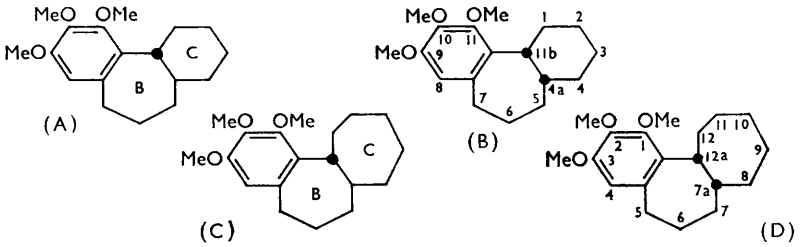
# 284. *Syntheses in the Colchicine Series. Part IV.*[1] *Structural and Conformational Aspects in Some Fused Seven-membered Ring Systems.*

By H. J. E. Loewenthal and P. Rona.

The synthesis, constitution, and stereochemistry of a number of compounds containing the ring systems (A), (B), (C), and (D) are discussed, particularly with regard to their bearing on possible conformational analysis in a fused seven-membered ring.



Work described in this and earlier papers [1] involves a number of compounds containing substituents in seven-membered ring systems in which the stereochemistry of the ring junctions has been fairly well established. These compounds offer an opportunity of investigating the conformation of fused seven-membered rings, on which little work has been done in contrast with the effort spent on fused six-membered ring systems.




In this paper we use the prefixes *cis*- and *trans*- always to denote the stereochemistry of the B/C ring-junction (*i.e.*, B and D, or A and C respectively). Asymmetry at other positions is denoted by α or β with reference to the 11b- or 12a-hydrogen atom which is arbitrarily named β. The compounds are, however, all racemates.

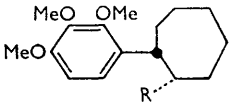
The primary object of this work was the synthesis [2] of the tricyclic compound (XIII) which contains the carbon skeleton of colchicine, from which it is obtainable by degradation.[3,4] This synthesis started from 2-(2,3,4-trimethoxyphenyl)cyclohept-1-enecarboxylic acid,[5] whose reduction with lithium in liquid ammonia gave predominantly the *cis*-acid (IVa). The methyl ester of this was largely transformed into that of the accompanying *trans*-acid (Ia) by equilibration with sodium methoxide. The formerly provisional assignment of these configurations is now supported by accumulating evidence [6] that configurational preferences in 1,2-disubstituted cycloheptanes are similar to those obtaining in the corresponding cyclohexanes.

At first this work was continued in the *cis*-series,[2] towards obtaining the system (D) on the basis of previous experience [1] with the model systems (A) and (B). However, later work started mainly from the *trans*-acid (Ia). This was elaborated to the propionic acid (Ic), by the general method described in the preceding paper, that is, through the alcohol (Ib) and its toluene-*p*-sulphonate. Cyclisation of this acid gave the tricyclic *trans*-ketone (II), whose conversion into the olefin (IIIa) also followed the earlier procedures. In the same way the acid (IVa) gave the *cis*-olefin (VIa). As in the preparation of the analogous ketones in the 6,7,6-systems (A) and (B), the conditions of cyclisation of the propionic acids (Ic) and (IVc) to 6,7,7-ring ketones (IIa) and (Va) with polyphosphoric acid had to be carefully studied in order to obtain optimum yields.

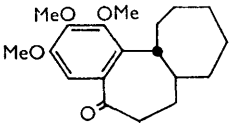
Selenium dioxide oxidised the *trans*-olefin (IIIa) in boiling pyridine stereospecifically

[1] Part II, Loewenthal, *J.*, 1958, 1367; Part III, Loewenthal, preceding paper.
[2] Preliminary communication, Loewenthal and Rona, *Proc. Chem. Soc.*, 1958, 114.
[3] Rapoport, Williams, Campion, and Pack, *J. Amer. Chem. Soc.*, 1954, **76**, 3693.
[4] Rapoport, Campion, and Gordon, *J. Amer. Chem. Soc.*, 1955, **77**, 2389.
[5] Boekelheide and Pennington, *J. Amer. Chem. Soc.*, 1952, **74**, 1558.
[6] *E.g.*, Ayres and Raphael, *J.*, 1958, 1779.

