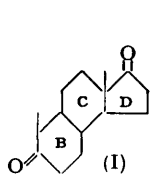
221. *Experiments on the Synthesis of Substances related to the Sterols. Part L. The A→BCD Route. Part III.**

By A. R. Pinder and Sir Robert Robinson.

The oily, tricyclic ketone obtained by Inhoffen and Huang-Minlon (*Ber.*, 1939, **72**, 1686) by the ozonolysis of cholesta-1 : 4-dien-3-one has been obtained crystalline (m. p. 52°), and an improved method of preparation devised. The ketone has been converted into the Windaus keto-acid (VII) which has already been converted by way of cholestenone into cholesterol.

Some model experiments with 1-methyl-*cis*-2-decalone and 1-methyl-*trans*-2-decalone are described, and a new synthesis of the latter ketone is reported. A striking contrast in the reactivity of these ketones was encountered in connexion with their conversion into hydrophenanthrene derivatives.

In Part XLI (Martin and Robinson *J.*, 1943, 491) and Part XLIX (*idem*, *J.*, 1949, 1866) an attempt to add ring A to the synthetic BCD tricyclic diketone (I), using the Mannich-base methiodide reaction, was described. The product was shown to be a mixture of stereoisomerides of the BCDE tetracyclic ketone (II), rather than of stereoisomeric androstenediones (III).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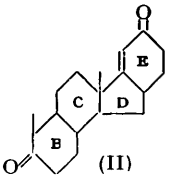
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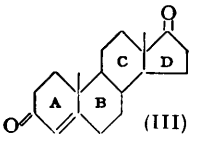
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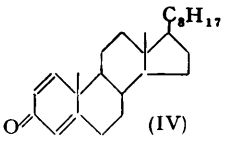
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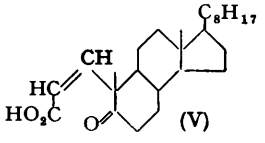
The objective of the present experiments was to achieve the addition of ring A to a BCD-tricyclic substance which latter, it was hoped, might eventually be linked with the BCD synthetic series. The first stage of this programme has been realised and a brief preliminary announcement has been made (*Nature*, 1951, **167**, 484).

In 1938, Inhoffen and Huang-Minlon (*Ber.*, 1938, **71**, 1720) showed that the ozonolysis of cholesta-1 : 4-dien-3-one (IV) gave an unsaturated acid (V), ring A in the dienone being ruptured. Subsequently, the same authors found that the acid was accompanied by a neutral product, considered to be the BCD-tricyclic ketone (VI) (*Ber.*, 1939, **72**, 1686), which was oily but formed a crystalline semicarbazone.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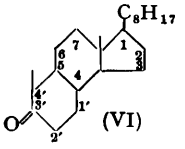
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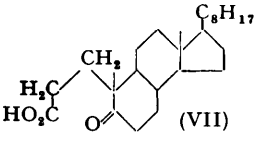
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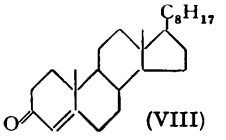

(VIII)

We have re-investigated the formation of this neutral ketone and have confirmed its assumed relation to cholestenone and its structure as 1-(1 : 5-dimethylhexyl)perhydro-3′-keto-7*a* : 4′-dimethyl-4 : 5-benzindene (VI).† After model experiments with simple 2-decalones, the ketone was successfully converted into the keto-acid (VII), obtained as a degradation product of cholestenone by Windaus (*Ber.*, 1906, **39**, 2008). This acid has recently been converted into cholest-4-en-3-one (VIII) (Turner, *J. Amer. Chem. Soc.*,

* Part XLIX and Part II, *J.*, 1949, 1866.

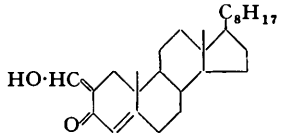
† This name is cumbrous and we suggest that cholestane stripped of the four methylene groups of ring A could be termed *des-A-cholestane*. It will be simplest in this case to retain the cholestane numbering system and Inhoffen's ketone becomes des-A-cholestan-5-one.

This system is especially useful for derivatives; the substance itself can still be termed the Inhoffen ketone.

Furthermore, the des-names specify the stereochemistry which is neglected in the systematic name used above and added in the Experimental section.

(" des " is preferred to the customary British " de " in this usage so as to avoid ambiguity in speech; *e.g.*, des-D is preferable in speech to de-D.)

