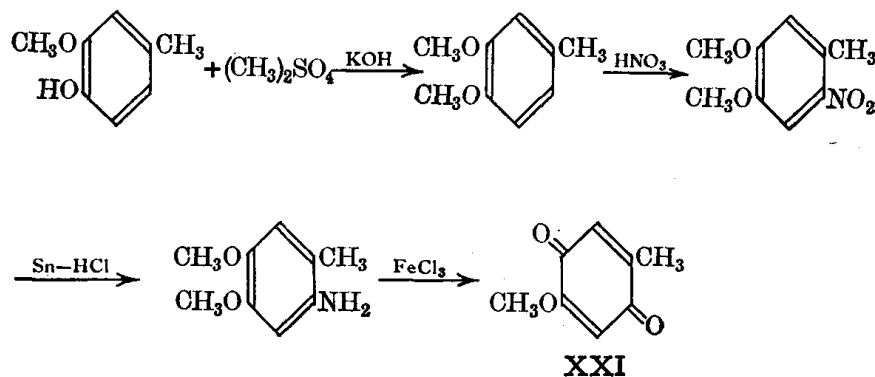


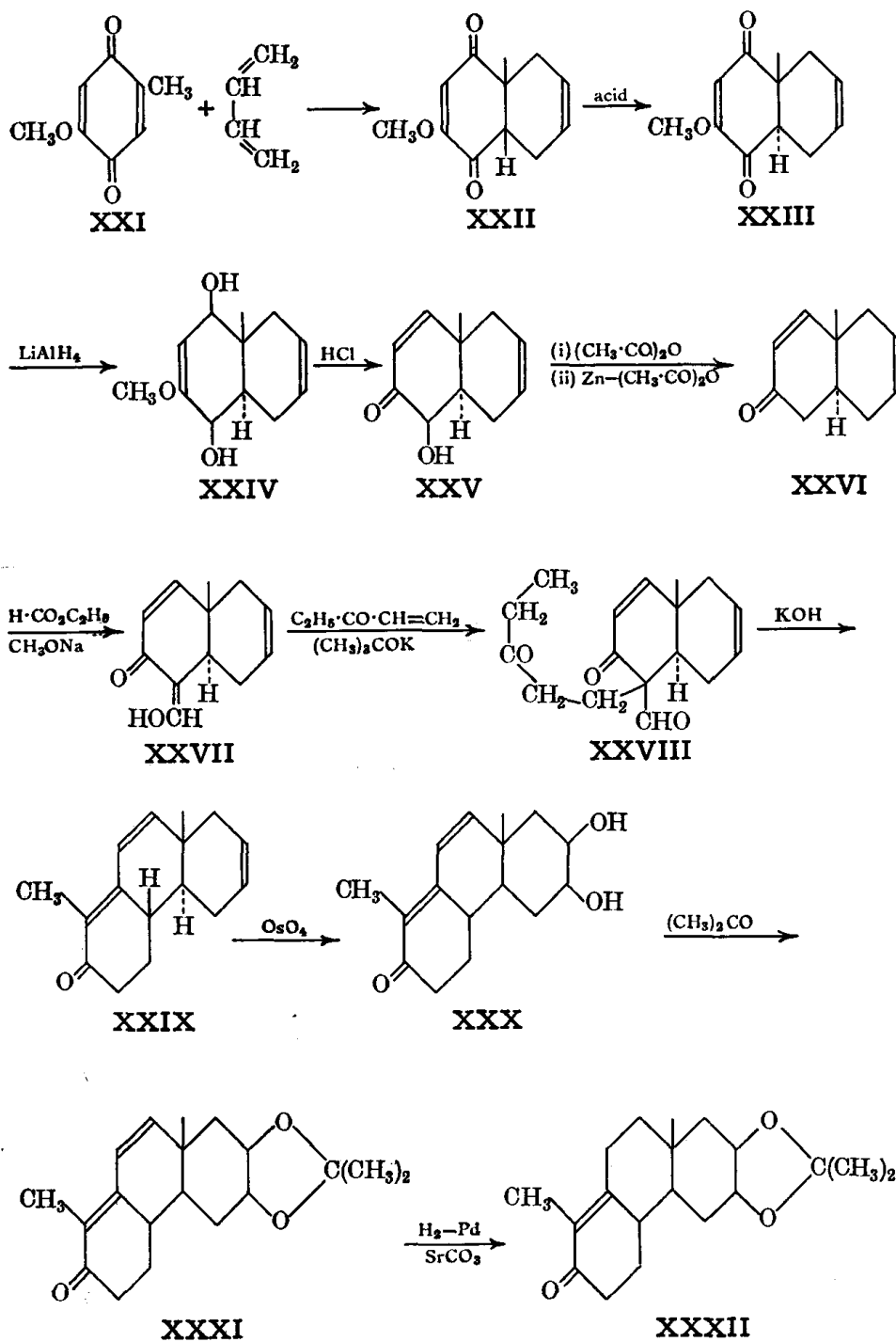
oxyl group in XX was shown to be attached to a tertiary carbon atom, and so it follows that there is a methyl group at 13 or 14. XX was then shown to have the *trans* configuration, *i.e.*, the two carboxyl groups are *trans*. Thus its precursor XIX must have its two rings in the *trans* configuration (the methyl group and hydrogen atom at the junction of the rings are thus *trans*). Theoretical considerations of the strain involved in the *cis*- and *trans*-forms of XIX suggest that the *cis*-form of XIX would have been obtained had the methyl group been at position 14. Thus the position of this angular methyl group appears (from this evidence) to be at 13, and this is supported by the fact that ætiobilianic acid (XV, section iii) gives 1 : 2-dimethylphenanthrene (XVI) on dehydrogenation with selenium. Had the angular methyl group been at position 14, 1-methylphenanthrene would most likely have been obtained.

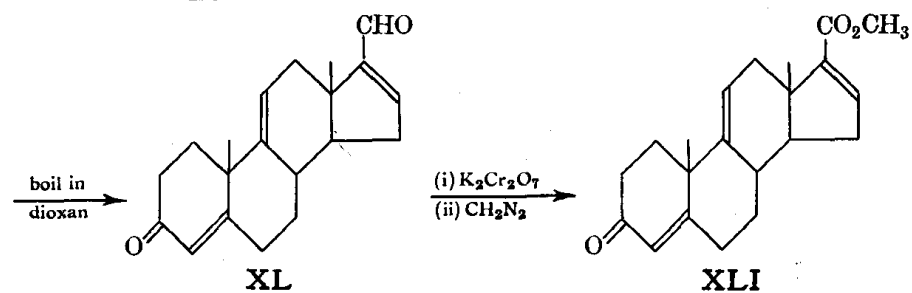
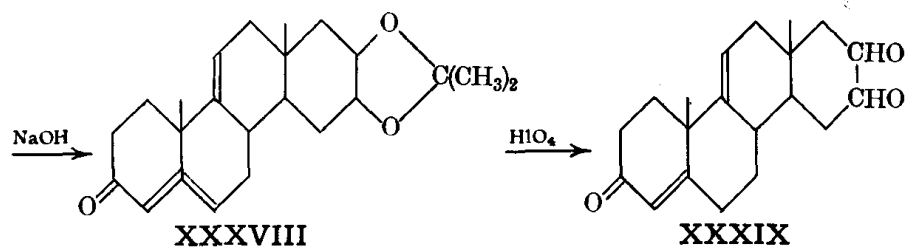
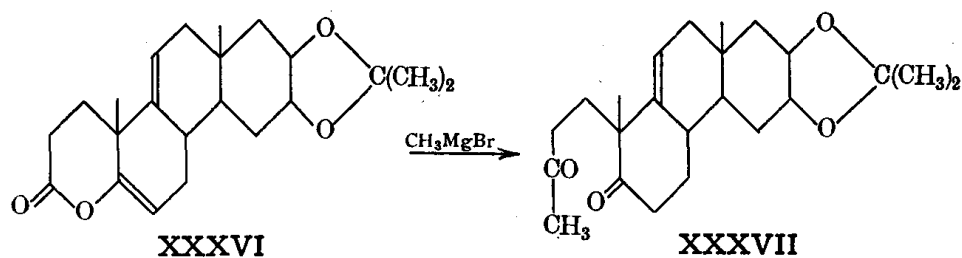
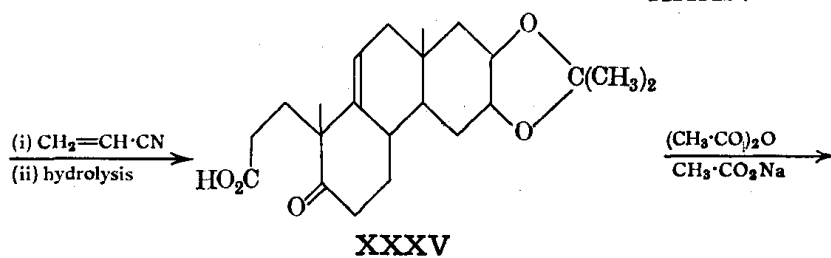
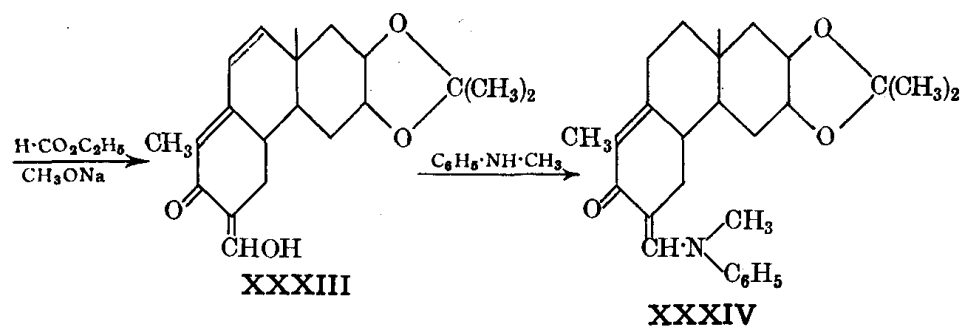
