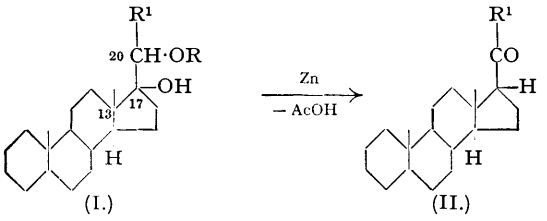
360. *Steroids and the Walden Inversion. Part V. The Serini Reaction.*

By C. W. Shoppee.

The mechanism of the Serini reaction is discussed. The reaction is considered to proceed by way of a 17 : 20-oxide; on this basis the stereochemical outcome at C_{17} of the reaction depends on the orientation of the oxide and the geometrical form of the transition state, and must always involve inversion of configuration at C_{17}. The existing evidence is shown to support this deduction, which is experimentally further substantiated by the conversion of Reichstein's substance O diacetate (a C_{17}-*normal* compound) into 17*iso-allo*pregnan-3β-ol-20-one.

In this series of papers it is intended to examine the stereochemical course of substitution reactions at the various positions in the steroid nucleus. Previous communications have dealt with certain aspects of substitution at C_3; the present paper deals with a reaction involving substitution at C_{17}.

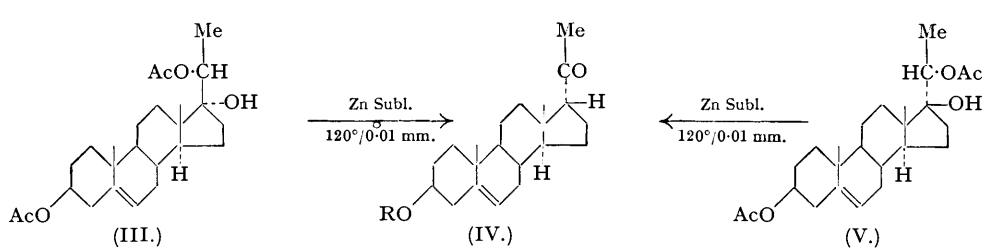
The Serini reaction was discovered by Slotta and Neisser (*Ber.*, 1938, **71**, 2342), and involves the conversion of the secondary acetate of a secondary–tertiary 1 : 2-glycol into a ketone by treatment with zinc dust. It was first employed in the steroid field by Serini, Logemann, and Hildebrand (*Ber.*, 1939, **72**, 391), and subsequently by the author (Shoppee and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 729; Shoppee, *ibid.*, 1940, **23**, 925), and provides a valuable method



(I.) (II.)

for the transformation of a steroid 17 : 20-diol 20-acetate (I; R = Ac) into a steroid 20-ketone (II) with elimination of the elements of acetic acid. Fieser and Fieser (*Experientia*, 1948, **4**, 285) have recently given a concise and useful summary of the available examples.

There appears to be no direct evidence as to the mechanism of the Serini reaction, and Fieser and Fieser (*loc. cit.*) postulate that an enol-acetate, a 17 : 20-oxide, or a cyclic ortho-ester is formed as an intermediate by suitable elimination or cyclisation. On the basis of the stereochemical form (C_{13}-Me/C_{20}-R^1: *cis* or *trans*) of such an intermediate they achieve an empirical correlation of the existing data, and are able to account for the apparent production, through a *trans*-intermediate of the 17*iso*-20-ketone (IV; R = Ac) from *both* the 17*n*-20β-



(III.) (IV.) (V.)

M. p. 153° [a], 159° [b]; $[\alpha]_D$ − 36° [E][a], − 35° [A].[b] *

M. p. 171°, $[\alpha]_D$ − 126° [E].[a] R = Ac.

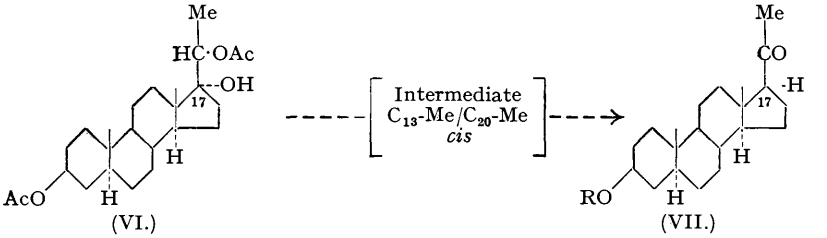
M. p. 182° [a], 185° [b]; $[\alpha]_D$ − 74° [E][a], − 73° [A].[b]

[a] Butenandt, Schmidt-Thomé, and Paul, *Ber.*, 1939, **72**, 1112.
[b] Prins and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 1498.

* Here and later, [A], [C], [D], [E], and [M] indicate rotations determined in acetone, chloroform, dioxan, ethanol, and methanol, respectively.

acetate * (III) and the 17*iso*-20α-acetate * (V) (Butenandt, Schmidt-Thomé, and Paul, *Ber.*, 1939, **72**, 1112).

On the same stereochemical basis, however, Fieser and Fieser predict that a 17*n*-20α-acetate, *e.g.*, Reichstein's substance O diacetate (*allo*pregnane-3β : 17α : 20α-triol 3 : 20-diacetate) (VI) should undergo the Serini reaction to give, through a *cis*-intermediate, *allo*pregnan-3β-ol-20-one acetate (VII; R = Ac) with preservation of configuration at C_{17}:



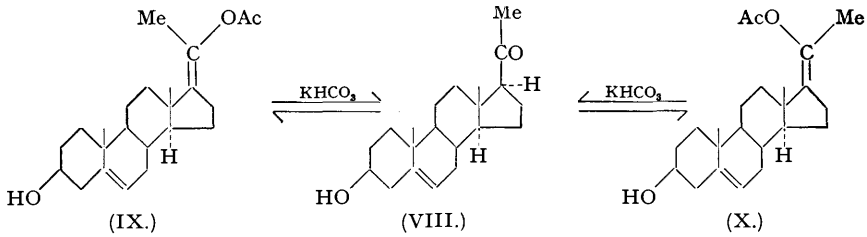
(VI.) (VII.)

Diol: m. p. 222°, $[\alpha]_D$ −13° [M].[c]
Diacetate: m. p. 250°, $[\alpha]_D$ −30° [A].[c]

Alcohol: m. p. 194°, $[\alpha]_D$ + 91° [E][d], + 96° [C].[e]
Acetate: m. p. 144°[d], $[\alpha]_D$ + 77° [C].[e]

[c] Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 546.
[d] Butenandt and Mamoli, *Ber.*, 1935, **68**, 1847.
[e] Barton, private communication.