1950, **72**, 579), which has in turn been converted into cholesterol (Dauben and Eastham, *ibid.*, p. 2305; Birch, *J.*, 1950, 2325).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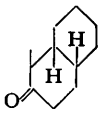
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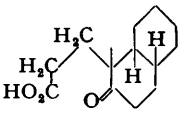
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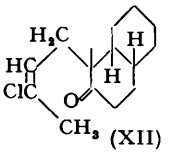
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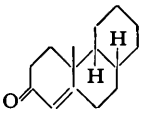

(XIII)

Cholesta-1 : 4-dien-3-one (IV) was prepared by dehydrobromination of 2 : 4-dibromocholestan-3-one (Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712). We have found that by starting with the pure dibromo-ketone yields of 70% of the pure dienone (m. p. 111—111·5°) could be obtained without adopting the tedious chromatographic purification described by these authors. Ozonolysis of the dienone gave a neutral gum, which when purified by adsorption on alumina gave a 15% yield of the crystalline Inhoffen ketone, m. p. 52°. The ketone was first obtained crystalline, m. p. 42°, in this laboratory by Dr. R. P. A. Sneeden (Thesis, Oxford, 1950).

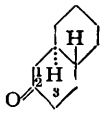
During attempts to improve the preparation it was found that oxidation of the dienone (IV) by permanganate also afforded the ketone, though in smaller yield. A more convenient method was the permanganate oxidation of 2-hydroxymethylenecholest-4-en-3-one (IX), obtained by the condensation of cholestenone and ethyl formate with the help of sodium methoxide. The idea here was to sensitise the ring-A carbon atoms by progressive enolisation.

With the object of finding the best method of adding ring A to the Inhoffen ketone, the behaviour of two model ketones in standard reactions was studied. It was realised that 1-methyl-*cis*-2-decalone (X) * was not a suitable model, because of the *cis*-decalin system present, yet it was felt that it would be of interest to study its reactions, as it was comparatively readily available (Robinson and Weygand, *J.*, 1941, 391). The addition of acrylonitrile to this ketone (cf. Bruson, "Organic Reactions," Vol. V, p. 79, New York, 1949) gave, after hydrolysis, a monocarboxylic acid in high yield. The structure (XI) has been assigned to this acid, since *cis*-2-decalones are known to be more reactive at $C_{(1)}$ than at $C_{(3)}$ (Butenandt and Wolff, *Ber.*, 1935, **68**, 2091). Further, the reactivity of acrylonitrile is such that substitution usually occurs at all reactive positions in the ketone (Bruson, *loc. cit.*); the monocarboxylic character of the only acid isolated from the reaction suggests that the side-chain is at $C_{(1)}$. This is in harmony with Robinson and Weygand's observation (*loc. cit.*) that condensation of 1-methyl-*cis*-2-decalone with diethylaminobutanone methiodide gave the reduced phenanthrene ketone (XIII) exclusively, none of the isomeric ketone with an anthracene skeleton being obtained. Further, we have observed that condensation of the decalone with 1 : 3-dichlorobut-2-ene (cf. Wichterle, *Coll. Czech. Chem. Comm.*, 1947, **12**, 93; 1948, **13**, 300; Prelog, Barman, and Zimmermann, *Helv. Chim. Acta*, 1949, **32**, 1284) gives 1-(3-chlorobut-2-enyl)-1-methyl-*cis*-2-decalone (XII), which cyclises smoothly in sulphuric acid to give the tricyclic ketone (XIII), identical with Robinson and Weygand's product.

A better model ketone was 1-methyl-*trans*-2-decalone (XVII), which Rao and Kuppuswamy (*J. Annamalai Univ.*, 1937, **7**, 22) claim to have prepared by direct methylation of *trans*-2-decalone (XIV) with sodamide and methyl iodide. It is, however, doubtful if their product contained any of the desired ketone, in view of the greater reactivity of *trans*-2-decalone at $C_{(3)}$ (Butenandt and Wolff, *loc. cit.*). English and Cavaglieri (*J. Amer. Chem. Soc.*, 1943, **65**, 1088) prepared the ketone by a series of steps from *trans*-1-decalone, the over-all yield being 20%. We have synthesised the ketone from the accessible *trans*-2-decalol (m. p. 75°), oxidation of which by means of chromic acid gave *trans*-2-decalone (XIV) (Hückel, *Annalen*, 1925, **441**, 19). Necessary blockage of the 3-position in *trans*-

* In this and other decalin formulæ, the sterol convention of full and broken lines is used for the ring-junction hydrogen atoms. It is not however intended to specify the configuration at other positions of the decalin rings.

2-decalone was effected by condensation with ethyl formate, giving 3-hydroxymethylene-*trans*-2-decalone (XV), which condensed with methylaniline (cf. Birch and Robinson, *J.*, 1944, 501) furnishing 3-methylanilinomethylene-*trans*-2-decalone (XVI). Methylation of this compound, followed by removal of the blocking group and prolonged treatment with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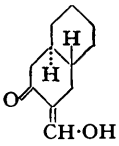
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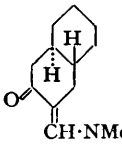
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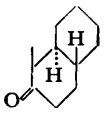
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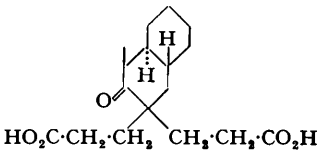
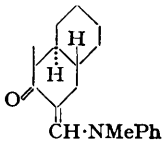