(v) **Synthesis of cholesterol.** Two groups of workers, *viz.*, Sir R. Robinson *et al.* (1951) and Woodward *et al.* (1951), have synthesised cholesterol. One of the outstanding difficulties in the synthesis of steroids is the stereochemical problem. The cholesterol nucleus contains eight asymmetric carbon atoms and so 256 optical isomers are possible (see also §4 for further details). Thus every step in the synthesis which produced a new asymmetric carbon atom had to result in the formation of some (the more the better) of the desired stereoisomer, and at the same time resolution of racemic modifications also had to be practicable. Another difficulty was attacking a particular point in the molecule without affecting other parts. This problem led to the development of specific reagents. The following is an outline of the Woodward synthesis. 4-Methoxy-2 : 5-toluquinone, XXI, was prepared from 2-methoxy-*p*-cresol as follows:

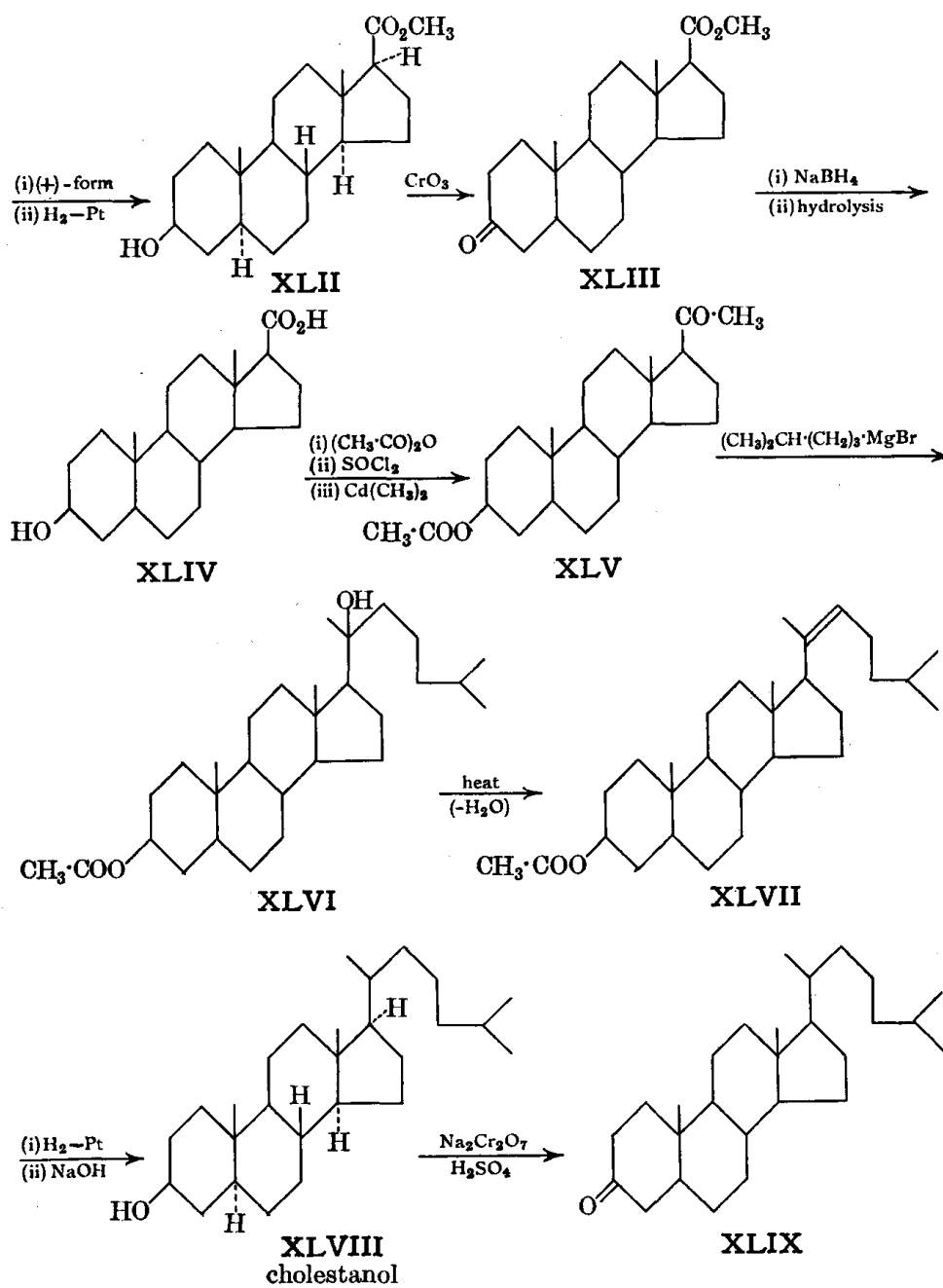


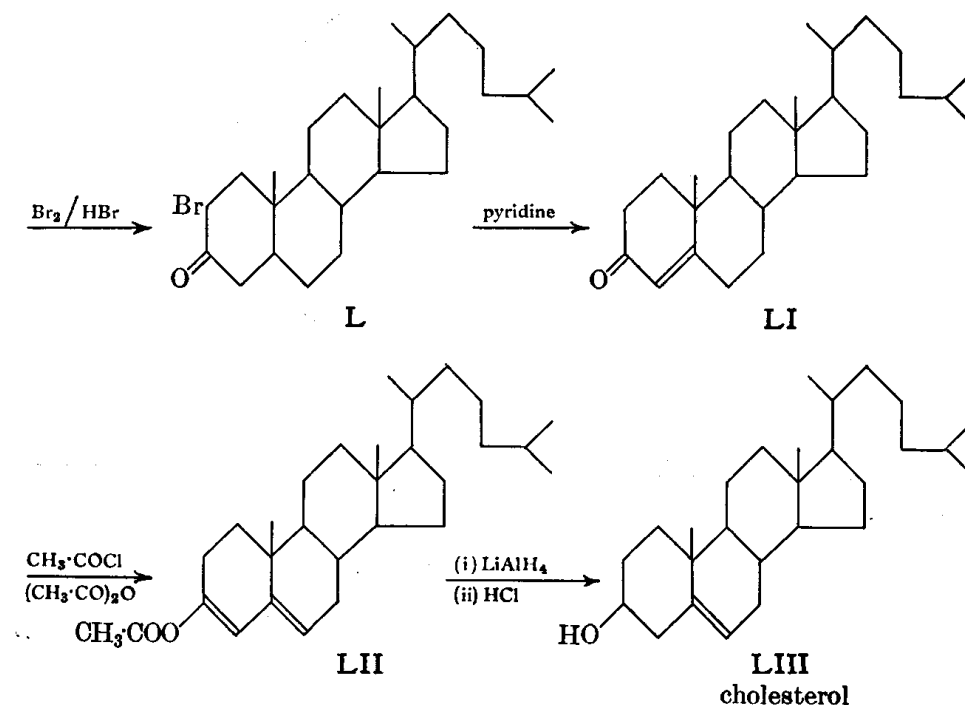
XXI was condensed with butadiene (Diels-Alder reaction) to give XXII. This had the *cis* configuration and was isomerised (quantitatively) to the *trans*-isomer XXIII by dissolving in aqueous alkali, adding a seed crystal of the *trans*-form, and then acidifying. XXIII, on reduction with lithium aluminium hydride, gave the glycol XXIV, and this, on treatment with aqueous acid, gave XXV. Conversion of XXV to XXVI by removal of the hydroxyl group was carried out by a new technique: XXV was acetylated and the product, the ketol acetate, was heated with zinc in acetic