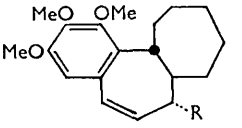
and in reasonable yield to the unsaturated alcohol (IIIb); but similar oxidation of the *cis*-olefin (VIa), even under milder conditions, gave mainly the diene (XX) [which was also obtained by dehydration of the monounsaturated alcohol (IIIb) with dilute acid],



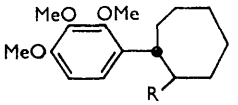
Ia: R = $CO_2H$
Ib: R = $CH_2$·OH
Ic: R = $[CH_2]_2$·$CO_2H$



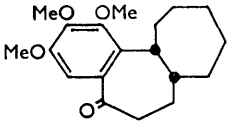
(II)



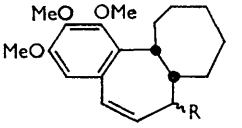
IIIa: R = H
IIIb: R = OH



IVa: R = $CO_2H$
IVb: R = $CH_2$·OH
IVc: R = $[CH_2]_2$·$CO_2H$

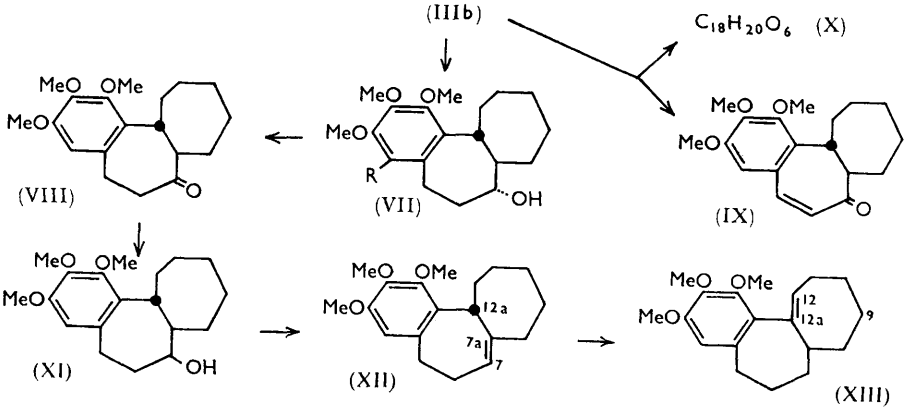


(V)



VIa: R = H
VIb: R = OH

together with very small amounts of both the *cis*- (VIb) and the *trans*-alcohol (IIIb). Isolation of the *trans*-alcohol was probably due to the fact that the low-melting *cis*-acid (IVa) could not at first be obtained entirely free from its *trans*-epimer.



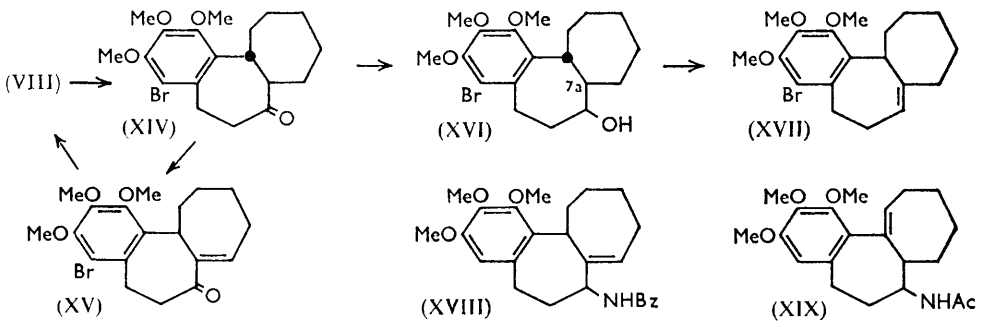

Treatment of the *trans*-alcohol (IIIb) with manganese dioxide gave some of the expected unsaturated ketone (IX), but the main product was a yellow substance, $C_{18}H_{20}O_6$ (*X* in the chart), whose properties are not consistent with retention of the 1,2,3-trimethoxybenzene entity and which is still under examination. A similar compound was obtained under the same conditions from the 9β-acetoxy-analogue (XXXIV) described in the preceding paper

The saturated *trans*-7α-alcohol (VII; R=H) was obtained from the unsaturated alcohol (IIIb) by catalytic hydrogenation and was oxidised to the *trans*-ketone (VIII). This could not be epimerised to a *cis*-epimer under alkaline conditions. Its reduction with lithium hydridotri-t-butoxyaluminate led to the epimeric *trans*-alcohol (XI).