The application by Serini *et al.* (*loc. cit.*) of the procedure of Slotta and Neisser to an acetate (I; R = Ac) was preceded by the discovery by Serini and Logemann (*Ber.*, 1938, **71**, 1362) that treatment of the free 17 : 20-diol (I; R = H) with dehydrating agents (*e.g.*, formic acid) furnished the ketone (II) in small yield, presumably by pinacolic change. The pyrolytic procedure of Serini *et al.* (*loc. cit.*) (150°/0·0001 mm.) applied to an acetate (I; R = Ac) would not, however, be inconsistent with the occurrence of dehydration, whereby (I; R = Ac) could furnish the geometrically isomeric 17 : 20-unsaturated enol acetates (as IX; C_{13}-Me/C_{20}-Me *cis*), (as X; C_{13}-Me/C_{20}-Me *trans*). The conditions used by Serini can, however, with advantage be replaced by working in boiling toluene (~111°/760 mm.); further, the intermediate formation of an enol-acetate would require some operation involving hydrolysis in order to furnish the ketone (II), whereas the Serini reaction gives the ketonic product directly. Finally, Fieser and Huang-Minlon (private communication) have prepared from pregnenolone (VIII) the isomeric enol acetates (IX) and (X) (cf. also Marshall *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1837), and find that they are both very easily hydrolysed by cold aqueous-alcoholic potassium hydrogen carbonate and that they both yield pregnenolone. Enol acetates therefore cannot be intermediates in the Serini reaction.



(IX.) (VIII.) (X.)

The present author has since 1939 regarded the Serini reaction as an example of pinacolic electron displacement (cf. Shoppee, *Proc. Leeds Lit. Phil. Soc.*, 1928, **1**, 301). The first stage of the reaction is considered to be the separation of an acetate ion from the 20-acetate (XI) under the influence of zinc atoms (positively charged ions surrounded by valency electrons);

* The nomenclature proposed by Fieser and Fieser (*loc. cit.*) with a view to international adoption is used here and supersedes that formerly employed by the writer: "α" and "β" remain as trivial indices; (α) and (β), denoting orientation of nuclear substituents, become α and β, and their use is extended to C_{20} *only* in the side-chain for configurations which can be related to configuration at C_{17} in accordance with the convention suggested by Fieser and Fieser; α and β, denoting configuration in the side-chain, become a and b, *e.g.*, for configurations at C_{20} in the pregnane-3 : 20-diols and at C_{24} in the phytosterols which are not related to the configuration at C_{17}.

This system eliminates the use of parentheses but maintains the distinction which they signified; it can therefore be used in respect of continental nomenclature, *e.g.*, androstandiol-(3α, 11β)-on-17 in which the parentheses were and are still used only typographically.

FIG. 1.

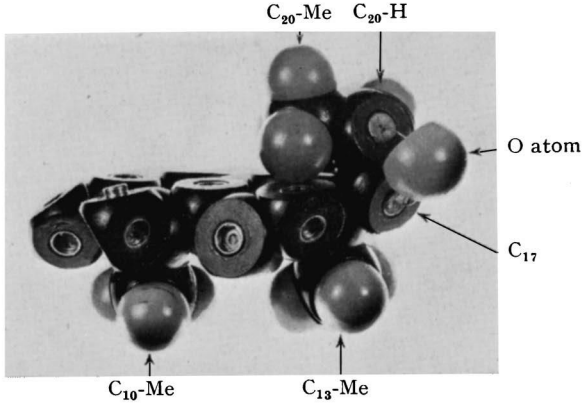


FIG. 2.

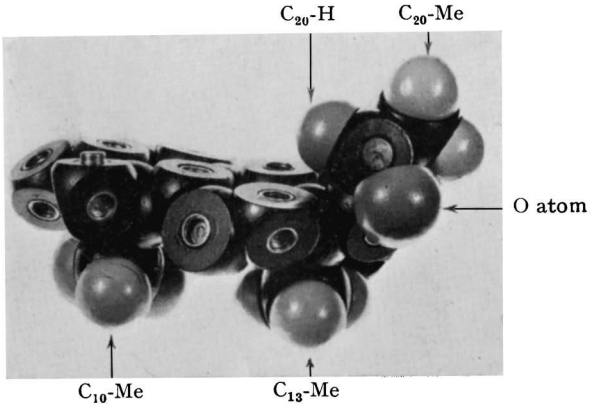


FIG. 3.

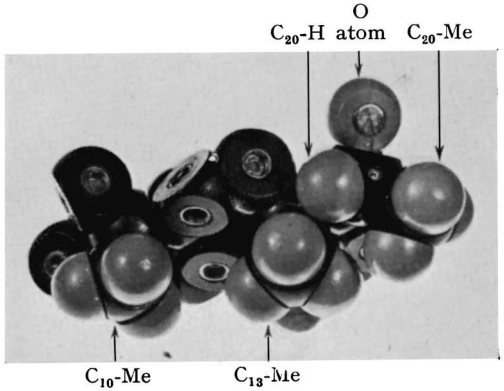
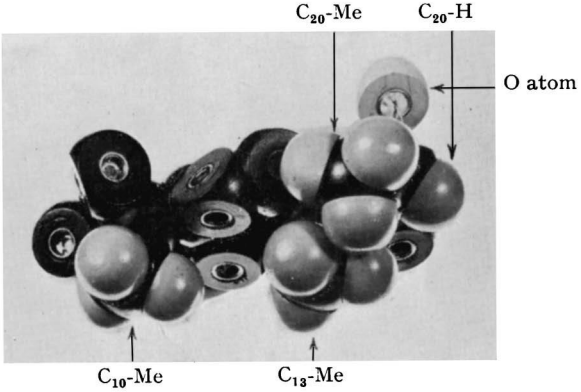
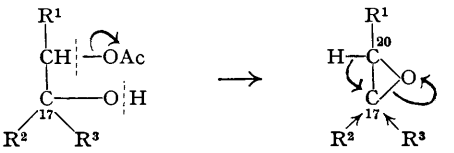


FIG. 4.