(XVIII)

alkali (cf. Hückel, *loc. cit.*), gave a stereochemically homogeneous ketone, one of the two forms of 1-methyl-*trans*-2-decalone (XVII). The product was identical with that of English and Cavaglieri (*loc. cit.*). We are grateful to Professor J. English, of Yale University, for providing specimens for comparison. The identity of these products provides formal proof that, in its reaction with ethyl formate, *trans*-2-decalone is attacked at $C_{(3)}$.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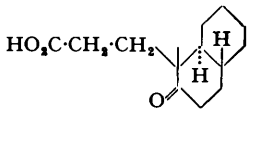
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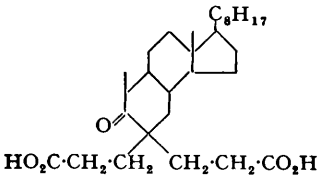
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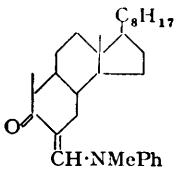
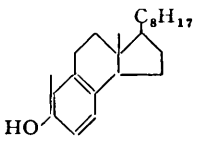

(XXII)

The reaction of 1-methyl-*trans*-2-decalone with acrylonitrile (1 mol.), followed by hydrolysis, gave a 40% yield of a dicarboxylic acid $C_{11}H_{16}O(CH_2{\cdot}CH_2{\cdot}CO_2H)_2$. We have formulated this acid as (XVIII), since the parent ketone is more reactive at $C_{(3)}$ than at $C_{(1)}$. This behaviour is in marked contrast to that of 1-methyl-*cis*-2-decalone. 1-Methyl-*trans*-2-decalone was reconverted into 1-methyl-3-methylanilinomethylene-*trans*-2-decalone (XIX; already made in a less homogeneous form by methylation of XVI), which reacted with acrylonitrile to give, after hydrolysis and elimination of the methylanilinomethylene group, 1-2′-carboxyethyl-1-methyl-*trans*-2-decalone (XX), in 10% yield.

Turning to the Inhoffen ketone, we attempted unsuccessfully to convert the ketone directly into cholestenone (VIII) by condensation with diethylaminobutanone methiodide, or with 1 : 3-dichlorobut-2-ene. Reaction of the ketone with acrylonitrile gave, after hydrolysis, a dicarboxylic acid, formulated by analogy as (XXI). Blockage of the 7-position in the ketone by the usual technique gave the 7-methylanilinomethylene ketone (XXII). The reaction of the latter with acrylonitrile, followed by hydrolysis and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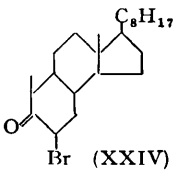
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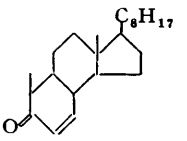
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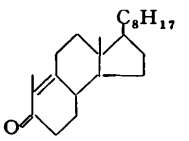
(XXVI)

removal of the blocking group, gave a small yield of a crystalline, monocarboxylic acid, m. p. 154°, which was identical in all respects with an authentic specimen of the Windaus keto-acid (VII), prepared by the ozonolysis of cholest-4-en-3-one (Turner, *loc. cit.*). We are grateful to Mrs. D. M. Hodgkin, who kindly carried out *X*-ray crystallographic investigations of the two specimens and reported that they were identical. The chain of reactions whereby Inhoffen ketone may be transformed into cholesterol is now complete.

We are now attempting the dehydrogenation of ring B of the Inhoffen ketone, the objective being the phenol (XXIII). Direct dehydrogenation of the ketone with sulphur, selenium, or palladium–charcoal has not given a phenolic product, owing to elimination of

the oxygen atom. Bromination of the ketone with an excess of bromine gave a monobromo-ketone, dehydrobromination of which with collidine gave an enone whose ultraviolet absorption spectrum showed $\lambda_{max.}$ 235 mμ (ε_{molar} = 15 850). The product is evidently des-A-cholest-6-en-5-one (XXV) [$\lambda_{max.}$ (calc.) 227 mμ] rather than (XXVI) [$\lambda_{max.}$ (calc.) 254 mμ], and the intermediate bromo-ketone is 6-bromodes-A-cholesten-5-one (XXIV). Efforts to dehydrogenate (XXV) to (XXIII) have not so far proved successful, nor has it been found possible to introduce a second bromine atom into (XXIV) at $C_{(10)}$.

Experimental

(Alumina was Type A from Messrs. Peter Spence & Co.)