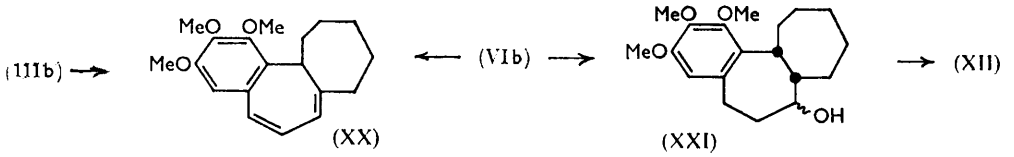
The olefin (XII) was obtained from both the *trans*- (VII; R=H) and the *cis*-alcohol (XXI) by reaction of their toluene-*p*-sulphonates with collidine. With phosphorus oxychloride in pyridine the former alcohol gave a phosphate ester, but the *trans*-7β-epimer (XI) was smoothly dehydrated to the pure olefin (XII). Treatment of this with the boron trifluoride–ether complex in benzene or, preferably, with hydrogen chloride in

chloroform, caused rearrangement to the desired product (XIII), and this was identical with the product obtained when we degraded colchicine by the method described by Rapoport and his co-workers.[4]

The next aim was the synthesis of the colchicine degradation product[3] (XIX). A number of ways were explored to introduce simultaneously the amide group and the styrene double bond. This double bond is known to resist catalytic hydrogenation. Attempts to use the enol acetate of the *trans*-ketone (VIII), by its reaction with peracids or bromine, gave no useful product and will not be described in detail. Bromination of this ketone under buffered conditions gave only the monobromo-ketone (XIV)—the position of the bromine is proved because the aromatic infrared band at 6·26 μ, shown by




all previous compounds in this series, was practically absent. Further bromination of this product in the presence of hydrogen bromide gave an oily dibromo-ketone, in which the position of the carbonyl band in its infrared spectrum was not displaced. Dehydrobromination of this with pyridine or with lithium chloride and lithium carbonate in dimethylformamide[7] led to an unsaturated ketone whose formulation as (XV) is based on the expected αβ-unsaturated carbonyl band at 5·99 μ while the ultraviolet spectrum excluded the presence of a double bond conjugated with the aromatic ring.



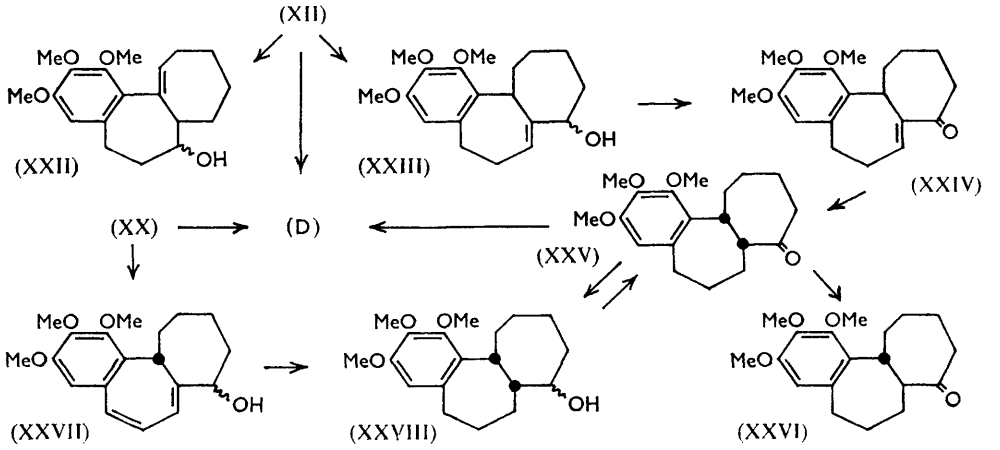

Next the bromo-ketone (XIV) was reduced to the alcohol (XVI), which was smoothly dehydrated to the olefin (XVII). Addition of bromine to the double bond in this, followed by treatment with ammonia and acetylation, appeared to lead to an unsaturated amide. This, however, was clearly not related to the desired compound (XIX), since on catalytic hydrogenation the double bond was reduced before the bromine was removed from the aromatic ring.

