of paraformaldehyde, was passed through the solution with a stream of dry nitrogen. Subsequently, a saturated solution of ammonium chloride was added, the organic product was extracted with ether, the ethereal solution was washed with water and was dried over sodium sulfate. Evaporation of the solvent gave 3.43 g of a solid, m.p. 185-198°. Recrystallization from dichloromethane-methanol gave 2.21 g (65% yield) of 17-hydroxymethylpregnenolone (6), m.p. 215-218°. A sample was recrystallized three times from dichloromethane-methanol for analysis; colorless prisms, m.p. 223-225°; $[\alpha]_D^{23}$ +36.3° (c, 1.000 in methanol); ν_{max} (KBr) 3370 (OH), 1680 (20-ketone), 1060, 1030 cm^{-1} (OH); δ 0.67 (s, 3 H) (18-CH_3), 1.02 (s, 3 H) (19-CH_3), 2.22 (s, 3 H) (methyl ketone), 3.60 (d, J = 10 Hz) and 4.17 (d, J = 10 Hz) (17[1]-CH_2-OH), 5.35 (m) (6-H).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.17; H, 9.83.

The mother liquors were evaporated to dryness and the residue (1.12 g) was recrystallized from aqueous methanol. Thus, 407 mg (12.9%) of pregnenolone (1), m.p. 188-191°, was obtained. Considering this recovery, the over-all yield amounted to 72%.

17[1]-Monoacetate 6a. - To a solution of 519 mg of 17-hydroxymethylpregnenolone (6), m.p. 215-218°, in 5 ml of pyridine, 170 mg of acetic anhydride was added at 0° and the solution was left for 20 h at that temperature (by that time all the starting material had disappeared, as evidenced by thin-layer analysis - solvent system ether-petroleum ether 2:1). A few drops of methanol was added, the solvents were removed in vacuo, and the product was further dried by evaporating it repeatedly with benzene. The crystalline residue (580 mg), containing - according to t.l.c. - analysis (ether-petroleum ether 2:1) - also ~10% of the diacetate 6b (cf. below), was recrystallized twice from ether-hexane, to give 493 mg (85% yield) of 3β-hydroxy-17-acetoxymethyl-5-pregnen-20-one (6a), m.p. 200-202°. A sample was recrystallized three times from ether-hexane; colorless needles, m.p. 208-210°; $[\alpha]_D^{23}$ +28.3° (c, 1.000 in $CHCl_3$); ν_{max} (KBr) 3500-3400 (broad) (OH), 1735 (acetate), 1687 (20-ketone), 1260 cm^{-1} (acetate); δ 0.68 (s, 3 H) (18-CH_3), 1.00 (s, 3 H) (19-CH_3), 2.0 (s, 3 H) (acetate), 2.13 (s, 3 H) (methyl ketone), 4.15 (d) and 4.44 (d) (2 H, J = 10 Hz) (CH_2-OAc), 5.3 (m, 1 H) (6-H).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.98; H, 9.31.

Diacetate 6b. - To a solution of 2 g of 17-hydroxymethylpregnenolone (6), m.p. 215-218°, in 6 ml of absolute pyridine, 3 ml of acetic anhydride was added and the mixture was kept for 12 h at room temperature. A few ml of methanol was added and the solvents were removed under reduced pressure. The crystalline residue (2.44 g, 98.5% yield), m.p. 172-175°, represented 3β-acetoxy-17-acetoxymethyl-5-pregnen-20-one (6b). A sample was recrystallized twice from ether-hexane for analysis; colorless prisms, m.p. 173-174° [lit. (5) 167.5-169.5°]; $[\alpha]_D^{23}$ +17.5° (c, 0.950 in $CHCl_3$); ν_{max} (KBr) 1735 (acetates), 1700 (20-ketone), 1255 cm^{-1} (acetates); δ 0.62 (s, 3 H) (18-CH_3), 0.95 (s, 3 H) (19-CH_3), 2.05 (s, 6 H) (3β- and 17[1]-acetates), 2.13 (s, 3 H) (methyl ketone), 4.15 (d) and 4.44 (d) (2 H, J = 10 Hz) (17α-CH_2-OAc), 5.35 (m, 1 H) (6-H).

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.45; H, 8.93.

17-Acetoxymethylprogesterone (4a). - To a solution of 200 mg of 17-acetoxymethylpregnenolone (6a), m.p. 200-202°, in 25 ml of absolute acetone, there was added, at 0°, dropwise and with stirring, 0.5 ml of Jones' reagent (14). The mixture was stirred at room temperature for 15 min. and poured into cold water. The organic material was extracted with ether, the ethereal solution was washed with a saturated

sodium bicarbonate solution and with water, and was dried over sodium sulfate. The solvents were removed and the amorphous residue (198 mg) was dissolved in 20 ml of methanol and one drop of conc. hydrochloric acid. The solution was heated in a hot-water bath for one min. and was then cooled and poured into cold water. The precipitate was extracted with ether, the ethereal layer was washed with a cold saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvents gave 196 mg of partly crystalline material which, upon recrystallization from ether-hexane, afforded 158 mg (79% yield) of 17-acetoxymethylprogesterone (17-acetoxymethyl-4-pregnene-3,20-dione) (4a), m.p. 168-170°. The structure of the product was confirmed by the determination of a mixture melting point and by the comparison of its infrared spectrum with that of an authentic sample (2, 10).

