The Steroid Series. Part III. Synthesis of Methyl 3β-Acetoxybisnor*allo*cholanoate from Dehydro*epi*androsterone Acetate.*

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The Reformatsky reaction between an ethyl α-halogenopropionate and dehydro*epi*androsterone acetate (I) gives the esters of a mixture of isomeric acids (II—V). Two of these (II and III), when dehydrated, give the esters of 3β-acetoxy-20β-pregna-5 : 16-dien-20-oic acid (VII) and 3β-acetoxypregna-5 : 17(20)-dien-(? *trans*-)20-oic acid (VIII), both of which after hydrogenation yield methyl 3β-acetoxybisnor*allo*cholanoate (X). These results are considered to provide additional evidence for believing that this *allo*cholane derivative and the natural steroids have the β-configuration at $C_{(20)}$.

The ethyl esters of the four isomeric acids (II—V), differing in configuration at $C_{(17)}$ and $C_{(20)}$, are the possible products of a Reformatsky reaction between an ethyl α-halogenopropionate and dehydro*epi*androsterone acetate (I). Lardon and Reichstein (*Helv. Chim. Acta*, 1941, **24**, 1127), using ethyl α-bromopropionate, obtained two of these esters, one in 20% and the other in 5% yield, together with a small quantity of an incompletely characterised third product, m. p. 124—126°, corresponding to such an ester which had been dehydrated. Addition reactions at the CO group at position 17 involving, *e.g.*, hydrogen, Grignard reagents, potassium acetylide, osmium tetroxide, or perbenzoic acid are known to proceed in such a way that the chief product results from the entering group's coming from behind the molecule (cf. Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, p. 410; Gallagher and Kritchevsky, *J. Amer. Chem. Soc.*, 1950, **72**, 882), so that Lardon and Reichstein's main product probably has a β-hydroxyl group at $C_{(17)}$.

During the present work this Reformatsky reaction has been investigated under various conditions. Ethyl α-iodopropionate has been found to give higher yields than the bromo-ester. Reaction in dioxan was tried under the conditions used by Greenhalgh, Henbest, and Jones (*J.*, 1951, 1190) but, as sometimes happens in this solvent (Ruzicka, Reichstein, and Fürst, *Helv. Chim. Acta*, 1941, **24**, 76), dehydration occurred: two products were isolated, one of which appeared to be identical with the compound, m. p. 124—126°, obtained by Lardon and Reichstein (*loc. cit.*). The best yields for the Reformatsky reaction were achieved by using ethyl α-iodopropionate in benzene: four compounds were isolated in addition to dehydro*epi*androsterone. One of the products was the dehydrated compound, m. p. 124—126°, and the others are three of the possible hydroxy-esters. The main product (32%) was Lardon and Reichstein's 17β-hydroxy-compound which, for reasons to be given later, is considered to be methyl ester of 3β-acetoxy-17β-hydroxy-20β-pregn-5-en-20-oic acid (II). Neither of the other two esters is identical with Lardon and Reichstein's second hydroxy-ester. The chief product (II) and one of the minor ones (III) give, on dehydration, the same two acids (VII and VIII). One of these is 3β-acetoxy-20β-pregna-5 : 16-dien-20-oic acid (VII), which shows that the original hydroxy-acids have the same configuration at $C_{(20)}$ and differ only at $C_{(17)}$. Hydrogenation of the methyl ester of this diene gives methyl 3β-acetoxybisnor*allo*cholanoate (X), which shows that the configuration at $C_{(20)}$ in all these compounds is that of the natural steroids. The second diene obtained in the dehydration has an ultra-violet absorption spectrum very similar to that of α-*cyclo*hexylidenepropionic acid and different from that of the other diene—in particular there is the peak at 224 mμ characteristic of αβ unsaturated acids—and is, therefore, regarded as 3β-acetoxypregna-5 : 17(20)-dien-20-oic acid. No experimental evidence is available to decide whether it has the *cis*- or the *trans*-configuration, but inspection of molecular models shows that in the compound with the carboxyl group *cis* to the nucleus there is considerable hindrance of the carboxyl group by the atoms at $C_{(12)}$ and $C_{(18)}$, whereas in the *trans*-form there is comparative freedom. Consequently it is likely that the