Subsequently it was found possible to add bromine to the double bond in compound (XII) without accompanying aromatic bromination. Amination of the resulting dibromide, followed by benzoylation, led to an unsaturated amide in low yield. This again was not related to compound (XIX), on the evidence of its ultraviolet spectrum; it is therefore formulated as (XVIII).

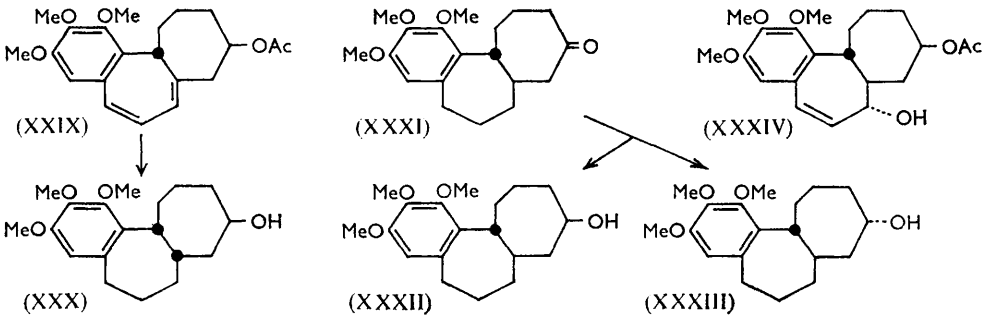
These results, though disappointing, were of value in showing the difficulty of forming a stynene double bond by elimination of a substituent from position 7a under conditions not involving direct protonation. Much the same conclusion was reached on elaboration

[7] Joly, Warnant, Nominé, and Bertin, *Bull. Soc. chim. France*, 1958, 366.

of some products of oxidation of the diene (XX) and the olefin (XII). Treatment of the latter with selenious acid, in a reaction reminiscent of that shown by $\Delta^7$-steroids,[8] gave two unsaturated alcohols, (XXII) and (XXIII). The former showed styrene absorption in its ultraviolet spectrum, but it was obtained in very small yield and could not be




utilised further. The latter was oxidised to an unsaturated ketone (XXIV), whose catalytic hydrogenation gave the ketone (XXV). In this the *cis*-junction between the two seven-membered rings was demonstrated by its conversion, through a thioketal, into the parent *cis*-compound (D). As expected, this ketone was epimerised to the *trans*-ketone (XXVI) by treatment with sodium methoxide.




Oxidation of compound (XX) with selenium dioxide in pyridine gave a single unsaturated alcohol (XXVII) which on catalytic hydrogenation gave the alcohol (XXVIII). This alcohol afforded the previous *cis*-ketone (XXV) and was regenerated from it by reduction with lithium hydridotri-t-butoxyaluminate; with phosphorus oxychloride in pyridine it gave a phosphate.

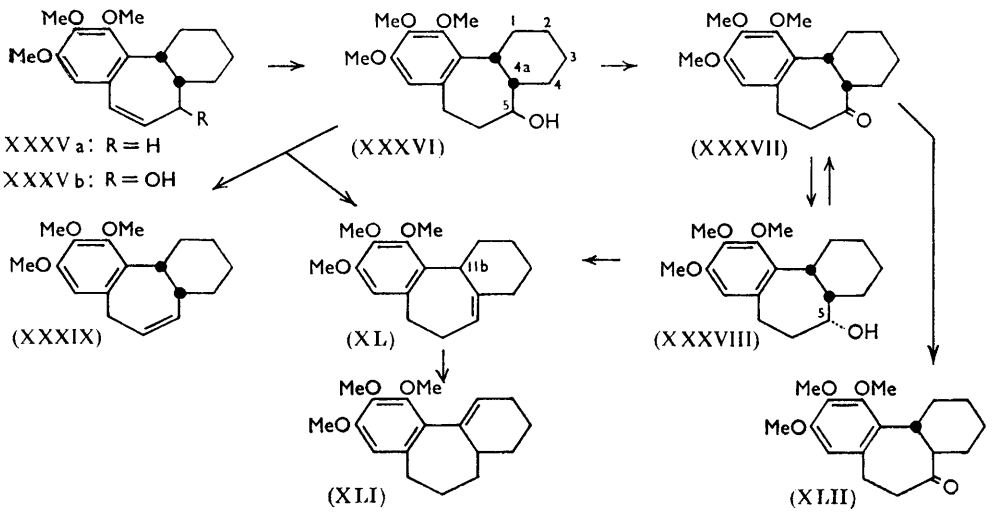
Some further transformations in this series are illustrated in formulæ (XXIX)—(XXXIII). Their significance is discussed below.

