520. *Chemical Actions of Ionising Radiations in Solution. Part VI. Radiation Chemistry of Sterols. The Action of X-Rays on Cholesterol and 3β-Hydroxypregn-5-en-20-one.*

By Max Keller and Joseph Weiss.

In continuation of previous work on the chemical action of ionising radiations and the formation of free radicals and atoms in these processes (Parts I—IV, *J.*, 1949, 3241—3263; Part V, *J.*, 1950, 2704) we have investigated the action of *X*-rays on cholesterol and 3β-hydroxypregn-5-en-20-one in aqueous systems. From the irradiated solutions we were able to isolate, and to characterise by unambiguous methods, from the former cholestane-3β : 5α : 6β-triol and 3β-hydroxycholest-5-ene-7-one, and from the latter 3β : 5 : 6β-trihydroxy*allo*pregnane-20-one. These substances are formed in relatively good yields and account for 80—90% of the starting materials. The outline of a mechanism of the formation of these compounds is given on the basis of the general theory put forward in 1944 (Weiss, *Nature*, **153**, 748), and some possible biological implications of these findings are briefly discussed.

Steroid compounds are widely distributed in the human and animal body and it is well known that steroid hormones are among the controlling factors in metabolism. In recent years it has also become increasingly more probable that sterol metabolism has a bearing on the incidence of cancer; it is well known that irradiation by *X*-rays can both lead to cancer and, conversely, arrest the development of malignant tissue already present in the organism. For these reasons and also from a general chemical point of view, it seemed of interest to study the chemical changes produced by ionising radiations on naturally occurring sterols and related compounds, particularly as no relevant information appears to exist in the literature.

In the present paper we report a study of the action of *X*-rays on cholesterol (I) and 3β-hydroxypregn-5-en-20-one (IX) in aqueous systems.

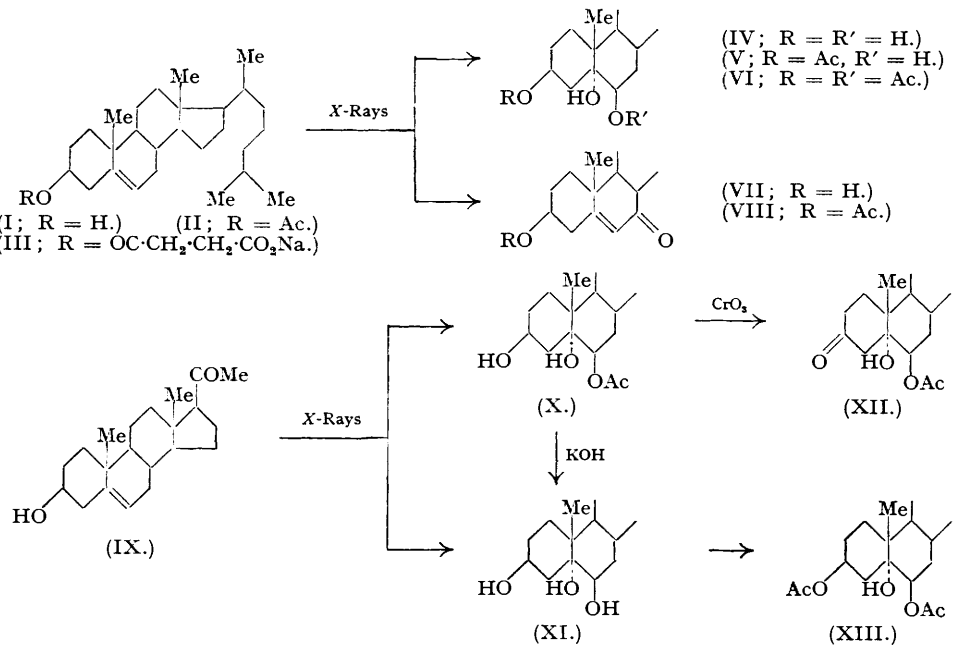
Irradiation of cholesterol and pregn-5-enolone by X*-rays.*