1-*Methyl*-cis-2-*decalone* (X).—Methylenebis-2-naphthol (Fries and Hübner, *Ber.*, 1906, **39**, 440) was reduced to 1-methyl-2-naphthol (Cornforth, Cornforth, and Robinson, *J.*, 1942, 682) and then to stereoisomeric 1-methyl-*cis*-2-decalols (Robinson and Weygand, *loc. cit.*). Chromic acid oxidation of the decalol gave 1-methyl-2-decalone (one of the two possible *cis*-forms; Robinson and Weygand, *loc. cit.*). The ketone distilled at 140—145° (bath)/12 mm. and gave a semicarbazone, elongated colourless prisms, m. p. 183—184° (Found: N, 19·0. Calc. for $C_{12}H_{21}ON_3$: N, 18·8%). Robinson and Weygand (*loc. cit.*) give m. p. 185—191°.

1-2′-*Carboxyethyl*-1-*methyl*-cis-2-*decalone* (XI).—"Triton B" (1 c.c.; commercial 20% aqueous benzyltrimethylammonium hydroxide; Rohm and Haas Inc.), followed by acrylonitrile (0·38 g., 1 mol.), was added with shaking and cooling to a solution of 1-methyl-*cis*-2-decalone (1·2 g.) in dioxan (5 c.c.). After 48 hours at room temperature the solution was acidified and the dioxan evaporated *in vacuo*. The residual oil, isolated with ether, was heated under reflux for 20 hours with aqueous potassium hydroxide (30 c.c. of 20%). The cooled solution was diluted with water, and neutral matter extracted with ether. Acidification and ether-extraction of the alkaline solution gave a colourless gum (1·0 g.) which soon crystallised. 1-2′-*Carboxyethyl*-1-*methyl*-cis-2-*decalone* crystallised from dilute acetic acid in clusters of small, colourless, prisms m. p. 116° (Found: C, 70·1; H, 9·2%; equiv., 236·0. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·2%; equiv. 238).

$\Delta^{1(11)}$-*Dodecahydro*-2-*keto*-12-*methylphenanthrene* (XIII).—A solution of 1-methyl-*cis*-2-decalone (4·15 g.; 1 mol.) in dry ether (25 c.c.) was added to a cooled ethereal solution of triphenylmethylsodium (190 c.c. of 0·13M), under nitrogen. After 30 minutes a solution of 1 : 3-dichlorobut-2-ene (3·2 g., 1 mol.) in dry ether (20 c.c.) was introduced with cooling and swirling. Next day the mixture was refluxed on the steam-bath for 3 hours; some sodium chloride then separated. The cooled mixture was poured into water, and the organic layer separated, dried, and distilled. The residual syrup was mixed with a little methanol and kept at 0° for several hours, after which crystals of triphenylmethane were collected and washed with cold methanol. Evaporation of the filtrate left an oil which was distilled. The fore-run, b. p. 120—150° (bath)/0·09 mm. (3·1 g.), was mainly unchanged ketone. The next fraction, b. p. 150—170° (bath)/0·09 mm. (1·7 g.), was 1-(3-chlorobut-2-enyl)-1-methyl-*cis*-2-decalone (XII). Sulphuric acid (4 c.c.) was added with cooling and the mixture kept until the evolution of hydrogen chloride ceased (*ca.* 3 hours). Ice was added and the product isolated by means of ether. The yellow gum (1·48 g.) which contained some triphenylmethane was taken up in light petroleum (b. p. 40—60°), and the solution passed through an alumina column. A pale yellow (in ultra-violet light) band was obtained uppermost; elutions with ether and methanol gave $\Delta^{1(11)}$-*dodecahydro*-2-*keto*-12-*methylphenanthrene* as a pale yellow oil (0·3 g.), b. p. 165—170° (bath)/0·08 mm. (Found: C, 82·3; H, 10·0. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%). The ultra-violet absorption spectrum showed a maximum at 245 mμ (log ε_{molar} = 3·6).

The semicarbazone separated from absolute alcohol in small needles, m. p. 224—225° (decomp.) (Found: C, 70·2; H, 8·9; N, 14·4. Calc. for $C_{16}H_{25}ON_3$: C, 69·8; H, 9·1; N, 15·3%). Robinson and Weygand (*loc. cit.*) give m. p. 225—230° (decomp.).

trans-2-*Decalone* (XIV).—Oxidation of commercially available *trans*-2-decalol (m. p. 75°) with chromic acid gave *trans*-2-decalone in 75% yield (Hückel, *Annalen*, 1925, **441**, 19), purified through its bisulphite compound. The ketone distilled at 128—129°/23 mm.

3-*Methylanilinomethylene*-trans-2-*decalone* (XVI).—Alcohol-free sodium methoxide (from 1·5 g. of sodium) was suspended in dry ether (65 c.c.) and powdered as thoroughly as possible. Ethyl formate (5·0 g.) was added with shaking and cooling, followed by *trans*-2-decalone (5·0 g.) in dry ether (10 c.c.), dropwise. Next morning, the mixture was decomposed with ice, and the organic layer separated and washed with dilute alkali. Acidification of the combined alkaline solutions furnished a yellow oil which was taken up in ether. Evaporation of the dried ethereal

solution gave 3-hydroxymethylene-*trans*-2-decalone (XV) as a yellow syrup (5·8 g.) which was not purified; it gave a purple ferric reaction.