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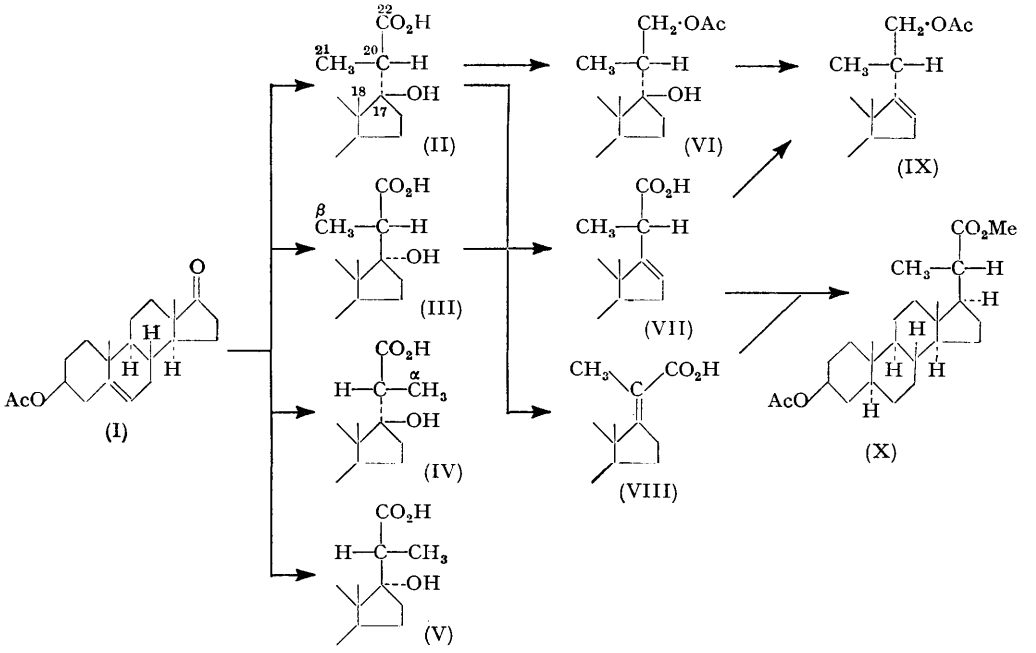
compound obtained is the *trans*-20-oic acid (VIII). Hydrogenation in acetic acid over Adams platinum catalyst gives methyl 3β-acetoxybisnor*allo*cholanoate (X). If in this reaction *cis*-addition of hydrogen at $C_{(17)}$ and $C_{(20)}$ proceeds from behind the molecule, as is to be expected from work by Linstead, Doering, Davis, Levine, and Whetstone (*J. Amer. Chem. Soc.*, 1942, **64**, 1985), then the resulting product will have the β-configuration at $C_{(20)}$. This provides additional evidence that the configuration



is β at $C_{(20)}$ in the natural steroids. Considerable evidence has already accumulated for this view, notably from the work of Wieland and Miescher (*Helv. Chim. Acta*, 1949, **32**, 1922), Gallagher and Kritchevsky (*loc. cit.*), and Ryer and Gebert (*J. Amer. Chem. Soc.*, 1952, **74**, 41). It follows that the main product of the Reformatsky reaction is 3β-acetoxy-17β-hydroxy-20β-pregn-5-en-20-oic acid (II) and that the minor product, whose dehydration has now been examined, is the 17α-hydroxy-epimer (III).

The two remaining hydroxy-acids, one obtained by Lardon and Reichstein and the other during the present work, are the 20α-epimers. Bergmann and Low (*J. Org. Chem.*, 1947, **12**, 67) have pointed out that 20β-compounds are slightly more dextrorotatory than the 20α-epimers in the case of the 3β-hydroxynor*allo*cholanic acids and their derivatives; the average difference in $[M]_D$ is +14°. Similarly, three of the four 3 : 12-dihydroxybisnorcholanic acid derivatives are more dextrorotatory than the 20α-epimers. The specific rotations recorded by Lardon and Reichstein show that their major product is the more dextrorotatory, the $[M]_D$ being +17°. Consequently, the second hydroxy-acid isolated by Lardon and Reichstein is tentatively considered to be 3-β-acetoxy-17β-hydroxy-20α-pregn-5-en-20-oic acid (IV). The remaining isomer, isolated in our work is, by elimination, 3β-acetoxy-17α-hydroxy-20α-pregn-5-en-20-oic acid (V).

The dehydrated ester, m. p. 124—126°, was considered by Lardon and Reichstein to be a 5 : 17(20)-diene. Its ultra-violet absorption spectrum has now been found to be similar to that of 3β-acetoxy-20β-pregna-5 : 16-dien-20-oic acid, without the characteristic peak of an αβ-unsaturated acid. Consequently this compound is formulated as methyl 3β-acetoxy-20α-pregna-5 : 16-dien-20-oate.