Substance irradiated.	Solvent.	Dose (approx.), 10^6 r.	Products.	Yield, %.	
Na cholesteryl succinate (III), 0·25% solution (in air)	Water	1·8	Cholestane-3β : 5α : 6β-triol (IV)	19	84
			Unidentified oil	~15	
			Starting material	50	
Cholesteryl acetate (II), 0·17% solution (in air)	Aqueous acetic acid (10% of water)	1·8	3β : 6β-Diacetoxycholestan-5-α-ol (VI)	32	80
			3β-Acetoxycholestane-5α : 6β-diol (V)	48	
Cholesterol (I), 0·16% solution (in air)	Aqueous acetic acid (10% of water)	3·6	Cholesteryl acetate (II)	4·5	80
			3β-Cholest-5-en-7-one (VII)	17·5	
			Cholestane-3β : 5α : 6β-triol (IV)	27·5	
			Unidentified oil	~5	
			Starting material	25	
Cholesterol (I), 0·5% solution (in a vacuum)	Glacial acetic acid	2·1	Cholesteryl acetate (II)	7	94
			3β : 6β-Diacetoxycholestan-5α-ol (VI)	4	
			3β-Hydroxycholest-5-en-7-one (VII)	7	
			Unidentified oil	~4	
			Starting material	72	
3β-Hydroxypregn-5-en-20-one (IX), 0·3% solution (in air)	Aqueous acetic acid (10% of water)	2·7	6β-Acetoxy-3β : 5α-dihydroxy*allo*pregnan-20-one (X)	18	74
			3β : 5α : 6β-Trihydroxy*allo*pregnan-20-one (XI)	25	
			Starting material	31	

Cholesterol is present in the human blood-stream and in living tissue and is known to be a precursor in the biosynthesis of the sex hormones and of the hormones of the adrenal cortex (cf. Pincus and Thimann, " The Hormones," Vol. I, New York, 1948). Pregn-5-enolone, which is chemically similar to cholesterol (it differs in the side chain), is closely related to the sex hormones. In view of the absolute lack of knowledge regarding these *X*-radiation reactions our first aim was to establish with certainty the nature of the chemical compounds formed. Since purely physical methods did not appear sufficiently conclusive we have isolated the reaction products and characterised them by unambiguous methods. Therefore, as in our previous work (*loc. cit.*) we had to employ fairly large doses (of the order of 10^6 r.). For separating the reaction products we used elution chromatography, which gave recoveries so good that we were always able to account for 80—90% of the starting material (see Table). Our aim was to work in aqueous systems as these most closely correspond to biological conditions. Cholesterol being itself insoluble in water we first irradiated aqueous solutions of sodium cholesteryl succinate. We found, however, that similar products were obtained in aqueous acetic acid and have used the latter solvent extensively for our sterol work.

In order to study the role of the acetic acid itself we have also carried out irradiations in anhydrous acetic acid. Table I summarises the results obtained under different conditions. *X*-Ray doses were always of the order of 10^6 r. with an average dose rate of approx. 3000 r. The products were identified by their melting points, mixed melting points, analyses, and optical rotations. From the hydroxy-compounds the acetyl derivatives were also prepared, and from 6β-acetoxy-3β : 5α-dihydroxy*allo*pregnan-20-one (X) the corresponding diketone (XII).

The annexed schemes show the products obtained. In general 0·5—1 g. of starting material was used, and in nearly all cases ample amounts were obtained for the identification. We also obtained a few substances as unidentified oils, and two crystalline substances in insufficient amount for complete analysis.



Among the substances which have been isolated cholestane-3β : 5α : 6β-triol is of particular interest as it has been isolated recently from arteriosclerotic aortas by Hardegger, Ruzicka, and Tagmann (*Helv. Chim. Acta*, 1943, **26**, 2205), from pig's testes by Ruzicka and Prelog (*ibid.*, p. 975), and from beef liver by Haslewood (*Biochem. J.*, 1941, **35**, 708). The 7-ketone (VII) has been isolated from bull's testes by Steinmann (*Helv. Chim. Acta*, 1943, **26**, 2222) and from pig's testes by Prelog, Tagmann, Liebermann, and Ruzicka (*ibid.*, 1947, **30**, 1080).