A mixture of the hydroxymethylene-ketone (11·9 g.), freshly distilled methylaniline (7·5 g.), and benzene (100 c.c.) was distilled slowly from the steam-bath during 2 hours (cf. Birch and Robinson, *J.*, 1944, 501), the remaining benzene being removed *in vacuo*. The residual orange-red oil (18·0 g.) crystallised entirely when kept. 3-*Methylanilinomethylene*-trans-2-*decalone* separated from light petroleum (b. p. 60—80°) in yellow, elongated prisms, m. p. 87° (Found: C, 80·2; H, 8·4. $C_{18}H_{23}ON$ requires C, 80·3; H, 8·6%).

1-*Methyl*-2-*decalone* (trans-*forms*) (XVII).—A solution of 3-methylanilinomethylene-*trans*-2-decalone (9·0 g., 1 mol.) in dry ether (120 c.c.) was added to a cooled ethereal solution of triphenylmethylsodium (280 c.c. of 0·12M), under a nitrogen atmosphere during 15 minutes, with swirling; methyl iodide (10 g., 2·1 mol.) in dry ether 25 c.c. was then introduced. The mixture was refluxed gently on the steam-bath for 2 hours, then poured into water, and the organic layer separated, dried, and evaporated. The oily residue was refluxed for 30 minutes with 10% hydrochloric acid (200 c.c.), and the mixture cooled and extracted with ether. The ethereal solution was extracted several times with cold, dilute alkali, and the combined alkaline solutions were acidified. The oil liberated was taken up in ether, the ether evaporated, and the residue hydrolysed by boiling it with sodium hydroxide solution (60 c.c. of 15%) for 30 minutes. The cooled mixture was extracted several times with ether. Evaporation of the solvent gave a mixture of the two forms of 1-methyl-*trans*-2-decalone, which distilled at 110—113°/10 mm. (3·9 g.) (Found: C, 79·3; H, 11·0. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

The 2 : 4-dinitrophenylhydrazone separated from alcohol in clusters of orange needles, m. p. 171—172° with previous softening at 165° (Found: C, 58·8; H, 6·3; N, 15·9. Calc. for $C_{17}H_{22}O_4N_4$: C, 58·9; H, 6·3; N, 16·2%). The semicarbazone crystallised from alcohol in colourless needles, m. p. 198—199° with previous softening at 195° (Found: C, 64·4; H, 9·3. Calc. for $C_{12}H_{21}ON_3$: C, 64·6; H, 9·4%).

By boiling the product (3·5 g.) under reflux for 16 hours with 4N-potassium hydroxide (60 c.c.), it was converted into a stereochemically homogeneous ketone, one of the two forms of 1-methyl-*trans*-2-decalone, isolated with ether. The ketone distilled at 110°/11 mm. (Found: C, 79·1; H, 11·1. Calc. for $C_{11}H_{18}O$: C, 79·5; H, 10·8%).

The 2 : 4-dinitrophenylhydrazone separated from alcohol in orange needles, m. p. 171—172° with no previous softening. The semicarbazone separated from alcohol in colourless prisms, m. p. 204—205°, with no previous softening. These two derivatives showed no m. p. depression on admixture respectively with specimens kindly supplied by Professor J. English, of Yale University (English and Cavaglieri, *loc. cit.*).

3 : 3-*Bis*-2′-*carboxyethyl*-1-*methyl*-trans-2-*decalone* (XVIII).—The reaction of 1-methyl-*trans*-2-decalone (2·0 g.) (stereochemically homogeneous) in dioxan (10 c.c.) with acrylonitrile (0·64 g.), in the presence of " Triton B " under the usual conditions, furnished an oil which on hydrolysis gave an acidic gum (1·0 g.) which crystallised readily. 3 : 3-*Bis*-2′-*carboxyethyl*-1-*methyl*-trans-2-*decalone* separated from acetone in colourless rods, m. p. 192° (Found: C, 65·7; H, 8·1%; equiv., 153·2. $C_{17}H_{26}O_5$ requires C, 65·8; H, 8·4%; equiv., 155).

1-*Methyl*-3-*methylanilinomethylene*-trans-2-*decalone* (XIX).—This compound, an intermediate in the conversion of 3-methylanilinomethylene-*trans*-2-decalone (XVI) into 1-methyl-*trans*-2-decalone, was made in a pure state from the latter substance. Condensation of 1-methyl-*trans*-2-decalone (3·3 g.) with ethyl formate (3·0 g.) in the presence of sodium methoxide (from 1·0 g. of sodium) under the usual conditions furnished 3-hydroxymethylene-1-methyl-*trans*-2-decalone (3·8 g.) as a syrup. This was heated on the steam-bath with benzene (40 c.c.) and methylaniline (2·2 g.) for 2 hours, and the solvent slowly distilled. 1-*Methyl*-3-*methylanilinomethylene*-trans-2-*decalone*, isolated in the usual manner, separated from light petroleum (b. p. 60—80°) in pale yellow prisms (4·0 g.), m. p. 105° (Found: C, 80·8; H, 9·0. $C_{19}H_{25}ON$ requires C, 80·6; H, 8·8%).