Reduction of methyl 3β-acetoxy-20β-pregna-5 : 16-dien-20-oate by lithium aluminium hydride, followed by acetylation, gives 20β-pregna-5 : 16-diene-3β : 22-diol diacetate (IX), which also results from the similar reduction, followed by partial acetylation

and dehydration of methyl 3β-acetoxy-17β-hydroxy-20β-pregn-5-en-20-oate (II). This confirms the structure proposed by Lardon and Reichstein for the compound they obtained in a similar manner.

Experimental

Unless specified, the light petroleum used had b. p. 40—60°. During the isolation of products, ethereal solutions were purified by washing them with dilute hydrochloric acid and/or aqueous sodium carbonate (5%), then with water, and were dried (Na_2SO_4 or $CaCl_2$) before evaporation.

*Reformatsky Reactions between Dehydro*epi*androsterone Acetate and Ethyl α-Halogeno-propionates.*—(1) *With ethyl α-iodopropionate in benzene.* Activated zinc (10 g.) was added to dehydro*epi*androsterone acetate (10 g.) in dry benzene (50 ml.) (moisture excluded). Some benzene (10 ml.) was distilled off and then about a fifth of a solution prepared from ethyl α-iodo-propionate (16 g.), pyridine (4 drops), and benzene (10 ml.) was added. The remainder of the iodo-ester solution was added gradually during 1 hr., together with two further amounts of activated zinc (1 g. each). When addition was complete the reactants were boiled for another hour and then cooled. Hydrochloric acid (200 ml., 20%) was added and the benzene layer was separated. The aqueous phase was extracted with ether and the extracts were added to the benzene. The benzene–ether solutions, while being washed with aqueous sodium carbonate, deposited the solid sodium salt of an acid (5%), which was filtered off. An aqueous suspension of this salt was acidified. The ethereal extract of this was washed and dried before addition of a solution of diazomethane (0·3 g.) in ether (15 ml.) to it. Next morning the ether was evaporated and the residue (0·5 g.) was purified by chromatography on alumina from light petroleum–benzene (3 : 2). Elution with benzene gave, after recrystallisation from ether–light petroleum, the dehydrated compound regarded as methyl 3β-acetoxy-20α-pregna-5 : 16-dien-20-oate (0·2 g.), m. p. 122—124° (Found : C, 77·2; H, 9·4. Calc. for $C_{23}H_{34}O_3$: C, 77·1; H, 9·5%). Lardon and Reichstein (*loc. cit.*) record m. p. 124—126°.

The above benzene–ether solution was evaporated. The residue was boiled for 30 min. with potassium hydroxide (10 g.) in methanol (90 ml.). The cooled solution was poured into water and extracted with ether. From the extracts there was isolated dehydro*epi*androsterone (56%). Acidification of the aqueous-methanolic alkaline solution precipitated a crude acid (26%) which was filtered off, dried *in vacuo*, and recrystallised from acetone. This was 3β : 17β-dihydroxy-20β-pregn-5-en-20-oic acid (1·15 g.), m. p. 229—232°, for which Lardon and Reichstein (*loc. cit.*) record m. p. 230—234°. The mother-liquors from these recrystallisations were evaporated, and the residue was methylated in ether with diazomethane. Evaporation of the washed ethereal solution left a residue which was acetylated in pyridine (10 ml.) with acetic anhydride (5 ml.) for 18 hr. at room temperature. The pyridine solution was extensively diluted with water and the resulting solid was dissolved in ether. Evaporation of the washed and dried solution left a gum (2·3 g.) which was chromatographed on alumina from light petroleum–benzene (6 : 1). Elution with light petroleum–benzene (2 : 1) gave, after recrystallisation from methanol, *methyl 3β-acetoxy-17α-hydroxy-20β-pregn-5-en-20-oate* (0·5 g.), m. p. 149—150·5°, $[\alpha]_D^{20}$ −45·7° (*c*, 0·62 in $CHCl_3$) (Found : C, 71·2; H, 9·2. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·1%).

Elution of the column with benzene gave an oil (0·35 g.) which was rechromatographed from light petroleum–benzene (5 : 1). Elution with benzene followed by two recrystallisations from methanol gave *methyl 3β-acetoxy-17α-hydroxy-20α-pregn-5-en-20-oate* (0·05 g.), m. p. 154—155° (Found : C, 71·3; H, 9·1%).