[*To face p.* 1673.

the function of the toluene appears to lie in bringing up the solute molecules in turn to the zinc surface. The resulting oxide (XII) then undergoes pinacolic rearrangement, many examples of which are known, and the direction of which depends on the relative electron-release capacities of the groups, R^1, R^2, and R^3 (Ingold, *Ann. Reports*, 1928, **25**, 135). In the case of steroid 17 : 20-oxides, usually $R^1 = {}^-CH_3$ or $^-CH_2{\cdot}OAc$, whilst $R^2 = C_{12}<^{C_{18}}_{C_{14}}>C_{13}$- and $R^3 = C_8<^{C_{13}}>C_{14}{\cdot}C_{15}{\cdot}C_{16}$-, *i.e.*, R^2 and R^3 are higher alkyl groups with electron-release capacities greater than that of the methyl group, so that the direction of rearrangement clearly must be that depicted in (XII), whereby the electron pair constituting the C_{17}–O bond leaves



(XI.) (XII.)

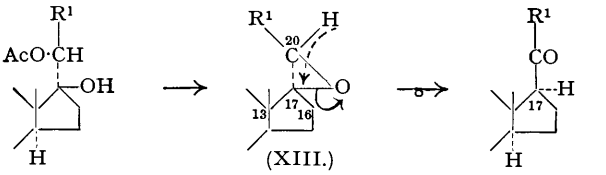
the octet of C_{17} to which the hydrogen atom attached to C_{20} migrates with its electron pair.*

The factors which determine the stereochemical outcome of the pinacolic rearrangement of the oxide (XII) are the geometry of the transition state and the orientation of the oxide ring.

In general, a transition state of linear type X . . . C . . . Y is intrinsically more probable than one of pyramidal type C<X Y, because the repulsive interaction energy integrals will be minimised in the former type; in the present instance (XII), the formation of a linear-type transition state is to be expected and exemplifies the principle of *trans*-interchange in molecular rearrangements, and has as its inevitable consequence inversion of configuration at C_{17} in the ketonic product of the rearrangement.

In the formation from the acetate (XI) of the oxide (XII), the C_{17}–O bond remains unbroken and will therefore retain its original orientation; two types of oxide arise according as the oxide is a 17β : 20β- or a 17α : 20α-oxide. Although as will be shown, contrary to the suggestion of Fieser and Fieser, the orientation of the hydrogen atom (or, conversely, the orientation of the group R^1) attached to C_{20} relative to the C_{13}-methyl group is not a factor in the situation, four cases must be considered according as the initial acetate (XI) is a 20β- or a 20α-acetate.

Case 1.

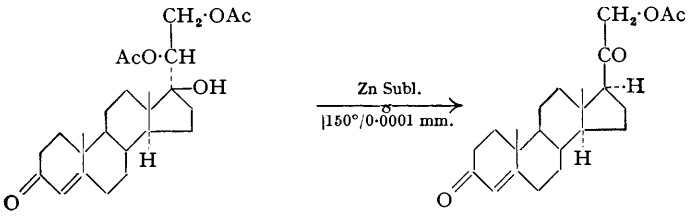


17*iso*-20β-Acetate. 17β : 20β-Oxide (C_{13}-Me/C_{20}-R^1 : *cis*). (XIII.) 17*n*-20-Ketone.

[The dotted arrow from C_{20} to C_{17} indicates attack at the rear-face of C_{17}.]

The intermediate oxide (XIII) is a 17β : 20β-oxide derived from a 17*iso*-20β-acetate, and the case is represented by the original example of Serini *et al.* (*loc. cit.*), whereby 17*iso*-pregn-4-ene-17β : 20β : 21-triol-3-one diacetate (XIV) gives a 59% yield of 11-deoxycorticosterone acetate (XV). In the oxide (XIII), the hydrogen atom attached to C_{20}, which must migrate, lies well behind C_{16} (see Fig. 1) and, to furnish a linear transition state, H . . . . C . . . . O, must attack the rear-face of C_{17} with eventual inversion of configuration at C_{17} to give a 17*n*-ketone (as XV).

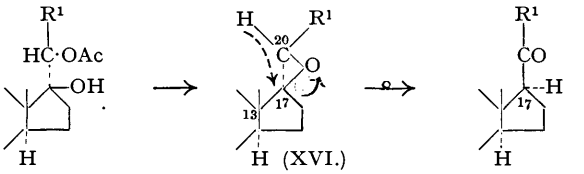
* The other possibilities, which do not appear to arise in the present instance, involve (i) migration of the C_{13}-methyl group to C_{17} (for an example see Shoppee and Prins, *Helv. Chim. Acta*, 1943, **26**, 1004) or (ii) migration of the C_{13}–C_{14} bond to give a C_{14}–C_{17} link.



(XIV.) M. p. 178°, $[\alpha]_D$ + 43° [D].[f] (XV.) M. p. 157°, $[\alpha]_D$ + 173° [D].[g]

[f] Serini, Logemann, and Hildebrand, *Ber.*, 1938, **71**, 1366.
[g] von Euw and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 988.

Case 2.

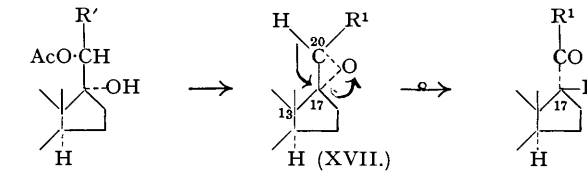


17*iso*-20α-Acetate. 17β : 20β-Oxide (C_{13}-Me/C_{20}-R^1 : *trans*). 17*n*-20-Ketone.

[The dotted arrow from C_{20}–H to C_{17} indicates attack at the rear-face of C_{17}.]

In case 2 the intermediate oxide (XVI) is again a 17β : 20β-oxide, but derived from a 17*iso*-20α-acetate, and the case should be represented by the rearrangement of 17*iso*-pregn-5-ene-3β : 17β : 20α-triol diacetate (V). In the oxide (XVI), the hydrogen atom attached to C_{20} lies directly behind C_{13} (see Fig. 2) and should attack the rear-face of C_{17} to furnish a linear transition state with eventual inversion of configuration at C_{17} to yield a 17*n*-ketone. Butenandt *et al.* (*loc. cit.*) describe in detail the rearrangement of one *or* the other of the isomerides (III) or (V) by sublimation with zinc dust (120°/0·01 mm.) to 17*iso*-pregn-5-en-3β-ol-20-one acetate (IV; R = Ac) in 64% yield, but it is impossible to tell from the text which isomeride was actually used. If these workers used the 17*n*-20β-isomeride (III), this result is in accord with theoretical expectation (see case 3); they state, however, without experimental details that *either* isomeride, (III) or (V), or a mixture, may be used and affords the same product (IV; R = Ac). As Fieser and Fieser (*loc. cit.*) write " this one reported instance of retention of configuration (V ⟶ IV), is not well documented and has not been confirmed; " the work is being repeated by Dr. Huang-Minlon in Prof. Fieser's laboratory.*

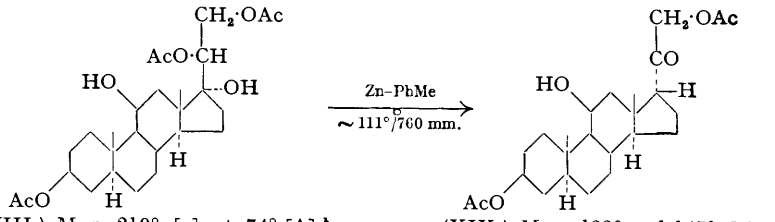
Case 3.