1-2′-*Carboxyethyl*-1-*methyl*-trans-2-*decalone* (XX).—" Triton B " (3 c.c.), followed by acrylonitrile (0·72 g.), was added with cooling to a solution of 1-methyl-3-methylanilinomethylene-*trans*-2-decalone (3·5 g.) in dioxan (20 c.c.). After 60 hours at room temperature, the solution was acidified and the dioxan evaporated *in vacuo*. The oil which separated was isolated by means of ether and heated under reflux for 30 minutes with hydrochloric acid (60 c.c. of 10%). The solution was cooled and the organic material isolated with ether and heated under reflux for 20 hours with aqueous potassium hydroxide (80 c.c. of 20%). The cooled, diluted solution was freed from neutral matter with ether and acidified. The liberated acid was taken up in ether; evaporation gave a gum (0·4 g.) which crystallised on trituration with acetone.

1-2′-*Carboxyethyl*-1-*methyl*-trans-2-*decalone* separated from acetone in glistening, elongated prisms, m. p. 139—140° (Found : C, 70·7; H, 9·2%; equiv., 238·2. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·2%; equiv., 238).

An uncrystallisable gum (0·2 g.) obtained from the acetone mother-liquors may consist in part of the epimeric form of the acid.

Cholesta-1 : 4-*dien*-3-*one* (IV).—The following modification of the procedure of Wilds and Djerassi (*loc. cit.*) gave consistent yields of 70% of pure material, m. p. 111—111·5°. A solution of pure 2 : 4-dibromocholestan-3-one (5 g.; m. p. 193—194°; Wilds and Djerassi, *loc. cit.*) in purified collidine (20 c.c.) was heated under reflux at 185° (bath-temp.) for 80 minutes. The cooled solution was filtered and the collidine hydrobromide (theoretical yield) thoroughly washed with ether. The ether and excess of collidine were evaporated, finally *in vacuo*, and the dark, oily residue taken up in ether. The ethereal solution was washed in turn with dilute acid, sodium hydrogen carbonate solution, and water, then dried, and the solvent was evaporated. The brown residual oil crystallised readily; crystallisation from a small volume of light petroleum (b. p. 40—60°) gave cholesta-1 : 4-dien-3-one as pale fawn-coloured rhombs, m. p. 111—111·5° (2·5 g., 71%). Wilds and Djerassi (*loc. cit.*) give m. p. 110—112°. The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate in minute, deep-red prisms, m. p. 184—185° (Found : C, 70·2; H, 8·2. Calc. for $C_{33}H_{46}O_4N_4$: C, 70·5; H, 8·2%). Djerassi (*J. Amer. Chem. Soc.*, 1949, **71**, 1008) gives m. p. 183—184°.

1-(1 : 5-*Dimethylhexyl*)*perhydro*-3′-*keto*-7a : 4′-*dimethyl*-4 : 5-*benzindene* (*Inhoffen's ketone ; des*-A-*cholestan*-5-*one*) (VI).—The following modification of Inhoffen and Huang-Minlon's procedure (*loc. cit.*) was employed. A solution of cholesta-1 : 4-dien-3-one (3 g.) in acetic acid (10 c.c.) was ozonised for 24 hours at room temperature. The solution was diluted with water (30 c.c.) and refluxed for 30 minutes. The cooled, oily suspension was diluted with water and extracted twice with ether. The ethereal solution was thoroughly extracted with 5% aqueous potassium hydroxide, washed with water, and dried. Evaporation of the ether gave a pale yellow gum (0·8 g.) which did not crystallise. It was dissolved in light petroleum (b. p. 40—60°) and adsorbed on a 10-cm. column of alumina (*ca.* 10 g.). The ketone formed a pale-blue band, easily visible in ultra-violet light, and easily eluted with 1 : 1 light petroleum (b. p. 40—60°)–benzene. Evaporation of the eluate gave an almost colourless oil (0·4 g.) which crystallised entirely, m. p. 51—52°. *Des*-A-*cholestan*-5-*one* separated from light petroleum (b. p. 40—60°), with ice-cooling, in fine, white prisms, m. p. 52°, $[\alpha]_D^{18}$ +14·2° in chloroform (Found : C, 83·4; H, 12·1. $C_{23}H_{40}O$ requires C, 83·1; H, 12·1%). The semicarbazone separated from ethanol in minute, elongated prisms, m. p. 225—226° (decomp.). Inhoffen and Huang-Minlon (*loc. cit.*) give m. p. 224—225° (decomp.). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in clusters of orange-yellow prisms, m. p. 179° (Found : C, 68·0; H, 8·7. $C_{29}H_{44}O_4N_4$ requires C, 68·0; H, 8·6%).

