266. *Studies in the Sterol Group. Part LI.* Reactions between 17-Keto-steroids and Organometallic Compounds.*

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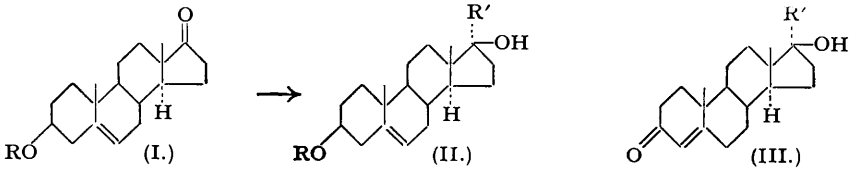
The reaction between 17-keto-steroids and Grignard reagents (other than methyl) is known to lead chiefly to reduction of the carbonyl group. It has now been found that the reaction between dehydro*epi*androsterone (the 3β-hydroxyl-group being protected as a tetrahydropyranyl ether) and various alkyl-lithium compounds leads to less reduction, and that 17α-alkyl-17β-alcohols can thus be prepared in moderate yields.

Dehydro*epi*androsterone undergoes a Reformatsky type of reaction with propargyl bromide, to give the 17α-propargyl-17β-alcohol. Hydrolysis and Oppenauer oxidation yield 17α-propargyltestosterone, a homologue of the progesterone substitute, 17α-ethynyltestosterone.

It is now well established that the reaction between 17-keto-steroids and nucleophilic reagents leads predominantly to 17α-substituted 17β-hydroxy-compounds (cf. Shoppee, *Ann. Reports*, 1946, **43**, 200), the reaction being envisaged as taking place by "rear attack" at $C_{(17)}$. For example, the reaction of dehydro*epi*androsterone (I; R = H) with potassium acetylide in liquid ammonia gives a 50% yield of the 17α-ethynyl compound (Ruzicka and Hofmann, *Helv. Chim. Acta*, 1937, **20**, 1280), accompanied by less than 1% of the 17β-isomer (Meystre and Reichstein, *ibid.*, 1939, **22**, 728). Similarly, ethoxyacetylene gives the 17α-ethoxyethynyl compound in good yield (65%) (Heusser, Eichenberger, and Plattner, *ibid.*, 1950, **33**, 370).

The reaction between 17-keto-steroids and Grignard reagents has been investigated by Butenandt and by Ruzicka and their collaborators. 17α-Methyl-17β-alcohols are obtained in satisfactory yields (65%) (Ruzicka, Goldberg, and Meyer, *ibid.*, 1935, **18**, 994), but with ethylmagnesium halides the expected 17α-ethyl-17β-alcohol is accompanied by the product formed by reduction of the 17-keto-group (mainly 17β-hydroxy-compound) (Butenandt, Schmidt-



Thomé, and Paul, *Ber.*, 1938, **71**, 1313; 1939, **72**, 1112). With *n*-propylmagnesium iodide, reduction of the 17-keto-group is the main reaction, the 17α-*n*-propyl compound not being isolated (Ruzicka and Rosenberg, *Helv. Chim. Acta*, 1936, **19**, 357). Allylmagnesium bromide

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gives a very good yield (90%) of the 17α-allyl derivative (Butenandt and Peters, *Ber.*, 1938, **71**, 2688).

Organolithium reagents will often undergo normal 1 : 2-addition to many hindered ketones that are reduced by Grignard reagents (cf. Wittig and Thurtle, " Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York). The reaction between dehydro-*epi*androsterone (I; R = H) and certain alkyl-lithium compounds has therefore been investigated in the expectation that an improved route to 17-alkyl-carbinols would result. A general method for elaborating 17-alkyl side-chains could then be envisaged, for dehydration of the 17-alkyl-carbinols to $\Delta^{17(20)}$-compounds (cf. Butenandt, Schmidt-Thomé, and Paul, *loc. cit.*), followed by hydrogenation (a further example of " rear attack "; cf. Plattner, Bucher, and Hardegger, *Helv. Chim. Acta*, 1944, **27**, 1177) would lead to 17-alkyl substituents possessing the natural β-configuration.

Accordingly, the reaction between *n*-propyl-lithium and dehydro*epi*androsterone was investigated in various solvents. In each case, an insoluble, unreactive complex resulting from the reaction of the organolithium compound with the 3-hydroxyl group was quickly precipitated. Fairly prolonged reaction gave a 5% yield of the 17α-*n*-propyl compound (II; R = H, R′ = Pr^n) in ethereal solution and an 8% yield in benzene solution, most of the ketone being recovered unchanged. Fieser and Huang-Minlon (*J. Amer. Chem. Soc.*, 1949, **71**, 1840) have recently mentioned that the reaction between dehydro*epi*androsterone and ethyl-lithium gives a low yield of the 17α-ethyl compound, but no experimental details were recorded.