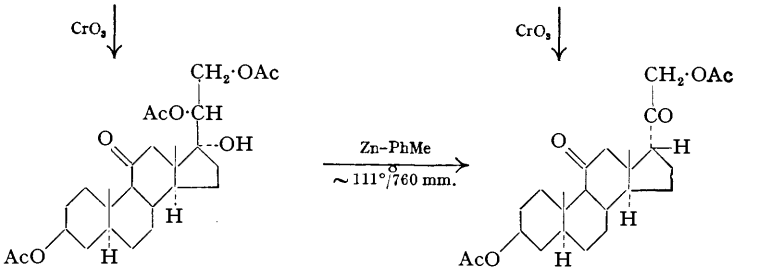
17*n*-20β-Acetate. 17α : 20α-Oxide (C_{13}-Me/C_{20}-R^1 : *trans*). 17*iso*-20-Ketone.

The intermediate oxide (XVII) is now a 17α : 20α-oxide derived from a 17*n*-20β-acetate, and the case is illustrated by three well-established examples; these are the conversion of Reichstein's substance A triacetate (XVIII) into substance 17*iso*-R diacetate (XIX) (Shoppee and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 729), the conversion of the 11-keto-analogue (XX) of substance A triacetate into substance 17*iso*-N diacetate (XXI) (Shoppee and Reichstein, *loc. cit.*), and the preparation from pregn-4-ene-17α : 20β : 21-triol-3-one diacetate (XXII) of 17*iso*-11-deoxycorticosterone acetate (XXIII) (Shoppee, *Helv. Chim. Acta*, 1940, **23**, 925):

* Added, May 23rd, 1949.—Dr. Huang-Minlon has found that, contrary to the statement of Butenandt, Schmidt-Thomé, and Paul (*Ber.*, 1939, **72**, 1112), the acetate (V) undergoes the Serini reaction with inversion of configuration at C_{17} to give, not (IV; R = Ac), but the acetate of (VIII) (Fieser and Fieser, *Experientia*, 1948, **4**, 295, Addendum).

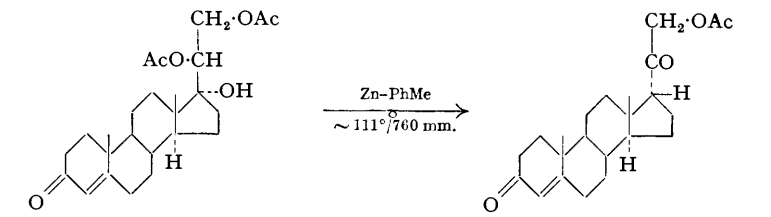


(XVIII.) M. p. 219°, $[\alpha]_D$ + 74° [A].[h] (XIX.) M. p. 133° and 147°, $[\alpha]_D$ − 60° [A].[h]



(XX.) M. p. 183°, 211°, $[\alpha]_D$ + 69° [A].[h] (XXI.) M. p. 131°, $[\alpha]_D$ − 44° [A].[h]

[h] Shoppee and Reichstein, *Helv. Chem. Acta*, 1940, **23**, 729.



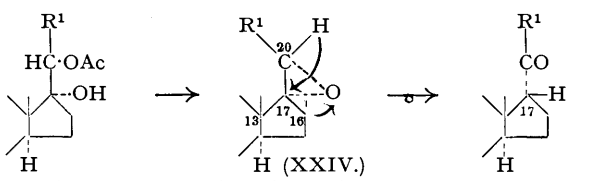
(XXII.) M. p. 170° and 190°.[i] (XXIII.) M. p. 137°, 174°; $[\alpha]_D$ − 26° [A].[i]

[i] Shoppee, *Helv. Chim. Acta*, 1940, **23**, 925.

If Butenandt, Schmidt-Thomé, and Paul (*loc. cit.*) actually used pregn-5-ene-3β : 17α : 20β-triol diacetate (III) in the preparation of 17*iso*-pregn-5-en-3β-ol-20-one acetate (IV; R = Ac), this would constitute a fourth example.

In (XVII), the hydrogen atom attached to C_{20} lies to the front of the general plane of the ring-system and above the C_{13}-angular methyl group (cf. Fig. 3); it should therefore attack the front face of C_{17} to furnish a linear transition state and, with consequent inversion at C_{17}, to give a 17*iso*-20-ketone. This is the result found experimentally in all three (? four) examples cited above.

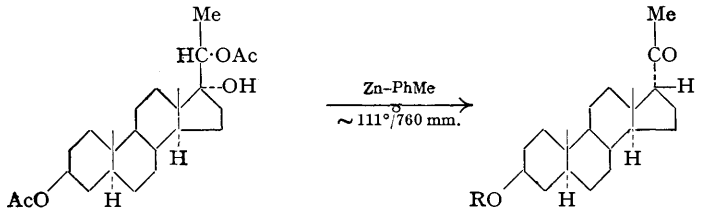
Case 4.



17*n*-20α-Acetate. 17α : 20α-Oxide (C_{13}-Me/C_{20}-R¹ : *cis*). (XXIV.) 17*iso*-20-Ketone.

The intermediate oxide (XXIV) is again a 17α : 20α-oxide, but derived from a 17*n*-20α-acetate; the hydrogen atom attached to C_{20}, which must migrate, lies over and somewhat in front of C_{16} (cf. Fig. 4) and should attack the front face of C_{17} to give a linear transition state, with subsequent inversion at C_{17} to yield a 17*iso*-ketone, and not a 17*n*-ketone as predicted by Fieser and Fieser (*loc. cit.*).