Although relatively large doses of *X*-rays had to be employed in this work the excellent yields and the relatively simple changes involved make it highly probable that essentially the

same substances would be also formed with the small doses which are used under biological conditions.

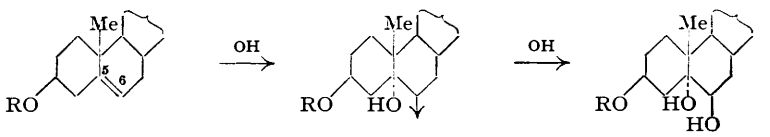
Discussion.—Until relatively recently the chemical action of ionising radiations was considered to involve intervention of special excited molecules or ionic species not encountered in " ordinary " chemistry. The general theory put forward in 1944 (Weiss, *Nature*, **153**, 748) in a sense reduces radiation chemistry to the chemistry of free radicals, about which we already possess information from independent sources. In radiation chemistry the formation of free radicals is based on the assumption that the primarily-formed ionic species are unstable (especially in the presence of a polar solvent) and decompose rapidly into radicals and atoms and more stable ions. In the case of water the active radicals were shown to be hydroxyl radicals and hydrogen atoms (Parts II—V, *loc. cit.*) which are presumed to be formed from the primary ions :

$$H_2O^+ \rightleftarrows OH + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$H_2O^- \rightleftarrows H + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

For aqueous solutions this accounts for all the experimental facts, and the formation of hydroxyl radicals and hydrogen atoms has been amply confirmed (*loc. cit.*). On the basis of the results already obtained it seemed hopeful to study the action of ionising radiations on more complicated molecules of biological importance [cf. Part IV (amino acids) and work on nucleic acids (Scholes, Stein, and Weiss, *Nature*, 1949, **164**, 709].

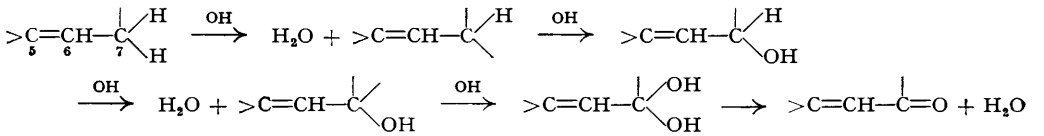
The formation of the triol (IV) is explained by the action of hydroxyl radicals, followed by further addition of hydroxyl radicals to the double bond :



with the intermediate formation of a free radical either from $C_{(5)}$ or from $C_{(6)}$ according to which end of the double bond is attacked first.

A similar process presumably takes place in the aqueous acetic acid solutions of cholesterol (I) or of 3β-hydroxypregn-5-en-20-one (IX), the corresponding triols (IV) and (XI) having been isolated from the irradiated solutions.

The starting materials differ only in their side chain and it is reasonable to expect that this, being rather remote from the point of attack, does not appreciably influence the reactivity of the double bond. In the case of cholesterol the 7-ketone has also been isolated. This can be explained by an attack of the 7-position by hydroxyl radicals, *e.g.*, in the following stages :



The fact that the formation of the ketone requires (by almost any reasonable mechanism) four steps makes its production perhaps less probable, although 4-step processes are by no means uncommon as a result of *X*-ray action (cf. the formation of catechol or quinol from benzene, Part II, *loc. cit.*).