Further interesting results were obtained in the *cis*-dibenzo[*a*,*c*]cycloheptatriene system (B). The *trans*-5β-alcohol * (XXXVI), obtained from the unsaturated alcohol [1] (XXXVb), resisted dehydration by phosphorus oxychloride in pyridine, while the 5α-epimer (XXXVIII) obtained by reduction of the *cis*-ketone (XXXVII) afforded the olefin (XL)

* Note the change of numbering for the reduced 6,7,6-ring system.

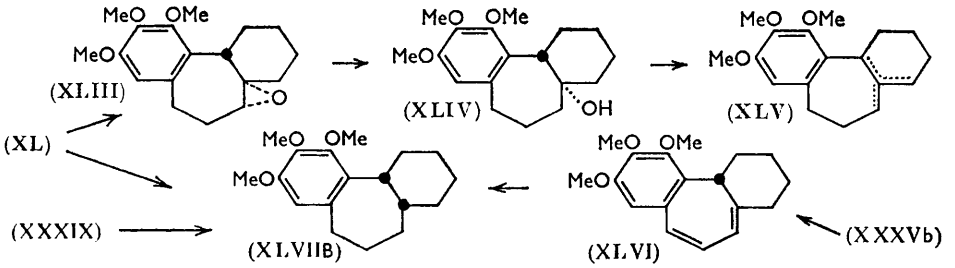
[8] Fieser and Ourisson, *J. Amer. Chem. Soc.*, 1953, **75**, 4404.

under the same conditions. This olefin was obtained also by treatment of the toluene-*p*-sulphonate of the 5β-alcohol (XXXVI) with collidine, but was then contaminated with the isomeric olefin (XXXIX): the mixture was separated by epoxidation which led selectively and stereospecifically to the epoxide (XLIII) and left the 5,6-unsaturated compound (XXXIX) unchanged. This resistance inclined us to formulate the latter




compound as containing a cyclopropane ring in ring B, but that seems to be excluded by the fact that hydrogenation to the *cis*-compound (XLVIIB) is rapid in the presence of palladium–calcium carbonate.

Lithium aluminium hydride reduced the epoxide (XLIII) to a tertiary alcohol (XLIV). Although the hydroxyl group in this compound probably has a conformation favourable for its ionic elimination (see below), dehydration was very difficult. Thionyl chloride in pyridine, or phosphorus oxychloride in the same solvent at 100°, gave a mixture of olefins (XLV) in which only part was of styrene character as judged by the ultraviolet absorption. An attempt to open the epoxide ring by treatment with ammonia under pressure at 120° was unsuccessful.

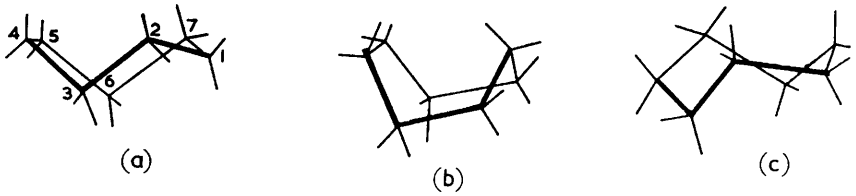



*Stereochemistry.*—As discussed by Allinger,[9] the two basic forms of cycloheptane are the chair and the boat form, as in cyclohexane, and here too the chair form appears to be the more stable. An energy difference of 5·5—8·1 kcal./mole between the two forms, calculated by Pauncz and Ginsburg,[10] is of the same order as that (5·3 kcal./mole) found experimentally by Johnson and his co-workers [11] for cyclohexane.

[9] Allinger, *J. Amer. Chem. Soc.*, 1959, **81**, 5727.
[10] Pauncz and Ginsburg, *Tetrahedron*, 1960, **9**, 40.