There is no known example of case 4, but with the kind co-operation of Prof. T. Reichstein, who most generously provided 100 mg. of substance O diacetate, the matter has now been investigated. By treatment with zinc dust in hot toluene, substance O diacetate (VI) gives a 45% yield of 17iso-allo*pregnane*-3β-*ol*-20-*one acetate* (XXV; R = Ac), m. p. 118—119°, $[\alpha]_D$ −73° (in ethanol).



(VI.) M. p. 250°, $[\alpha]_D$ − 30° [A]. (XXV.) M. p. 118°, $[\alpha]_D$ − 73° [E].

This substance is identified beyond all doubt as a 17*iso*-compound by its large negative specific rotation (see later); it was further identified by comparison with a synthetic specimen, m. p. 119—122°, $[\alpha]_D$ −75° (EtOH), prepared as described below, and by hydrolysis with cold potassium hydrogen carbonate to the free 17*iso*-ketol (XXV; R = H), m. p. 139°, $[\alpha]_D$ −71° (in ethanol), which was also identified by comparison with a synthetic specimen, m. p. 139°, $[\alpha]_D$ −78° (in ethanol).

The 17*iso*-ketol (XXV; R = H), its acetate, and the derived 17*iso*-3 : 20-diketone were first described by Butenandt and Mamoli (*Ber.*, 1935, **68**, 1847); these workers found that treatment of the 17*n*-ketol (VII; R = H) or its acetate (VII; R = Ac) with hot alcoholic potassium hydroxide led to the production of a proportion (estimated at about 30%) of the 17*iso*-ketol, and, conversely, that similar treatment of their 17*iso*-ketol appeared to regenerate the 17*n*-ketol. They correctly interpreted these observations in terms of an equilibrium between the 17*n*- and 17*iso*-ketols resulting from a keto–enol change catalysed by hydroxide and ethoxide ions. The physical constants recorded by Butenandt and Mamoli are given in Table I.

TABLE I.

	17*iso*-Ketol.	17*iso*-Acetoxy-ketone.	17*iso*-3 : 20-Diketone.
M. p.	148°	101°	134—135°
$[\alpha]_D$ (EtOH)	+6°	—	−14·5°

TABLE II.

	M. p.	$[\alpha]_D$.	$[M]_D$.	$\Delta[M]_D$.
17*n*-Pregn-5-en-3β-ol-20-one	190°	+ 28° [E][1], + 25° [C] [2]	+ 88°	− 532°
17*iso*- ,, ,, ...	172	− 140·5 [E] [1]	− 444	
17*n*- ,, ,, acetate ...	146	+ 20 [E][1], + 14 [C] [2]	+ 72	− 523
17*iso*- ,, ,, ,, ...	170	− 126 [E] [1]	− 451	
Substance P diacetate	208	+ 44·5 [D] [4]	+ 193	− 488
,, 17*iso*-P diacetate	159	− 68 [D] [4]	− 295	
Substance N diacetate	144	+ 77·5 [A] [3]	+ 335	− 525
,, 17*iso*-N diacetate	131	− 44 [A][3], + 85·6 [D] [4]	− 190	
Substance R diacetate	173	+ 92 [A][4], + 83·7 [D] [4]	+ 364 *	− 624
,, 17*iso*-R diacetate	133 and 147	− 60 [A] [3]	− 260	
11-Deoxycorticosterone	141	+ 178 [E] [5]	+ 587	− 785
17*iso*-11-Deoxycorticosterone	179	− 6 [E] [6]	− 198	
11-Deoxycorticosterone acetate	157	+ 169·5 [A][6], + 164 [A][4], + 174 [D] [4]	+ 665	− 816
17*iso*-11-11-Deoxy ,, ...	137 and 174	− 26 [A] [6]	− 151	

* Owing to the unusual circumstance that the rotation in acetone is greater than that in dioxan, the value in dioxan has been preferred.

[1] Butenandt and Fleischer, *Ber.*, 1937, **70**, 96. [2] D. H. R. Barton, private communication. [3] Shoppee and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 729. [4] von Euw and Reichstein, *ibid.*, 1942, **25**, 988. [5] Steiger and Reichstein, *ibid.*, 1937, **20**, 1164. [6] Shoppee, *ibid.*, 1940, **23**, 925.

A specimen (15 mg.) of the reputed 17*iso*-ketol, m. p. 147° (in a capillary tube), prepared by the method of Butenandt and Mamoli by Dr. D. H. R. Barton and kindly made available by him, had $[\alpha]_D^{28°}$ $-1° \pm 3°$ in ethanol, but, when examined microscopically on a Kofler block, behaved as a mixture rather than as a pure individual, commencing to melt at 135° to give a turbid liquid at about 150°, from which the last crystalline material disappeared only at 157°; and in fact the experimental details given by Butenandt and Mamoli show that their " pure " 17*iso*-ketol, m. p. 148°, was contaminated with at least 15% of the 17*n*-ketol; thus by oxidation at 20° with chromium trioxide in acetic acid, isolation of the product by dilution with water, and crystallisation from ethanol—conditions under which tautomeric change would be unlikely and has been shown (see later) not to occur—90 mg. of the 17*iso*-ketol yielded 13 mg. of pure 17*n*-5-*allo*pregnane-3 : 20-dione, m. p. 200·5°, $[\alpha]_D$ +127° (in ethanol).

Calculations of molecular-rotation differences also show that the 17*iso*-compounds of Butenandt and Mamoli were contaminated with considerable quantities of their 17*n*-isomerides. 17*iso*-Pregnenolone (IV; R = H) and its acetate (IV; R = Ac), originally obtained by Butenandt, Schmidt-Thomé, and Paul (*Ber.*, 1939, **72**, 1112) by the Serini reaction, are characterised by relatively large negative rotatory powers as compared with their 17*n*-isomerides; Table II sets out the specific and molecular rotations for these substances and other 17-epimeric pairs, and the molecular-rotation differences.

Omitting the last two pairs, in which the effect of inversion of configuration at C_{17} is clear but the influence of the Δ^4-3-ketonic grouping is also apparent (cf. Barton and Cox, *J.*, 1948, 783), and taking for the change 17*n* ⟶ 17*iso* an average value $\Delta[M]_D = -538°$, we can use this difference to calculate approximate values for the molecular and specific rotations of the saturated 17*iso*-ketol and its acetate (XXV), and the related 17*iso*-3 : 20-diketone, from the experimentally determined specific rotations of their 17*n*-epimerides. The results of these calculations are given in Table III, and it is apparent from a comparison with Table I that Butenandt and Mamoli's preparations were seriously impure.