Further elution of the column with benzene–ether (10 : 1 ⟶ 1 : 1) gave, after recrystallisation from acetone, methyl 3β-acetoxy-17β-hydroxy-20β-pregn-5-en-20-oate (0·45 g.), m. p. 198—201°, $[\alpha]_D^{20}$ −62·5° (*c*, 1·0 in $COMe_2$), for which Lardon and Reichstein record m. p. 201—204°, $[\alpha]_D^{20}$ −67°.

(2) *With ethyl α-bromopropionate in benzene.* About half of a solution of freshly distilled ethyl α-bromopropionate (6 g.) in dry benzene (10 ml.) and pyridine (4 drops) was added to activated zinc (2 g.) and dehydro*epi*androsterone acetate (2 g.) in boiling dry benzene (10 ml.). After reaction started zinc (1 g.) was added, followed gradually by the rest of the benzene solution. After boiling for 2 hr. more the reactants were cooled, hydrolysed with dilute hydrochloric acid, and extracted with ether. The solid sodium salt was again obtained. The residue from the ethereal solution was treated with methanolic potassium hydroxide. The neutral fraction contained unchanged starting compound (1·47 g., 82%), whilst the acid fraction yielded the crude acid (0·3 g., 12%) obtained in (1).

(3) *With ethyl α-iodopropionate in benzene–ether.* This was carried out similarly and gave unchanged starting compound (62%) together with lower yields of the compounds described in (1).

(4) *With ethyl α-iodopropionate in dioxan.* Activated zinc (6 g.) was added to a solution of dehydro*epi*androsterone acetate (6 g.) in dry dioxan (100 ml.). Dioxan (40 ml.) was distilled off and ethyl α-iodopropionate (6 g.) was added. Three further quantities of zinc (1 g.) and of iodo-ester (2 g.) were added at 30-min. intervals and then the solution was refluxed for 30 min. more. When cold, the products were hydrolysed with 20% hydrochloric acid (200 ml.). Dehydro*epi*androsterone (2·5 g., 48%) and two crude reaction products were isolated by extraction with benzene. One of the reaction products was methylated with diazomethane and purified chromatographically, to give methyl 3β-acetoxy-20α-pregna-5 : 16-dien-20-oate, m. p. alone and mixed with the compound prepared as in (1), 122—124°. No other crystalline substances were obtained from the column. The second product was methylated with diazomethane and then acetylated with acetic anhydride in pyridine. The resulting gum (1·5 g.), purified by chromatography from light petroleum–benzene solution (3 : 1), followed by elution with benzene–ether, yielded the *acetate* of the methyl ester of an unsaturated acid; this had m. p. 158—159° (Found: C, 74·7; H, 9·5. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·0%). This compound (0·05 g.) was deactylated to give a compound, m. p. 226—228°.

Preparation of Methyl 3β-Acetoxy-17β-hydroxy-20β-pregn-5-en-20-oate.—Reaction of 3β : 17β-dihydroxy-20β-pregn-5-en-20-oic acid (1·1 g.) with diazomethane in ether suspension yielded, after recrystallisation from acetone, methyl 3β : 17β-dihydroxy-20β-pregn-5-en-20-oate (1·1 g.), m. p. 182—183°, $[\alpha]_D^{20}$ −58° (*c*, 1·5 in $COMe_2$). Lardon and Reichstein (*loc. cit.*) record m. p. 182—183°, $[\alpha]_D^{20}$ −61°. The ester was left overnight at room temperature in pyridine (9 ml.) containing acetic anhydride (3 ml.). The solution was poured into water and the resulting solid, recrystallised from acetone, was methyl 3β-acetoxy-17β-hydroxy-20β-pregn-5-en-20-oate (1 g.), m. p. 198—201° alone or admixed with the compound obtained directly from the Reformatsky reaction.

Dehydration of Methyl 3β-Acetoxy-17β-hydroxy-20β-pregn-5-en-20-oate.—The ester (0·4 g.) was boiled under reflux for 30 min. in pyridine (20 ml.) containing phosphorus oxychloride (1 ml.). The cold solution was poured into water, and the solid which separated was extracted with ether. The residue (0·31 g.), left after evaporation of the ether, was chromatographed on alumina from light petroleum. Elution of the column with benzene–light petroleum (1 : 10 ⟶ 1 : 1) gave, after recrystallisation from methanol, *methyl 3β-acetoxy-20β-pregna-5 : 16-dien-20-oate* (0·21 g.), m. p. 116—117°, $[\alpha]_D^{20}$ −34° (*c*, 0·8 in $CHCl_3$) (Found: C, 74·5; H, 9·2. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·0%). Elution of the column with benzene gave, after recrystallisation from methanol, *methyl 3β-acetoxypregna-5 : 17(20)-dien-(*? trans-*)20-oate* (0·05 g.), m. p. 160—162° (Found: C, 75·3; H, 9·3%).