To avoid the formation of insoluble complexes, the 3β-hydroxyl group was protected by formation of an adduct with 2 : 3-dihydropyran (Woods and Kramer, *ibid.*, 1947, **69**, 2246), such adducts being stable to organometallic reagents (Parham and Anderson, *ibid.*, 1948, **70**, 4187). Dehydro*epi*androsterone and cholesterol both formed adducts in high yields, from which the parent alcohol could be quantitatively recovered by treatment with methanol containing a little hydrochloric acid. Owing to the formation of a new centre of asymmetry in the pyran ring, each of these adducts might be expected to be a mixture of two stereoisomeric forms. The total dehydro*epi*androsterone adduct (m. p. 160—165°) was resolved by fractional crystallisation into about equal amounts of the two stereoisomers (m. p.s 188° and 176°; on admixture the melting point fell to 164—168°). The rotations of the two isomers were very noticeably different (−53° and +47°). The crystalline cholesterol adduct also appeared to be a mixture (from its melting point behaviour), but it was not easily resolvable by crystallisation.

The dihydropyran adduct of dehydro*epi*androsterone with various alkyl-lithium compounds (primary straight-chain alkyl groups only were used, R′ = Et, Pr^n, and *n*-C_8H_{17}) in homogeneous solution readily gave pure 17α-alkyl compounds in about 20% yield, independent of the nature of the alkyl group, reaction conditions, or method of isolation. The *n*-octyl compound is of interest for it should be possible to convert it into an isomer of cholesterol containing an unbranched side chain.

In these reactions with alkyl-lithium derivatives, reduction of the 17-keto-group was apparently the main side-reaction. Although no pure compounds were isolated after separation of the 17-alkyl compounds, the presence of 3β : 17-dihydroxyandrost-5-ene(s) in the mixture was indicated by means of a characteristic colour test devised by Boscott (*Nature*, 1948, **162**, 577). This colour test was found to be a satisfactory way of differentiating between secondary and tertiary $C_{(17)}$alcohols, and was also of use in assessing roughly the proportion of each in a mixture.

Reformatsky reactions can also be carried out with 17-keto-steroids, ethyl bromoacetate giving a 50% yield of hydroxy-ester (Reichstein, Müller, Meystre, and Sutter, *Helv. Chim. Acta*, 1939, **22**, 741). Propargyl bromide has recently been shown to undergo a Reformatsky type of reaction with various carbonyl compounds (Zeile and Meyer, *Ber.*, 1942, **75**, 356; Henbest, Jones, and Walls, *J.*, 1949, 2696; 1950, 3646). It was of interest to carry out this reaction with dehydro*epi*androsterone acetate (I; R = Ac) because Oppenauer oxidation of the 17-propargyl-3 : 17-diol obtained on hydrolysis should give a homologue of the orally active progestational compound 17α-ethynyltestosterone (pregneninolone). The reaction between dehydro*epi*androsterone acetate and propargyl bromide has been found to proceed readily in dioxan in the presence of zinc dust, to give a 40—50% yield of the 17α-propargyl compound (II; R = Ac; R′ = $CH_2{\cdot}C{\equiv}CH$). Hydrolysis then gave the corresponding 3β : 17β-diol, which was converted by Oppenauer oxidation into 17α-propargyltestosterone (III; R′ = $CH_2{\cdot}C{\equiv}CH$). The configuration of these compounds was shown to be the same as that of the 17α-alkyl compounds prepared by the Grignard or alkyl-lithium methods, by

mild hydrogenation of the propargyl-diol, the 17α-*n*-propyl compound (II; R = H, R′ = Pr^n) being produced in high yield. This compound was also prepared by hydrogenation of the allyl analogue (II; R = H, R′ = $CH_2 \cdot CH{=}CH_2$) under the same conditions.

Experimental.

(All rotations were measured in chloroform solutions unless otherwise stated. M. p.s were determined on a Kofler block and are corrected.)