TABLE III.

([A] = acetone, [C] = chloroform).

		$[\alpha]_D$.	$[M]_D$.
17*n*-5-*allo*Pregnan-3β-ol-20-one	.....	+ 91° [A] [1], + 96° [C] [2]	+ 290°
17*iso*-5-*allo* ,, ,,	(Calc.)	**− 78°**	− 538
			− 248
17*n*-5-*allo* ,, ,,	acetate	+ 77° [C] [2]	+ 277
17*iso*-5-*allo* ,, ,,	acetate (Calc.)	**− 73°**	− 538
			− 261
17*n*-5-*allo*Pregnane-3 : 20-dione	.....	+ 121° [A] [1], + 121° [C] [2]	+ 382
17*iso*-5-*allo* ,, ,,	(Calc.)	**− 49°**	− 538
			− 156

[1] Butenandt and Mamoli, *Ber.*, 1935, **68**, 1847.
[2] D. H. R. Barton, private communication.

In order completely to identify the product obtained from substance O diacetate by the Serini reaction, it therefore became necessary to prepare pure specimens of the 17*iso*-ketol and its acetate. This has been accomplished by utilising observations (cf. Gätzi and Reichstein, *Helv. Chim. Acta*, 1938 **21**, 1185, especially 1189) that the configuration at C_{17} has a marked influence on digitonide formation by a 3β-hydroxyl group. It seemed probable that, like its Δ^5-isomeride (Butenandt and Fleischer, *Ber.*, 1937, **70**, 96), the 17*iso*-ketol would not afford an insoluble digitonide despite the presence of a 3β-hydroxyl group, and, in fact, it was possible to find conditions under which the 17*n*-ketol was completely precipitated by digitonin while the 17*iso*-ketol remained in solution.

TABLE IV.

		17*iso*-Ketol.	17*iso*-Acetoxy-ketone.	17*iso*-3 : 20-Diketone.
Synthetic	M. p.	139°	119—122°	148—149°
	$[\alpha]_D$ [E]	$-78° \pm 2°$	$-75° \pm 3°$	$-49·5° \pm 2·5°$
From substance O diacetate	M. p.	139°	118—119°	—
	$[\alpha]_D$ [E]	$-71° \pm 4°$	$-73° \pm 2°$	—

The pure 17*n*-ketol, m. p. 193°, $[\alpha]_D$ +89° (in alcohol), was heated with ethanolic potassium hydroxide, and the resulting equilibrium mixture of 17*n*- and 17*iso*-ketols crystallised from

ethanol to remove a portion of the 17*n*-epimeride. The residual material was dissolved in warm 90% ethanol and treated with a warm 2% solution of digitonin in 90% ethanol; after being kept overnight, the precipitate was filtered off, and the material in solution recovered to give, after chromatographic purification, the pure 17*iso*-ketol, which was converted into its acetate and, by oxidation with chromium trioxide in acetic acid at 20°, furnished the pure 17*iso*-3 : 20-diketone. The physical constants of these three substances are set out in Table IV; the m. p. 148—149° for the 17*iso*-3 : 20-diketone has previously been recorded by Marker, Wittle, and Plambeck (*J. Amer. Chem. Soc.*, 1939, **61**, 1333). It will be noted that even hydrolysis of the 17*iso*-acetoxy-ketone with ice-cold potassium hydrogen carbonate appears to lead to traces of the 17*n*-ketol, as indicated by the specific rotation of −71° instead of −78°. Butenandt and Fleischer (*loc. cit.*) were unable to hydrolyse the Δ^5-17*iso*-acetoxy-ketone without causing inversion at C_{17}; in the present case, use of potassium carbonate at 20—25° gave a product, melting at 130—131° to a slightly turbid liquid which cleared at 154°, and having $[\alpha]_D$ −27°, which indicates that inversion to the 17*n*-ketol has occurred to the extent of some 30%.

These results establish the identity of the product obtained from substance O diacetate by the Serini reaction, substantiate the theoretical expectation of inversion of configuration at C_{17}, and so support the view here developed of the mechanism of the Serini reaction.

Experimental.

All m. p.s were determined thermo-electrically on a Kofler block: limit of error ±2°. Solvents for chromatographic analysis were rigorously purified and dried.

3β-*Acetoxy*-17iso-allo*pregnan*-20-*one* (XXV; R = Ac) *from Substance O Diacetate* (VI).—3β : 20α-Diacetoxy*allo*pregnan-17α-ol (substance O diacetate) (m. p. 250—251°; 100 mg.) was heated with zinc dust (1 g.) in toluene [washed with conc. sulphuric acid, dried (Na), and redistilled; 4 c.c.] under reflux with exclusion of moisture and in an atmosphere of nitrogen for 12 hours (bath-temperature 120—125°). The warm solution was filtered, and the excess of zinc well washed with warm acetone (purified through the sodium iodide compound); the filtrate was evaporated completely in a vacuum, and the crystalline residue recrystallised from ether. After this had been washed with ice-cold ether, the following fractions were obtained: (i) long thin prisms, m. p. 225—226°, (ii) thin prisms, m. p. 228—232°, (iii) thin prisms, m. p. 230—244°, and (iv) by evaporation of the final mother-liquor, thin prisms, m. p. 225—243°. Attempted use of acetone–pentane mixtures also failed to give a satisfactory separation of unaltered starting material from the reaction product. The material was reunited (99 mg.) and retreated with zinc (1 g.) in toluene (4 c.c.) as previously, but for 22 hours. The product (98 mg.) was dissolved in benzene (1 c.c.) and introduced onto a column of aluminium oxide (Merck–Brockmann, activity III—IV*; 3 g.) prepared in pentane (15 c.c.). The chromatogram was developed with various eluants (10 c.c.), each eluate (see Table V) being evaporated separately, and the residue crystallised from ether–pentane. In the case of fractions 5 and 6, the crystalline material was washed with pentane.

Table V.