Irradiation in aqueous acetic acid often leads to acetylated compounds. Irradiation of cholesterol in anhydrous acetic acid gave the diacetate of the triol (VI) and the 7-ketone (VII). These results suggest the following tentative picture for the action of *X*-rays on acetic acid. The primarily-formed ions are presumably $[CH_3{\cdot}CO_2H]^+$ and $[CH_3{\cdot}CO_2H]^-$, which can decompose in the following ways :

$$[CH_3{\cdot}CO_2H]^+ \longrightarrow CH_3{\cdot}CO^+ + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4a)$$

$$[CH_3{\cdot}CO_2H]^+ \longrightarrow CH_3{\cdot}CO_2 + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4b)$$

$$[CH_3{\cdot}CO_2H]^- \longrightarrow CH_3{\cdot}CO + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5a)$$

$$[CH_3{\cdot}CO_2H]^- \longrightarrow CH_3CO_2^- + H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5b)$$

Thus in irradiated acetic acid the same radicals (OH and H) could be formed as in water. The presence of hydroxyl radicals is supported by the facts that irradiation of cholesterol in anhydrous

acetic acid also yields 3β : 6β-diacetoxycholestan-5α-ol (VI) (which contains a hydroxyl group) and the 7-ketone (VII) (which is presumably also formed by the action of hydroxyl radicals (see above). On the other hand, in this experiment, carried out in the absence of atmospheric oxygen, no molecular hydrogen could be detected. This suggests that reaction (5*a*) takes place in preference to reaction (5*b*) or else, what seems less likely, that any hydrogen atoms formed are taken up by some of the other radicals, *e.g.*, $H + OH \longrightarrow H_2O$ or $H + CH_3{\cdot}CO_2 \longrightarrow CH_3{\cdot}CO_2H$, or by some of the other acceptors present. The presence of the acetylated products can be variously accounted for. A possible explanation is that the hydroxy-compounds are first formed by the action of hydroxyl radicals and then acetylated. According to recent work by Burton and Praill (*J.*, 1950, 1203) the acetylium ion, $CH_3{\cdot}CO^+$, which is formed here according to reaction (4*a*) is a very powerful acetylating agent, reacting with hydroxyl groups according to

$$R{\cdot}OH + CH_3{\cdot}CO^+ \longrightarrow RO{\cdot}CO{\cdot}CH_3 + H^+$$

In the presence of water it will presumably react preferentially therewith. However, there is also the possibility of a 2-step free-radical acetylation, *viz.* :

$$R{\cdot}OH + OH \longrightarrow RO{\cdot} + H_2O$$

or

$$R{\cdot}OH + CH_3{\cdot}CO_2 \longrightarrow RO{\cdot} + CH_3{\cdot}CO_2H$$

followed by

$$RO{\cdot} + CH_3{\cdot}CO \longrightarrow RO{\cdot}CO{\cdot}CH_3$$

and the acetyl group on $C_{(6)}$ could be formed also simply by the direct addition of $CH_3{\cdot}CO_2$ [formed in reaction (4*b*)] to the $C_{(6)}$ of the double bond. It should also be borne in mind that some of the radicals produced in the reactions (4) and (5) could form acetic anhydride. If $CH_3{\cdot}CO_2$ radicals are formed according to reaction (4*b*) or from the solvent by the reaction $CH_3{\cdot}CO_2H + OH \longrightarrow CH_3{\cdot}CO_2{\cdot} + H_2O$, one must also consider the appearance of methyl radicals and of carbon dioxide, the former of which can lead to the formation of methane, ethane, and other products (cf. Walker and Weiss, *Trans. Faraday Soc.*, 1935, **31**, 1011; Clusius and Schanzer, *Ber.*, 1942, **75**, 1795; *Z. physikal. Chem.*, 1943, **192**, *A*, 273).

We have also considered the possibility of the intermediate formation of epoxides which could be transformed into the triols or their acetylated products. However, no evidence could be obtained of the presence of an epoxide among the products of the irradiation of either cholesterol or the pregnenolone. Further, it is known that hydrolysis or acetolysis of the epoxides requires prolonged heating with acetic acid (cf. Lettré and Hagedorn, *Z. physiol. Chem.*, 1936, **242**, 210; Davis and Petrow, *J.*, 1950, 1185).