Acidification of the alkaline washings gave des-A-cholestan-5-one-10-β-acrylic acid (V) (2·1 g.) as a gum which crystallised readily. The acid separated from acetone in colourless needles, m. p. 206—207° (Found : equiv., 400·1. Calc. for a monobasic acid $C_{26}H_{42}O_3$: equiv., 402). Inhoffen and Huang-Minlon (*loc. cit.*) give m. p. 207—207·5°.

Alternative Methods of Preparation of the Inhoffen Ketone.—(a) *Permanganate oxidation of cholesta*-1 : 4-*dien*-3-*one*. A solution of cholestadienone (3 g.) in acetone (100 c.c.) was stirred at 0° during the addition of powdered potassium permanganate (9·0 g.) over 15 minutes. Stirring was continued for 2 hours, after which the mixture was filtered. The residue was dried at the room temperature for several hours, then suspended in water, and sulphur dioxide passed through, with cooling. The clear solution was acidified and extracted several times with ether. Evaporation of the solvent gave an acidic gum (2·9 g.) which was heated at 170—180° for 30 minutes. The cooled product was taken up in ether, and the solution extracted with dilute alkali. Evaporation of the ethereal solution left a pale yellow gum (0·3 g.) from which the Inhoffen ketone (0·2 g.; m. p. 52°) was obtained by application of the chromatographic procedure already described.

(b) *Permanganate oxidation of* 2-*hydroxymethylenecholest*-4-*en*-3-*one* (IX).—Ethyl formate (0·4 g.) was added with cooling to a suspension of alcohol-free sodium methoxide (from 0·12 g. of sodium) in dry benzene (5 c.c.). A solution of cholest-4-en-3-one (10 g.; *Org. Synth.*, 1941, **21**, 18) in benzene (5 c.c.) was added to the suspension with shaking and cooling. Next day ice-water was added and the yellow precipitate collected and washed with benzene. The dried residue was shaken with a mixture of ether and dilute hydrochloric acid. The ethereal layer was separated, dried, and evaporated, leaving 2-*hydroxymethylenecholest*-4-*en*-3-*one* (1·0 g.) as a gum which crystallised readily, and separated from light petroleum (b. p. 40—60°) in pale yellow, elongated prisms, m. p. 111—112° (Found : C, 81·3; H, 10·7. $C_{28}H_{44}O_2$ requires

C, 81·6; H, 10·7%). Meanwhile the preparation of this compound has been reported by Burr, Holton, and Webb (*J. Amer. Chem. Soc.*, 1950, **72**, 4903), who give m. p. 112—113°.

The product was soluble in dilute sodium hydroxide solution but the sparingly soluble sodium salt soon separated. With ferric chloride a deep reddish-purple colour was developed. Ultraviolet absorption maxima at 250 mμ (log ε 4·1) and 310 mμ (log ε 3·8) were observed.

Powdered potassium permanganate (25 g.) was added, in small quantities during 30 minutes, to a stirred solution of hydroxymethylene cholestenone (4·8 g.) in acetone (100 c.c.), the temperature being kept at 0—5°. The precipitate was collected, dried in air, and suspended in water (150 c.c.). Sulphur dioxide was passed into the suspension, with cooling, until a clear solution was obtained. The solution was acidified and extracted with ether. Evaporation gave an acidic gum which was heated at 170—180° for 30 minutes. The decarboxylated material was taken up in ether and extracted with alkali. Evaporation of the dried etheral solution gave a neutral gum (0·4 g.), which, when subjected to chromatography as previously described, gave the Inhoffen ketone (0·2 g.), m. p. 52°.

Des-A-cholestan-5-one-6 : *6-di-ββ-propionic Acid* [*2'* : *2'-Bis-2''-carboxyethyl-1-(1* : *5-dimethylhexyl)perhydro-3'-keto-7a* : *4'-dimethyl-4* : *5-benzindene*] (XXI).—A mixture of the Inhoffen ketone (1·11 g.), dioxan (5 c.c.), " Triton B " (1 c.c.), and acrylonitrile (0·18 g.) was kept for 40 hours at the room temperature and then acidified. Evaporation of the dioxan left an oil which was boiled for 22 hours with aqueous potassium hydroxide (30 c.c. of 20%). The cooled and diluted solution was freed from neutral matter with ether, acidified, and extracted with ether. Evaporation of the ether gave a gum (0·15 g.) which slowly crystallised on trituration with acetone. The *acid* separated from a large volume of acetone in rhombs, m. p. 275—277° (decomp.) (Found : C, 72·8; H, 10·1%; equiv., 243·0. $C_{29}H_{48}O_5$ requires C, 73·1; H, 10·1%; equiv., 238).