3β-2′-*Tetrahydropyranyloxycholest-5-ene*.—2 : 3-Dihydropyran (20 c.c.; purified by agitation with potassium hydroxide pellets, followed by distillation) was added to a solution of cholesterol (50 g.) in chloroform (150 c.c.), followed by phosphorus oxychloride (0·3 c.c.). The solution was warmed to 30°; a mildly exothermic reaction took place, the temperature rising to 38°. The solution was kept until the temperature had fallen to 30°, whereafter it was shaken with sodium carbonate solution to remove acidic materials. The solvent was evaporated *in vacuo*, and the solid residue recrystallised from ethyl acetate, to give 3β-2′-*tetrahydropyranyloxycholest-5-ene* (48 g.) as needles, m. p. 155—160°, $[\alpha]_D^{14}$ −27° (*c*, 1·64) (Found: C, 81·5; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·65; H, 11·55%).

Hydrolysis of this adduct was effected by adding a solution of concentrated hydrochloric acid (0·25 c.c.) in ethanol (10 c.c.) to a suspension of the compound (0·2 g.) in ethanol (5 c.c.). Warming to 50° gave a clear solution from which cholesterol (m. p. and mixed m. p. 145—147°) was obtained by cooling and addition of a little water.

3β-2′-*Tetrahydropyranyloxyandrost-5-en*-17-*one*.—Concentrated hydrochloric acid (3 drops) was added to a solution of dehydro*epi*androsterone (3·6 g.) in purified 2 : 3-dihydropyran (25 c.c.). The mixture was kept at room temperature for 1½ hours and then made alkaline with methanolic potassium hydroxide, and the product precipitated by the addition of aqueous methanol. A single recrystallisation from methanol gave the adduct (3·0 g.) as needles, m. p. 169—170°. This product is a mixture of two stereoisomers; repeated recrystallisation from methanol resulted in the isolation of the higher-melting *isomer* as flat needles, m. p. 187—188·5°, $[\alpha]_D^{22}$ −53° (*c*, 4·92) (Found: C, 77·35; H, 10·0. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·75%).

One pure stereoisomer having been isolated it was possible to obtain the other in a state of purity. Concentrated hydrochloric acid (one drop) was added to a solution of dehydro*epi*androsterone (1 g.) in 2 : 3-dihydropyran (4 c.c.). After 1 hour at room temperature, the solution was seeded with the isomer, m. p. 187—188·5°, which induced rapid crystallisation. The mixture was then made alkaline with methanolic potassium hydroxide (2 c.c.), and the crystalline product (0·5 g.), m. p. 183—189°, collected and washed with cold nitromethane. Two recrystallisations from nitromethane brought the m. p. to 187—188·5°. The mother-liquor from the reaction mixture was concentrated to give a solid product (0·43 g.), m. p. 171—175°, which after three recrystallisations from nitromethane gave the lower-melting *isomer* as flat needles, m. p. 175—176°, $[\alpha]_D^{22}$ + 47° (*c*, 2·16) (Found: C, 77·6; H, 9·85%). A mixture of the epimers melted at 164—168°.

3β : 17β-*Dihydroxy*-17α-*ethylandrost-5-ene* (II; R = H, R′ = Et).—In this and succeeding experiments solutions of alkyl-lithium compounds were prepared in light petroleum (b. p. 80—95°) by Fieser and Gates's procedure (*J. Amer. Chem. Soc.*, 1940, **62**, 2335), the lithium being beaten into thin sheets. After determination of the strength of the solution by addition to water followed by titration with acid, a suitable volume of the solution was used in the experiment. 3β-2′-Tetrahydropyranyloxyandrost-5-en-17-one (1·0 g.; m. p. 169—170°) was dissolved in light petroleum (50 c.c.; b. p. 80—95°), and a solution of ethyl-lithium (0·19 g., 10% excess) in light petroleum (25 c.c.) was added rapidly. A voluminous white precipitate formed which dissolved on the addition of dry ether (25 c.c.). The pale yellow solution was kept at room temperature in a stoppered flask for 48 hours; a test sample then gave a negative Zimmerman test. The above operations were performed in an atmosphere of nitrogen. The steroid was isolated with ether, and the gummy solid obtained was dissolved in methanol (5 c.c.). Concentrated hydrochloric acid (2 drops) was added and the solution was warmed at 50° for 3 minutes. Addition of water gave a solid product (0·86 g.) which was chromatographed on alumina (120 g., P. Spence, type O; solvent, 1 : 1 ether–benzene). Ether–benzene (1 : 1) eluted an inappreciable amount of material, but ether eluted a solid (280 mg.; m. p. 189—193°). Two recrystallisations of this product from ethyl acetate–methanol gave the 17α-ethyl-3β : 17β-diol as needles, m. p. 198—199°, $[\alpha]_D^{21}$ −66° (*c*, 3·22 in ethanol). Butenandt, Cobler, and Schmidt (*Ber.*, 1936, **69**, 448) give m. p. 198°; Ruzicka, Hofmann, and Meldahl (*Helv. Chim. Acta*, 1938, **21**, 597) give m. p. 200—202°, $[\alpha]_D$ −68·4° (*c*, 1·16 in ethanol) for a sample prepared by hydrogenation of the 17α-ethynyl compound.