The results available do not permit a full quantitative discussion, and only certain suggestions can be put forward at present. However, one may conclude that there is a great tendency for hydroxyl radicals to attack an isolated double bond in the sterol ring, yielding dihydroxylated products if these are sufficiently stable. If the latter is not the case, fission of the ring may occur (unpublished results). However, the attack by hydroxyl radicals does not appear to be altogether confined to the double bonds and can also involve labile hydrogen atoms in partly unsaturated or even in saturated sterol systems. The former is shown, for instance, by the formation of the 7-ketone.

Perhaps one of the most striking features of the work reported in this paper is that in the action of *X*-rays only one or two products are formed predominantly and in relatively high yields. This is, at first sight, surprising but it is most fortunate from an experimental point of view. One must conclude that the 7-ketone and particularly the triols from cholesterol and pregnenolone are rather stable towards further attack. The formation of triols constitutes a relatively simple change of the molecule and probably occurs already with very small doses. It may well be that it is connected with steroid metabolism, particularly as the triol from cholesterol has been isolated from various tissues (*loc. cit.*).

Experimental.

Irradiations were carried out as described in Parts I, II, and IV of this series (*loc. cit.*).

Action of X-Rays on Sodium Cholesteryl Succinate in Aqueous Solution.—The sodium salt (III) (1·5 g.) in distilled water (600 ml.) was irradiated for 10 hours at 30—35°. The solution was then acidified with hydrochloric acid and extracted with ether, the ethereal extract washed till neutral and dried (Na_2SO_4), and the ether distilled off in a vacuum. The residue was heated under reflux with potassium carbonate (3·5 g.) in methanol (50 ml.) and water (10 ml.) for 1½ hours. The methanol was removed in a vacuum and the residue extracted with ether, the ethereal extract washed and dried (Na_2SO_4), the ether distilled off, and the crude product (about 1 g.) chromatographed through alumina (30 g.). Elution with ben-

zene and benzene–ether (10 : 1), followed by crystallisation from methanol, gave cholesterol (500 mg.), m. p. 145—147°, not depressed on admixture with a pure specimen. Elution with ether gave an oil (150 mg.) which could not be crystallised. Elution with chloroform–methanol (10 : 1) gave, after repeated crystallisation from methanol and ethyl acetate, cholestane-3β : 5α : 6β-triol (IV) (200 mg.), m. p. 231—235°, not depressed on admixture with an authentic specimen [prepared by hydrolysis of the diacetate (VI) which was kindly supplied by Dr. M. Davis (see Davis and Petrow, *J.*, 1949, 2536)] (Found : C, 76·5; H, 11·0. Calc. for $C_{27}H_{48}O_3$: C, 77·1; H, 11·5%). Acetylation gave the 3β : 6β-diacetate, m. p. 168—169° (from methanol) (not depressed on admixture with authentic specimen obtained from Dr. Davis), $[\alpha]_D^{17}$ − 46·12° ± 2° (*c*, 4·098 in chloroform) (Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872, give $[\alpha]_D$ −44·9°, −47·5° in chloroform).