anhydride to give XXVI (reduction with metal and acid usually reduces α : β -unsaturated bonds in ketones). XXVI, on treatment with ethyl formate in the presence of sodium methoxide, gave the hydroxymethylene ketone XXVII (Claisen condensation). When this was treated with ethyl vinyl ketone in the presence of potassium *tert*-butoxide, XXVIII was formed (Michael condensation). The object of the double bond in the ketone ring in XXVI is to prevent formylation occurring on that side of the keto group, and the purpose of the formyl group is to produce an active methylene

group (this is now flanked on *both* sides by carbonyl groups). The necessity for this "activation" lies in the fact that ethyl vinyl ketone tends to self-condense, and consequently decrease the yield of XXVIII. XXVIII was now cyclised (quantitatively) by means of potassium hydroxide in aqueous dioxan to the single product XXIX. This is the desired compound; the other possible isomer (XXIX with the two hydrogens *cis* instead of *trans* as shown) is not formed since the *cis*-isomer is less stable than the *trans*-. XXIX was then treated with osmium tetroxide to give two *cis*-glycols of structure XXX. These were separated, and the desired isomer (the one insoluble in benzene) was treated with acetone in the presence of anhydrous copper sulphate to give the *isopropylidene* derivative XXXI. This, on catalytic reduction (H_2 -Pd/SrCO₃) gave XXXII which was condensed with ethyl formate in the presence of sodium methoxide to give XXXIII, and this was then converted into XXXIV by means of methylaniline. The purpose of this treatment was to block undesired condensation reactions on this side of the keto group (at this position 3). When XXXIV was condensed with vinyl cyanide (cyanoethylation) and the product hydrolysed with alkali, the product was a mixture of two keto acids. These were separated and the stereoisomer XXXV (methyl group in front and propionic acid group behind the plane of the rings) was converted into the enol lactone XXXVI which, on treatment with methylmagnesium bromide, gave XXXVII, and this, on ring closure by means of alkali, gave XXXVIII. When this was oxidised with periodic acid in aqueous dioxan, the dialdehyde XXXIX was obtained, and this, when heated in benzene solution in the presence of a small amount of piperidine acetate, gave XL (and a small amount of an isomer). This ketoaldehyde was oxidised to the corresponding acid which was then converted into the methyl ester XLI with diazomethane. XLI, a racemate, was resolved by reduction of the keto group with sodium borohydride to the hydroxy esters [(\pm)-3 α - and (\pm)-3 β -]. The (+)-form of the 3 β -alcohol was preferentially precipitated by digitonin, and this stereoisomer was now oxidised (Oppenauer oxidation) to give