Acetylation of the ethyl-diol gave the 3β-acetate as plates (from methanol), m. p. 164—165·5°, $[\alpha]_D^{19}$ −85° (*c*, 0·4). Butenandt, Schmidt-Thomé, and Paul (*loc. cit.*) give m. p. 167—168°.

Further elution of the chromatogram in the above experiment with ether–methanol gave a gummy solid which in the Boscott colour test gave a magenta colour with no appreciable green fluorescence, indicating the presence of one or both of the 3β : 17-dihydroxyandrost-5-enes, and the absence of the 17α-ethyl-diol.

3β : 17β-*Dihydroxy*-17α-n-*propylandrost-5-ene* (II; R = H, R′ = Pr^n).—A solution of *n*-propyl-lithium (0·5 g.) in light petroleum (15 c.c.; b. p. 80—95°) was added rapidly to a stirred solution of 3β-2′-tetrahydropyranyloxyandrost-5-en-17-one (180 mg.; m. p. 187—188·5°) in light petroleum (15 c.c.; b. p. 80—95°) in an atmosphere of nitrogen. The slightly opalescent mixture was stirred at 80° for 4·5 hours during which the reaction mixture became yellow and a small amount of white solid was precipitated. The steroid was isolated with ether to give a solid, which after removal of the protecting group by treatment with methanolic hydrochloric acid gave a product which on recrystallisation from nitromethane gave the propyl-diol (102 mg.), m. p. 181—183°. Further recrystallisation from nitromethane–methanol gave the pure *diol*, m. p. 190—191·5°, $[\alpha]_D^{18}$ −76° (*c*, 0·60) (Found: C, 79·35; H, 10·8. $C_{22}H_{36}O_2$ requires C, 79·45; H, 10·9%).

In one experiment the intermediate dihydropyran adduct was isolated, and recrystallised from nitromethane–methanol to give plates, m. p. 157—159°.

The mother-liquor from the first recrystallisation gave a strong positive test for 3β : 17-dihydroxyandrost-5-ene in the Boscott colour test.

3β : 17β-*Dihydroxy*-17α-n-*octylandrost*-5-*ene* (II; R = H, R′ = n-C_8H_{17}).—3β-2′-Tetrahydropyranyloxyandrost-5-en-17-one (120 mg.; m. p. 164—168° or 186—188°) was dissolved in light petroleum (5 c.c.; b.p. 80—95°) by gentle warming, and the solution cooled to room temperature, some of the adduct crystallising. A solution of n-octyl-lithium (0·24 g.) in light petroleum (10 c.c.; b. p. 80—95°) was added rapidly—a white precipitate first formed which soon redissolved. The clear solution was kept at room temperature in a stoppered flask for 48 hours. Decomposition with water and isolation with ether gave a solid product. Hydrolysis of the protecting group by the method described previously gave a product which on trituration with nitromethane–methanol gave a gum. This was purified by placing it on a porous tile above light petroleum (b. p. 60—80°) in a closed container. The solid (40 mg.), m. p. 128—135°, was recrystallised from nitromethane–methanol, to give the pure *diol* as needles, m. p. 145—146°, $[\alpha]_D^{20}$ −55° (*c*, 0·40) (Found : C, 79·5, 80·9; H, 11·4, 10·7. $C_{27}H_{44}O_2$ requires C, 80·5; H, 11·5%). The yield could probably be improved by chromatography of the reaction product.

3β-*Acetoxy*-17β-*hydroxy*-17α-*propargylandrost*-5-*ene* (II; R = Ac, R′ = $CH_2{\cdot}C{\equiv}CH$).—Zinc dust (3 g.) was activated by stirring it with 2N-hydrochloric acid until effervescence commenced, the metal then being washed in turn with water, methanol, and dry ether. Dry dioxan (30 c.c.) and dehydro*epi*androsterone acetate (1·47 g.) were added immediately to the zinc, and some of the solvent (15 c.c) was removed by distillation to remove traces of moisture. Freshly distilled propargyl bromide (4·1 c.c.) was added dropwise to the boiling mixture. The reaction proceeded exothermally and the mixture became dark and viscous. When the reaction had subsided, the mixture was cooled and benzene and 2N-hydrochloric acid were added. The aqueous layer was again extracted with benzene, and the benzene extracts were evaporated *in vacuo* to give a dark tar. This tar was extracted with four 50-c.c. portions of hot light petroleum (b. p. 80—100°), and the filtered extracts were evaporated *in vacuo*, leaving a residue which solidified on trituration with methanol. Crystallisation from ethanol (together with chromatographic purification if the product was still rather dark) gave 3β-*acetoxy*-17β-*hydroxy*-17α-*propargylandrost*-5-*ene* as needles (0·57 g.), m. p. 147—148°, $[\alpha]_D^{20}$ −81° (*c*, 3·53) (Found : C, 77·15; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%). Low analytical values for carbon are often obtained with propargyl-carbinols (Henbest, Jones, and Walls, *loc. cit.*).