Action of X-*Rays on Cholesterol in Aqueous Acetic Acid.*—Cholesterol (1 g.; purified by chromatography) in aqueous acetic acid (600 ml.; containing 10% of water) was irradiated for 20 hours at 30—35°. The solvent was removed at reduced pressure at 35°, the residue extracted with ether, and the extract washed until neutral. After removal of the ether the crude product (0·95 g.) was chromatographed through alumina (30 g.). Elution with light petroleum–benzene (5 : 1) followed by crystallisation from methanol gave cholesteryl acetate (50 mg.), m. p. 113—115°, not depressed on admixture with an authentic specimen. Elution with benzene and with benzene–ether (5 : 2) gave unchanged cholesterol (250 mg.), m. p. 147—148°. Elution with benzene–ether (1 : 1) and crystallisation from methanol gave 3β-hydroxycholest-5-en-7-one (VII) (180 mg.) (Found : C, 80·5; H, 10·9. Calc. for $C_{27}H_{44}O_2$: C, 80·9; H, 11·1%), m. p. 165—167°, not depressed on admixture with an authentic specimen (prepared according to Windaus, Lettré, and Schenck, *Annalen*, 1935, **520**, 98), $[\alpha]_D^{18}$ − 109° ± 2° (*c*, 2·169 in chloroform) (Bergström and Wintersteiner, *J. Biol. Chem.*, 1941, **141**, 602, give $[\alpha]_D^{23}$ −104° in chloroform; Prelog, Liebermann, and Ruzicka, *Helv. Chim. Acta*, 1947, **30**, 1080, give $[\alpha]_D^{17}$ −111° in chloroform). Acetylation of (VII) in pyridine with acetic anhydride gave the 3β-acetate, m. p. 156—158° (from methanol), not depressed on admixture with an authentic specimen. Elution with ether resulted in an oil (50 mg.). This oil, by acetylation and crystallisation from methanol, gave 30 mg. of an unidentified substance (needles) having m. p. 105—107° (Found : C, 82·9; H, 10·9%). Elution with chloroform and chloroform–methanol (20 : 1) and crystallisation from methanol gave cholestane-3β : 5α : 6β-triol (IV) (300 mg.), m. p. 228—235°, not depressed on admixture with an authentic specimen (hydrolysis product of Dr. Davis's preparation). Acetylation of (IV) gave the diacetate (VI), m. p. 165—167° (from methanol) [not depressed on admixture with an authentic specimen (Dr. Davis)] (Found : C, 73·6; H, 10·3. Calc. for $C_{31}H_{52}O_5$: C, 73·8; H, 10·4%), $[\alpha]_D^{16}$ −49·1° ± 2° (*c*, 2·831 in chloroform).

Action of X-*Rays on Cholesteryl Acetate.*—Cholesteryl acetate (1·1 g.; purified by chromatography) in aqueous acetic acid (600 ml.; 10% of water) was irradiated for 10 hours at 30—35°. The irradiated solution was treated as in the case of cholesterol, and the crude product (1·5 g.) was subjected to chromatography. Elution with light petroleum–benzene (1 : 1) and benzene, followed by crystallisation from methanol, gave 3β : 6β-diacetoxycholestan-5α-ol (VI) (380 mg.), m. p. 168—169° [not depressed on admixture with an authentic specimen (Dr. Davis)] (Found : C, 73·6; H, 10·2%). Elution with benzene–ether (10 : 1, later 4 : 1), followed by crystallisation from methanol, gave 3β-acetoxycholestane-5α : 6β-diol (V) (523 mg.), m. p. 207—209° (not depressed on admixture with an authentic specimen) (Found : C, 75·3; H, 10·9. Calc. for $C_{29}H_{50}O_4$: C, 75·3; H, 10·9%). Acetylation gave the diacetate (VI), m. p. 168—169° (from methanol) (not depressed on admixture with authentic specimen) (Found : C, 73·4; H, 10·1%).

Action of X-*Rays on Cholesterol in Anhydrous Acetic Acid.*—A solution of cholesterol (500 mg.) in glacial acetic acid (100 ml.) was irradiated in absence of air for 12 hours at 30—35°. The crude product (503 mg.), isolated as above, was chromatographed through alumina (15 g.). Elution with light petroleum–benzene (2 : 1, later 3 : 2) followed by crystallisation from methanol gave cholesteryl acetate (40 mg.), m. p. 113—115°. Elution with benzene–ether (2 : 1, later 1 : 2) followed by crystallisation from ethanol gave unchanged starting material (361 mg.), m. p. 146—148°. Elution with benzene–ether (1 : 4) followed by crystallisation from methanol gave the diacetate (VI) (26 mg.), m. p. 165—166°, not depressed on admixture with an authentic specimen (from Dr. Davis). Elution with ether–chloroform (4 : 1, later 3 : 2) followed by crystallisation from ether–pentane gave 3β-hydroxycholest-5-en-7-one (VII) (30 mg.), m. p. 166—168°, not depressed on admixture with an authentic specimen. Elution with ether–chloroform (2 : 3) gave unidentified small needles (2 mg.), m. p. 139—141° (from methanol). Elution with chloroform resulted in an oil (18 mg.) which did not crystallise.