Fraction no.	Eluant.	Eluate.	M. p.
1, 2	Pentane	Traces of oil	—
3, 4	,,	—	—
5	Benzene–pentane (1 : 9)	Oil, cryst. on scratching	110—118°, softening at 105°
6	,, ,, ,,	,, ,,	111—118 , ,, 106
7	,, ,, ,,	Crystallised spontaneously	243—245
8	,, ,, (1 : 4)	,, ,,	246—248
9	,, ,, (1 : 1)	,, ,,	244—247
10	Benzene	,, ,,	245—247
11	Ether–benzene (1 : 9)	,, ,,	242—246
12	,, (1 : 4)	,, ,,	230—242
13	,, (1 : 1)	Traces of oil, could not be induced to crystallise	—
14, 15	Ether	—	—

Fractions 7—12 inclusive were united, and the material (83 mg.), consisting of unchanged starting material, was again treated with zinc dust (1 g.) in boiling toluene (4 c.c.) for 44 hours. The product (80 mg.) was analysed chromatographically using a column of aluminium oxide (Merck–Brockmann; 3 g.) prepared in pentane (see Table VI).

Fractions 5 and 6 of chromatogram 1 (Table V) and 4—14 of chromatogram 2 (Table VI) were united (55 mg.), and the product was subjected to fractionational sublimation at 0·001 mm. The fraction obtained at 90—100° (bath-temperature) consisted of 3β-*acetoxy*-17iso-allo*pregnan*-20-*one* (40 mg.), m. p. (crude) 108—110° with partial transformation into prisms, m. p. 117—118°, $[\alpha]_D^{23°}$ −53° ± 2° (*c*, 1·016 in ethanol); after two crystallisations from methanol, the compound formed prisms, m. p. 118—119°, $[\alpha]_D^{23°}$ −73° ± 2° (after drying at 60°/0·001 mm.; *c*, 1·006 in ethanol) {Found [after sublimation at 100°

* On the scale suggested by Brockmann and Schodder (*Ber.*, 1941, **74**, 73).

bath-temperature)/0·001 mm.] : C, 76·65; H, 9·97. $C_{23}H_{36}O_3$ requires C, 76·62; H, 10·06%}. Over the range 100—140° no sublimate was obtained from the small crystalline residue, but at ~200° this sublimed to give substance O diacetate (10 mg.), m. p. 250° (after recrystallisation from ether–pentane). Allowing for this recovered material, the yield is 46%. The acetate gave no precipitate with a 2% solution of digitonin in 90% ethanol.

3β-Hydroxy-17iso-allo*pregnan*-20-*one* (XXV; R = H).—(*a*) The above acetate (20 mg.), dissolved in methanol (3 c.c.), was treated with a solution of potassium carbonate (16 mg.) in water (0·25 c.c.) and set aside for 18 hours at 25°. After complete removal of methanol in a vacuum, and addition of water, the product was filtered off (18 mg.); it appeared to be a hydrate, m. p. ~90°, resolidifying, and remelting at 130—132°. It was fractionally sublimed at 120° (bath-temperature)/0·001 mm.; a portion of the sublimate melted at 130—131° to a turbid melt clearing at 148°. The sublimate was dissolved in ether, the solution concentrated, and, after addition of a little pentane, allowed completely to evaporate; the residual clusters of prisms softened at 125° and melted at 130—131° to a turbid melt clearing at 154°, $[\alpha]_D^{22°} -27° \pm 3°$ (*c*, 0·599 in ethanol) [Found (after drying at 60°/0·001 mm.) : C, 79·46; H, 10·90. Calc. for $C_{21}H_{34}O_2$: C, 79·20; H, 10·76%]. The product, dissolved in warm 90% ethanol (3 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol, gave a precipitate rapidly; after the mixture had been kept overnight at 20°, the precipitate was filtered off, well washed with 90% ethanol and with ether, and discarded. The filtrate was evaporated in a vacuum, and extracted with boiling ether (4 × 5 c.c.); the united extracts were filtered and evaporated, to furnish a crystalline residue contaminated with a little oil (9 mg.). This product, dissolved in a minimum of benzene (about 0·25 c.c.), was introduced on to a column of neutralised * aluminium oxide (300 mg.; activity II)

TABLE VI.

Fraction no.	Eluant.	Eluate.	M. p.
1, 2	Pentane	Traces of oil.	—
3	,,	Crystallised by rubbing with pentane.	80— 90°
4	,,	Crystallised after moistening with pentane.	105—115
5	Benzene–pentane (1 : 9)	,, ,, ,, ,,	117
6	,, ,,	,, ,, ,, ,,	118
7	,, ,,	,, ,, ,, ,,	121
8	,, ,,	Crystallised by seeding.	121
9	,, ,,	,, ,,	120
10	,, ,,	,, ,,	118
11	,, (1 : 4)	,, ,,	118
12	,, ,,	,, ,,	120
13	,, (1 : 1)	,, ,,	117
14	,, ,,	,, ,,	123—150 †
15, 16	Benzene	Uncrystallisable oil.	—
17	Ether–benzene (1 : 9)	Traces of uncrystallisable oil.	—
18	,, (1 : 4)	,, ,, ,,	—
19	,, (1 : 1)	,, ,, ,,	—
20	Ether	,, ,, ,,	—
21	Acetone–ether	—	—

† Turbid melt, clearing at 150°.

prepared in pentane (10 c.c.). The column was washed with pentane (5 × 2 c.c.), the last washing leaving no trace of oil on evaporation; elution with benzene–pentane (4 × 2 c.c.) gave diminishing quantities of oil which crystallised when scratched; elution with benzene (2 c.c.) gave a trace of crystalline material, but a second benzene eluate (2 c.c.) gave no appreciable residue on evaporation. The crystalline fractions were united and recrystallised from ether–pentane, to furnish rosettes of prisms, m. p. 139°, resolidifying in stout prisms at 138·5° (4 mg.); the quantity was insufficient for determination of the specific rotation, but the product gave no depression of melting point with a synthetic specimen of 3β-hydroxy-17*iso-allo*pregnan-20-one.

(*b*) The acetate (12 mg.), dissolved in methanol (1·5 c.c.), and a solution of potassium hydrogen carbonate (15 mg.) in water (0·4 c.c.) were mixed and set aside at 20° for 75 hours. After complete removal of methanol in a vacuum at <30° and addition of a little water, the precipitate was filtered off, washed with water until the washings gave no reaction with phenolphthalein, and dried in a desiccator ($CaCl_2$). The product (10 mg.) was crystallised twice from ether–pentane to give rosettes of prisms, m. p. 137—138° after slight softening at 133°, $[\alpha]_D^{21°} -71° \pm 4°$ (*c*, 0·488 in ethanol), consisting of almost pure 3β-hydroxy-17*iso-allo*pregnan-20-one.