17-Hydroxymethylprogesterone (4). (a) Via the Dibromo Diketone 5, obtained from Diol 6 by Bis(tri-n-butyltin)oxide-Bromine Oxidation. - To a solution of 1 g of 17-hydroxymethylpregnenolone (6), m.p. 215-218°, in 100 ml of dry dichloromethane, 2 ml of bis(tri-n-butyltin)-oxide was added under nitrogen and, subsequently, dropwise and with stirring, under nitrogen, a solution of 0.25 ml of bromine in 10 ml of dry dichloromethane, in the course of 30 min. Stirring at room temperature was continued for 2 h and the solvents were removed in vacuo. The oily residue gave upon addition of ether 1.36 g of a white solid, representing crude 5,6β-dibromo-17-hydroxymethyl-5α-pregnane-3,20-dione (5), giving a positive Beilstein test. Upon two recrystallizations from methanol, the product - colorless plates - melted with decomposition between 205 and 208°; ν_{max} (KBr) 3400 (broad) (OH), 1690 (20-ketone), 1030 cm^{-1} (OH).

This crude dibromo diketone 5 was dissolved in 50 ml of glacial acetic acid and 200 mg of activated zinc powder was added portionwise. The mixture became warm, was stirred at room temperature for 1 h, and was filtered. The filtrate was diluted with water, the precipitate was extracted with ether, the ethereal solution was washed with a cold saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Evaporation of the solvent gave 987 mg of an oily residue which crystallized upon addition of hexane. The crystals were filtered (800 mg, crude yield: 80.4%), m.p. 186-198°. Two recrystallizations from dichloromethane-methanol gave 483 mg (48.5%) of pure 17-hydroxymethylprogesterone (17-hydroxymethyl-4-pregnene-3,20-dione) (4), m.p. 217-220°. The identity of the product with an authentic sample (2, 10) was established by the determination of a mixture melting point and by the comparison of the infrared spectra.

(b) From Diol 6, via the Dibromo Dihydroxy Ketone 5a and the Dibromo Hydroxy Diketone 5. - To a solution of 500 mg of 17-hydroxymethylpregnenolone (6), m.p. 215-218°, in 50 ml of dichloromethane was added at room temperature, dropwise and with stirring, 240 mg of bromine in 10 ml of dichloromethane. The product was diluted with dichloromethane and the solution was washed with a 10% sodium sulfite solution and with water, and was dried over sodium sulfate. The

solvent was removed in vacuo and the residue (750 mg), representing crude 5,6β-dibromo-3β-hydroxy-17-hydroxymethyl-5α-pregnan-20-one (5a), was used without purification.

The product (5a) was dissolved in 100 ml of dioxane, 10 ml of methanol and 10 ml of water. To this solution 250 mg of N-bromoacetamide was added at room temperature, with stirring. The mixture was left at 5-10° for 13 h, in the dark. The resulting, orange-colored solution was poured into a 5% sodium sulfite solution and the organic material was extracted with dichloromethane. The organic solution was washed with water and was dried over sodium sulfate. Evaporation of the solvents gave 740 mg of a slightly yellow, amorphous solid, representing crude 5,6β-dibromo-17-hydroxymethyl-5α-pregnane-3,20-dione (5); ν_{max} (KBr) 3400 (broad) (OH), 1690 (20-ketone), 1030 cm^{-1} (OH).

This product was dissolved in 40 ml of acetic acid and 110 mg of activated zinc powder was added portionwise. The warm mixture was stirred at room temperature for 1 h and was worked up as described above. Thus, 491 mg (crude yield: 98.9%) of a product crystallizing upon addition of hexane was obtained, m.p. 180-192°. Two recrystallizations from dichloromethane-methanol gave 249 mg (50%) of pure 17-hydroxymethylprogesterone (17-hydroxymethyl-4-pregnene-3,20-dione) (4), m.p. 218-220°. The identity of the product with an authentic sample (2, 10) was established in the usual fashion. Recrystallization of the mother liquors furnished another 45 mg (9%) of slightly less pure 17-hydroxymethylprogesterone (4), m.p. 212-216°.

ACKNOWLEDGEMENTS

Sincere thanks are extended to Mrs. J. Capitaine for her excellent collaboration, and to Ms. D. Thibault, Mrs. Lise Lévesque, and Mr. Gaëtan Genest for devoted technical assistance. Part of the study was performed pursuant to contracts Nos. NO1-HD-2-2714 and NO1-HD-8-2812 with the National Institutes of Health, U.S. Department of Health, Education, and Welfare. We express our gratitude for this support and for the cooperation of the National Institute of Child Health and Human Development, especially to Drs. M. Karten and H. K. Kim. We also acknowledge with sincere thanks financial assistance and support from the National Research Council of Canada, the Natural Sciences and Engineering Research Council Canada, the Ministère de l'Education du Québec, and Ayerst Laboratories, Montreal.

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* For paper XLV, cf. ref. 1.

** An account of this investigation was included in a communication to the 62nd Chemical Conference and Exhibition of the Chemical Institute of Canada, Vancouver, B.C., June 3-6, 1979.

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