the desired stereoisomer (+)-XLI. This was catalytically reduced (H_2 -Pt) to XLII, which was then oxidised to XLIII which was a mixture of stereoisomers (from the mixture of XLII; H at 17 behind and in front). These were separated, reduced (sodium borohydride), and hydrolysed. The β -isomer, XLIV, was converted into the methyl ketone by first acetylating, then treating with thionyl chloride and finally with dimethylcadmium. This acetylated hydroxyketone, XLV, on treatment with *isohexylmagnesium* bromide, gave XLVI. This was a mixture of isomers (a new asymmetric carbon has been introduced at position 20). XLVI, on dehydration, gave one product, XLVII, and this, on catalytic hydrogenation (H_2 -Pt), gave a mixture of cholestanyl acetates (the asymmetric C₂₀ has been re-introduced). These acetates were separated and the desired isomer, on hydrolysis, gave cholestanol, XLVIII, which was identical with natural cholestanol. The conversion of cholestanol into cholesterol, LIII, is then carried out by a series of reactions introduced by various workers: XLVIII to XLIX (Bruce, 1943); XLIX to L (Butenandt *et al.*, 1935); L to LI (Ruzicka, 1938); LI to LII (Westphal, 1937); LII to LIII (Dauben *et al.*, 1950).

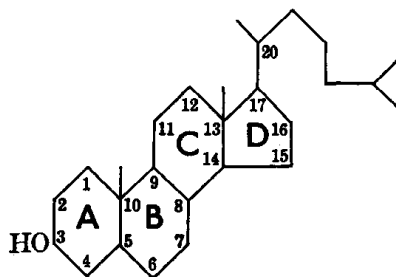