6-Methylanilinomethylenedes-A-cholestan-5-one [*1-(1* : *5-Dimethylhexyl)perhydro-3'-keto-7a* : *4-dimethyl-3'-N-methylanilinomethylene-4* : *5-benzindene*] (XXII).—The condensation of the Inhoffen ketone (2·3 g.) with ethyl formate (1·05 g.) in ether (10 c.c.) in the presence of sodium methoxide (from 0·4 g. of sodium) under the usual conditions (see above) furnished the hydroxymethylene derivative of the ketone as a yellow oil (2·4 g.), which gave a purplish-red colour in alcoholic ferric chloride. Reaction of the hydroxymethylene-ketone (2·1 g.) with methylaniline (0·75 g.) in benzene (10 c.c.), by the procedure described above in another example, afforded *6-methylanilinomethylenedes-A-cholestan-5-one* (2·4 g.) which separated from light petroleum (b. p. 40—60°) as cream-coloured needles, m. p. 116—117° (Found : C, 83·1; H, 10·2. $C_{31}H_{47}ON$ requires C, 82·9; H, 10·5%).

Des-A-cholestan-5-one-10-β-propionic Acid (*Windaus Acid*) (VII).—A mixture of the above methylanilinomethylene-ketone (6·6 g.), dioxan (90 c.c.), "Triton B " (7·5 c.c.), and acrylonitrile (1·0 g., 1·25 mol.) was kept at the room temperature for 48 hours. The mixture was acidified and the dioxan evaporated. The oily residue was boiled for 30 minutes with hydrochloric acid (120 c.c. of 10%), and the oil which separated taken up in ether, and the ether evaporated. The residual oil was heated under reflux with potassium hydroxide (150 c.c. of 20%) for 20 hours. The cooled and diluted solution was freed from neutral matter with ether and acidified. The acid solution was extracted four times with ether; evaporation left an acidic gum (0·7 g.), which was taken up in a little ether and kept at 0° for several days, a crystalline mass then forming slowly. The crystals were collected (0·6 g.), m. p. 143—144°, and recrystallised from ether–light petroleum (b. p. 40—60°). The product was so obtained in glistening needles, m. p. 154°, alone or mixed with a specimen made by oxidation of cholestenone (Windaus, *loc. cit.*). Mrs. D. M. Hodgkin kindly carried out *X*-ray diffraction determinations on the synthetic and the authentic material, and reported that the two specimens were identical.

Evaporation of the mother-liquors gave an acidic gum (0·1 g.) from which no further crystalline matter could be obtained. This gum probably contained some of the epimeric form of the Windaus acid.

Des-A-cholest-6-en-5-one [*1-(1* : *5-Dimethylhexyl)-Δ²'-decahydro-3'-keto-7a* : *4'-dimethyl-4* : *5-benzindene*] (XXV).—A solution of Inhoffen's ketone (1·0 g.) in acetic acid (40 c.c.) was cooled and shaken during the dropwise addition of a solution of bromine (1·0 g.) in acetic acid (10 c.c.). The mixture was poured into ice-water, and the oily product isolated with ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate until neutral, then dried, and the solvent evaporated. A dark-red, fuming syrup remained (1·5 g.). The same product was eventually obtained when half the quantity (1 mol.) of bromine was employed. The crude bromo-ketone (XXV) (1·5 g.) in collidine (10 c.c.) was heated under reflux at 185° for 1 hour. The cooled mixture was freed from collidine hydro-

bromide by filtration (yield, 0·75 g.) and the residue washed thoroughly with ether. The filtrate was concentrated, finally *in vacuo*, the dark oily product taken up in ether, and the ethereal solution washed with dilute acid. Evaporation of the dried ethereal solution gave a brown gum which distilled at 180—190° (bath)/0·0005 mm. (0·4 g.), and at 175—180° (bath)/0·0003 mm. (Found: C, 83·6; H, 11·6. $C_{23}H_{38}O$ requires C, 83·6; H, 11·5%). The product showed a maximum absorption in the ultra-violet at 235 mμ (log ε 4·2). This suggests that it is *des*-A-*cholest*-6-*en*-5-*one* (XXV), the calculated $\lambda_{max.}$ for this structure according to Woodward's rule (*J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76) being 227 mμ, and for the isomeric structure (XXVI), 254 mμ.

The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in glistening, deep-red plates, m. p. 175—176° (decomp.) (Found: C, 68·2; H, 8·4. $C_{29}H_{42}O_4N_4$ requires C, 68·2; H, 8·2%).

Grateful acknowledgment is made to the Royal Commissioners for the Exhibition of 1851 for the award of a Senior Studentship to one of us (A. R. P.). We thank Messrs. Charles Lennig and Co. Ltd., for a gift of " Triton B " and Messrs. E. I. du Pont de Nemours and Co., Inc., for a gift of 1 : 3-dichlorobut-2-ene.

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