Concentration of the mother-liquors gave a further 0·2 g. of the same quality. The yield based on keto-steroid was thus 45%. The propargyl compound gave a precipitate with ammoniacal silver nitrate in methanol, confirming the presence of an ethynyl group.

The rate at which the Reformatsky reaction proceeded was considerably influenced by the state of sub-division of the zinc dust, finer particle size leading to a faster and smoother reaction. Zinc wool gave no appreciable reaction.

3β : 17β-*Dihydroxy*-17α-*propargylandrost*-5-*ene* (II; R = H, R′ = $CH_2{\cdot}C{\equiv}CH$).—The above acetate (0·4 g.) was refluxed in methanol (11 c.c.) containing potassium hydroxide (0·28 g.) for 30 minutes. Water was added to the reaction mixture to precipitate the product (0·38 g.), m. p. 152—154°. Recrystallisation from ethanol or nitromethane gave the *diol* as flat needles, m. p. 156—157°, $[\alpha]_D^{18}$ −81° (*c*, 2·31) (Found : C, 79·85; H, 9·8. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

17β-*Hydroxy*-17α-*propargylandrost*-4-*en*-3-*one* (III; R′ = $CH_2{\cdot}C{\equiv}CH$).—The foregoing diol (0·29 g.) was dissolved in pure dry acetone (12 c.c.) and a solution of aluminium *tert.*-butoxide (1·1 g.) in dry benzene (22 c.c.) was added, the mixture then being heated under reflux for 5½ hours. The product was isolated with ether in the usual manner and chromatographed on alumina (90 g.; P. Spence, type O; solvent, benzene). Development with ether gave the crude ketone, which after two recrystallisations from methanol gave 17β-*hydroxy*-17α-*propargylandrost*-4-*en*-3-*one* (0·18 g., 60%) as needles, m. p. 135—137°, $[\alpha]_D^{20}$ +63° (*c*, 1·66) (Found : C, 80·4; H, 9·5. $C_{22}H_{30}O_2$ requires C, 80·95; H, 9·25%). Light absorption in EtOH : Maximum, 2400 A.; ε = 15,800.

As expected, the molecular-rotation differences between the above compounds are normal, *i.e.*, the 17α-propargyl-17β-hydroxy-groups do not exert a detectable vicinal effect at the 3-position : $[M_D]$3β-acetate (−300°) − $[M_D]$3β-sterol (−266°) = − 34° [Barton's (*J.*, 1945, 813) value, −35°]. $[M_D]\Delta^3$-3-ketone (+205°) − $[M_D]$3β-sterol (−266°) = +471° (Barton's value, +480°).

Partial Hydrogenation of 3β : 17β-*Dihydroxy*-17α-*propargylandrost*-5-*ene*.—The diol (17 mg.), dissolved in ethanol (5 c.c.), was hydrogenated in a micro-apparatus with a platinic oxide catalyst at room temperature and pressure. The uptake after 18 hours was 2·44 c.c. (corrected to N.T.P.) (theor. for two double bonds, 2·37 c.c.). The catalyst was removed by filtration, and the filtrate evaporated *in vacuo*, to give 3β : 17β-dihydroxy-17α-n-propylandrost-5-ene as needles, m. p. 190—191°, $[\alpha]_D^{18}$ −76° (*c*, 0·60). The m. p. was not depressed on admixture with an authentic sample prepared from dehydro*epi*androsterone and n-propyl-lithium (see above).

By using the same apparatus and experimental conditions, 17α-allyl-3β : 17β-dihydroxyandrost-5-ene [prepared from dehydro*epi*androsterone and allylmagnesium bromide by the procedure of Butenandt and Peters (*loc. cit.*)] took up one molecule of hydrogen, to give the same 17α-n-propyl compound, m. p. and mixed m. p. 189—190°.

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