§4. Stereochemistry of the steroids. If we examine the fully saturated sterol, we find that there are eight dissimilar asymmetric carbon atoms in the nucleus (3, 5, 8, 9, 10, 13, 14 and 17). Thus there are $2^8 = 256$ optical isomers possible. If we also include the asymmetric carbon atom in the side-chain (20), then there are 512 optical isomers possible.



The stereoisomerism of the steroids is conveniently classified into two types, one dealing with the way in which the rings are fused together, and the other with the configurations of substituent groups, particularly those at C_3 and C_{17} .

§4a. Configuration of the nucleus. There are six asymmetric carbon atoms in the nucleus (5, 8, 9, 10, 13 and 14), and therefore there are $2^6 = 64$ optically active forms possible. X-ray analysis has shown that the steroid molecule is long and *thin*, *i.e.*, the molecule is essentially *flat* (Bernal, 1932). This is only possible if rings B and C are fused together in a *trans* manner (*cf.* *trans*-decalin, §11 vii. IV); rings A/B and C/D could be *cis* or *trans*. It has been found that all naturally occurring saturated steroids, except those of the heart poisons, belong either to the *cholestane series* or to the *coprostane series*; in the former the rings A/B are *trans*, and in the latter *cis*, the rings B/C and C/D being *trans* in *both* series. By convention a full line represents groups above the plane of the molecule, and a dotted (or broken) line represents groups below the plane (see also §11 vii. IV for