3β-Hydroxy-17iso-allo*pregnan*-20-*one* (XXV; R = H) *from* 3β-*Hydroxy*allo*pregnan*-20-*one* (VII; R = H).—(*a*) A reputed specimen (15 mg.) of the 17*iso*-ketol (XXV; R = H) prepared from the 17*n*-ketol (VII; R = H) by Dr. Barton according to the procedure of Butenandt and Mamoli (*Ber.*, 1935, **68**, 1847) had m. p. 135—157°, $[\alpha]_D^{28°} -15° \pm 3°$ (*c*, 0·730 in ethanol). This product (14·3 mg.) was dissolved in warm 90% ethanol (2·5 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol (2·5 c.c.) and kept overnight at 20°. After filtration from the precipitate, material present in the filtrate was recovered (9·2 mg.) and purified chromatographically on neutralised aluminium oxide as described above. After repeated elution of the column with pentane, use of benzene gave a product which crystallised spontaneously, and, recrystallised from ether–pentane, formed clusters of prisms (4 mg.), m. p. 139°, mixed m. p. 139° with the preparation from substance O diacetate.

* By washing with warm dilute acetic acid and then to neutrality with water, and activated at 200° for 30 hours.

(*b*) The 17*n*-ketol {*allo*pregnanolone (VII; R = H), m. p. 193°, $[\alpha]_D^{20°}$ +89° (EtOH); 970 mg.} was heated with 4% methanolic potassium hydroxide (20 c.c.) under reflux for 2 hours. After addition of a few drops of water, saturation with carbon dioxide, removal of methanol in a vacuum, and addition of water, the precipitate was filtered off and crystallised from ethanol, crystallisation being induced by nucleation with the original specimen; this gave part of the unaltered original material (626 mg.), m. p. 193—194°. The mother-liquor, by complete evaporation in a vacuum, gave a crystalline residue (334 mg.), which was dissolved in warm 90% ethanol (55 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol (55 c.c.). A precipitate formed in a few minutes, and, after being kept overnight at 20°, was filtered off and well washed with ethanol and with ether. The filtrate was evaporated in a vacuum, and the residue extracted with boiling ether (5 × 20 c.c.) to furnish an oil (159 mg.), which crystallised on keeping overnight. The product, dissolved in benzene (0·5 c.c.), was introduced on to a column of neutralised aluminium oxide (4·8 g.; activity II) prepared in pentane (25 c.c.). The chromatogram was developed as shown in Table VII, each eluate (16 c.c.) being evaporated separately.

TABLE VII.

Fraction No.	Eluant.	Eluate.
1—4	Pentane	Decreasing quantities of oil.
5	,,	—
6	Benzene–pentane (1 : 1)	Trace of oil; no crystallisation by seeding.
7	,, ,,	Oil, crystallised by seeding.
8, 9	,, ,,	Crystallised spontaneously.
10	,, ,,	Crystallised spontaneously whilst hot.
11—14	Benzene	Crystallised spontaneously.
15	Ether–benzene (1 : 9)	Little oil, crystallised by scratching.
16	,, ,,	Traces of oil.

After examination, fractions 8—14 inclusive were united, and the product crystallised from ether–pentane to give 3β-*hydroxy*-17iso-allo*pregnan*-20-*one* (74 mg.) in rosettes of prisms, m. p. 139°, $[\alpha]_D^{22°}$ −77·7° ± 2° (*c*, 1·261 in ethanol), which gave no depression on admixture with the specimen prepared from substance O diacetate [Found (after grinding and drying at 80°/0·001 mm.): C, 79·35; H, 10·90. $C_{21}H_{34}O_2$ requires C, 79·20; H, 10·76%]. The mother-liquor yielded a second crop (5 mg.), m. p. 139°. The compound (5 mg.), dissolved in warm 90% ethanol (1 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol (1 c.c.), gave no precipitate; after 0·5 hour a faint opalescence was visible, whilst after some hours at 20° only a slight turbidity was observable. The acetate was prepared by dissolving the pure substance (20 mg.) in anhydrous pyridine (0·12 c.c.), adding redistilled acetic anhydride (0·10 c.c.), and allowing the mixture to stand for 16 hours at 20°; after removal of excess of the reagents in a vacuum, the residue was taken up in ether, the etheral solution washed twice with 2N-hydrochloric acid, with dilute ice-cold sodium hydrogen carbonate, and with water, dried (Na_2SO_4), and evaporated, to give a residue which crystallised spontaneously. Recrystallisation from methanol gave 3β-acetoxy-17*iso-allo*pregnan-20-one, prisms, m. p. 119—122°, $[\alpha]_D^{21°}$ −75 ± 3° (after drying at 60°/0·001 mm.; *c*, 0·692 in ethanol) [Found (after drying at 60°/0·001 mm.): C, 76·30; H, 9·80. Calc. for $C_{23}H_{36}O_3$: C, 76·62; H, 10·06%]. A mixture with the specimen prepared from substance O diacetate had m. p. 119—122°, the melt recrystallising on slight cooling to long prisms which remelted at 122°.

17iso-allo*Pregnane*-3 : 20-*dione*.—The 17*iso*-ketol (m. p. 139°, $[\alpha]_D^{22°}$ −77·7°; 25 mg.) was dissolved in acetic acid (redistilled over chromium trioxide; 0·4 c.c.), a 2% solution of chromium trioxide in 98% acetic acid (0·40 c.c.; 8 mg. of $CrO_3 \equiv 1\frac{1}{2}$ atoms of oxygen) added, and the mixture set aside for 16 hours at 20°. After evaporation almost to dryness (bath-temperature, 25—30°/10 mm.), and addition of a little water, the reaction product was extracted with ether; the aqueous solution contained an excess of chromium trioxide. The ethereal extract was washed with 0·01N-sulphuric acid, with ice-cold dilute sodium hydrogen carbonate, and several times with water; the alkaline washing contained an acid oxidation product. The ethereal solution was dried (Na_2SO_4), and evaporated to give a crystalline residue (24 mg.). Recrystallisation from acetone–pentane furnished 17iso-allo*pregnane*-3 : 20-*dione* as prisms, m. p. 148—149°, $[\alpha]_D^{21°}$ −49·5° ± 2·5° (after drying at 60°/0·001 mm.; *c* = 0·808 in ethanol) {Found [after sublimation at 140° (block-temperature)/0·001 mm.]: C, 79·70; H, 9·93. Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%}.

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