Dehydration of Methyl 3β-Acetoxy-17α-hydroxy-20β-pregn-5-en-20-oate.—Dehydration of this ester (0·4 g.) was carried out as described above: the crude product (0·35 g.) was chromatographed on alumina from light petroleum. Elution of the column with benzene–light petroleum (1 : 5) gave the same compounds as in the previous experiment, but the amounts were 0·05 g. and 0·25 g. respectively.

Deacetylation of Methyl 3β-Acetoxy-20β-pregna-5 : 16-dien-20-oate.—Catalytic deacetylation of this compound with sodium in methanol gave, after recrystallisation from methanol, *methyl 3β-hydroxy-20β-pregna-5 : 16-dien-20-oate*, m. p. 113—114° (Found: C, 76·8; H, 10·1. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·5%).

Preparation of 20β-Pregna-5 : 16-diene-3β : 22-diol Diacetate.—A solution of methyl 3β-acetoxy-17β-hydroxy-20β-pregn-5-en-21-oate (0·28 g.) in ether (30 ml.) was mixed with lithium aluminium hydride (0·5 g.) in ether (30 ml.) and left for 30 min. After the washing, the ethereal layer was evaporated. The residue was left overnight at room temperature in pyridine (2 ml.) containing acetic anhydride (1 ml.) and then poured into water. Extraction with ether, followed by evaporation and recrystallisation of the residue from ether–light petroleum (b. p. 60—80°), gave 20β-pregn-5-ene-3β : 17β : 22-triol 3 : 22-diacetate (0·08 g.), m. p. 160—161°, $[\alpha]_D^{20}$ −54·9° (*c*, 0·7 in $CHCl_3$), for which Lardon and Reichstein (*loc. cit.*) record m. p. 162—163°. A solution of this compound in pyridine (5 ml.) containing phosphorus oxychloride (0·5 ml.) was refluxed for 30 min. When cold the solution was diluted with water, and the solid which separated was extracted with ether. The residue, left on evaporation of the ether, was chromatographed on alumina from light petroleum (b. p. 40—60°). Elution with benzene afforded 20β-pregna-5 : 16-diene-3β : 22-diol diacetate (0·03 g.), which after recrystallisation from methyl alcohol had m. p. 112—114°. Lardon and Reichstein (*loc. cit.*) record m. p. 114—116°.

The same compound was obtained by the reduction of methyl 3β-acetoxy-20β-pregna-5 : 16-dien-20-oate with lithium aluminium hydride.

Hydrogenation of Methyl 3β-*Acetoxy*-20β-*pregna*-5 : 16-*dien*-20-*oate and of Methyl* 3β-*Acetoxy-pregna*-5 : 17(20)-*dien*-(? trans)-20-*oate*.—No reduction took place on use of hydrogen with Raney nickel catalyst for 2 hr. at atmospheric temperature and pressure.

Adams platinum oxide catalyst (0·1 g.) was added to a solution of methyl 3β-acetoxy-20β-pregna-5 : 16-dien-20-oate (0·09 g.) in acetic acid (10 ml.). No further hydrogen was absorbed after 2 hr.' shaking, so the solution was diluted with water and the precipitated solid was dissolved in ether. Recrystallisation of the residue obtained on evaporation of the ether gave methyl 3β-acetoxybisnor*allo*cholanoate (0·04 g.), m. p. 130—131°, mixed m. p. with an authentic specimen (m. p. 129—130°) 129—130°.

A small quantity of the product was deacetylated and gave methyl 3β-hydroxybisnor*allo*-cholanoate, m. p. 152—154°, for which Bergmann and Low (*J. Org. Chem.*, 1945, **10**, 570) record m. p. 153—156°.

Hydrogenation of methyl 3β-acetoxypregna-5 : 17(20)-dien-(? *trans*)-20-oate (0·03 g., m. p. 152—154°) under similar conditions afforded methyl 3β-acetoxybisnor*allo*cholanoate (0·015 g.), m. p. 124—127°, m. p. mixed with an authentic specimen, 124—130°.

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