Action of X-*Rays on* 3β-*Hydroxypregn-5-en-20-one in Aqueous Acetic Acid.*—A saturated solution of the substance (IX) (2 g.) in aqueous acetic acid (600 ml., containing 10% of water) was exposed to *X*-rays for 15 hours at 30—35°. The acetic acid was removed at reduced pressure at 35—40° and the oily residue extracted with ether. The extract was washed successively with 2N-sodium carbonate, water, 2N-hydrochloric acid, and water. After being dried (Na_2SO_4), the ethereal solution was evaporated and the residue chromatographed through alumina (60 g.). Elution with light petroleum–benzene gave unchanged starting material (620 mg.). Elution with ether–chloroform mixtures and with chloroform, followed by crystallisation from methanol, gave plates (476 mg.), m. p. 246—248°, $[\alpha]_D^{18}$ + 18·1° ± 3° (*c*, 4·529 in chloroform) (Found : C, 70·3; H, 9·3. Calc. for $C_{23}H_{36}O_5$: C, 70·4; H, 9·2%), shown to be 6β-acetoxy-3β : 5α-hydroxy*allo*pregnan-20-one (X) by comparison with the substance described by Ehrenstein and Stevens (*J. Org. Chem.*, 1941, **6**, 908), who give $[\alpha]_D^{22\cdot5}$ + 11·8° in acetone. Elution with chloroform–methanol (20 : 1), followed by repeated crystallisation from methanol, gave prisms (550 mg.), m. p. 250—253° (Found : C, 71·7; H, 9·9. Calc. for $C_{21}H_{34}O_4$: C, 72·0; H, 9·8%), identified as 3β : 5α : 6β-trihydroxy*allo*pregnan-20-one (XI) by comparison with the substance described by Ehrenstein and Stevens (*loc. cit.*; *J. Org. Chem.*, 1939, **4**, 506).

Derivatives.—A solution of (X) (0·1 g.) in pyridine (2 ml.) and acetic anhydride (1 ml.) was kept for 18 hours at room temperature and then evaporated under reduced pressure. An ethereal extract of the

residue was washed till neutral and dried (Na_2SO_4) and after crystallisation from methanol gave the 3β : 6β-diacetate (XIII) (88 mg.; m.p. 215—217°; $[\alpha]_D^{17}$ −12·2° ± 3° (*c*, 3·283 in chloroform); Ehrenstein and Stevens (*J. Org. Chem.*, 1940, **5**, 318) give $[\alpha]_D^{18}$ −2·0° in acetone). When similarly treated, (IX) (0·1 g.) gave (XIII) (95 mg.), m. p. 215—217° [not depressed on admixture with the substance obtained from (X)] $[\alpha]_D^{17}$ −10·8° ± 2° (*c*, 1·016 in acetone) (Found: C, 68·9; H, 8·8. Calc. for $C_{25}H_{38}O_6$: C, 69·1; H, 8·8%).

Hydrolysis of (X) (100 mg.) with potassium hydroxide (100 mg.) in boiling methanol (2 ml.) and water (0·3 ml.) for 2 hours, addition of water (5 ml.), and removal of the methanol under reduced pressure gave a residue which was extracted with ether. Isolation as usual and crystallisation from methanol gave (XI), m. p. 250—253°, not depressed on admixture with the substance obtained directly by irradiation.

Oxidation of (X) (40 mg.) according to Ehrenstein and Stevens' method (*J. Org. Chem.*, 1941, **6**, 908) gave (XII) (29 mg.) as prisms, m. p. 216—217° (from alcohol) in agreement with their data.

Optical rotations were kindly measured by Drs. A. Ruff and R. Casanova at University College, Swansea, to whom our thanks are offered. The values agreed with those given in the literature except for (X) and (XIII) (see above); the reason for these differences, which are beyond experimental error, is not clear. M.p.s are uncorrected. Microanalysis were by Drs. Weiler and Strauss (Oxford).

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