A number of reactions of 1,2-disubstituted cycloheptane derivatives has been studied in connection with the geometric and mechanistic criteria involved, by Sicher and his co-workers [12,13] and by Huffman and Engle.[14] The course of these reactions does not in all cases parallel that exhibited in the cyclohexane series; there may also be considerable

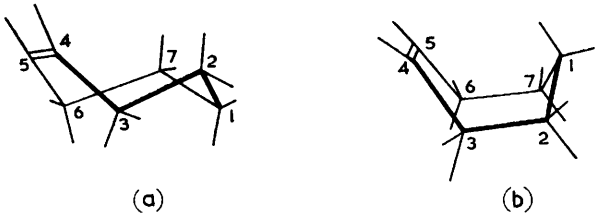
FIG. 1.




differences in the energies of activation for the same reaction in the two ring systems. The reason is clear on inspection of Dreiding models of 1,2-disubstituted cycloheptanes. Both chair and boat forms (Figs. 1a and b) can be easily transformed into a large number of alternatives, and these transformations are not accompanied by deformation of any tetrahedral valency angle. They can release the non-bonded interaction between the "axial" hydrogen atoms at positions 3 and 6, calculated [10] to be only 1·288 Å apart, by passage through an all-skew form [13] (Fig. 1c) in which total transannular interaction is at a minimum. (A slight change in valency angles at positions 4 and 5 in Fig. 1a could also reduce this interaction.[10]) Thus a *trans*-1,2-disubstituted cycloheptane derivative (the two substituents being different) can for the purposes of reaction pass through di-equatorial, equatorial-axial, and diaxial conformations. In such a case there are fourteen possible different chair conformations, of which six allow the two substituents to be both equatorial; and between all three pairs of these there exists an intermediate all-skew form.[15]

The case is somewhat different in cycloheptene, which can also exist in both chair and boat forms. The geometry of these has likewise been evaluated by vector methods [10] (Figs. 2a and b). Both these, especially the chair form, are more rigid than in the case of cycloheptane. Moreover, interaction between the two "axial" 3- and 6-hydrogen atoms is now much less, the separation being about 2·1 Å. Further, a small energy difference in favour of the boat form (0·67 kcal./mole) seems to be indicated.

FIG. 2.



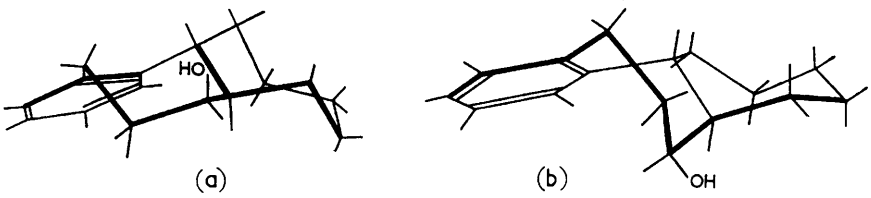

For systems containing fused cycloheptane and cycloheptene rings the possibilities of transformation are greatly reduced, depending to some extent on the stereochemistry of ring fusion (*cis* or *trans*). Indeed the great number of stereoselective reactions revealed in this work makes the presence of a rigid system imperative.

All the compounds described in our work contain a cycloheptene ring (B). Figs. 2a and b show that suitable geometry for, *e.g.*, *trans*-diaxial elimination is found only between

[11] Johnson, Margrave, Bauer, Frisch, Dreger, and Hubbard, *J. Amer. Chem. Soc.*, 1960, **82**, 1255.
[12] Sicher and Svoboda, *Coll. Czech. Chem. Comm.*, 1958, **23**, 2094.
[13] Sicher, Svoboda, Jonas, and Knessl, *Coll. Czech. Chem. Comm.*, 1958, **23**, 2141.
[14] Huffman and Engle, *J. Org. Chem.*, 1959, **24**, 1844.
[15] Cf. Hermans and Maan, *Rec. Trav. chim.*, 1939, **57**, 643.

positions 1, 2, and 7. For the ring systems (B) and (C), the ready elimination of water from the alcohols (XXXVIII) and (XI), to give the pure olefins (XL) and (XII) respectively, indicates that the hydroxyl groups and hydrogen atoms involved have a *trans*-diaxial relation. Further, from Figs. 3a and b, 4a and b, it is clear that for such eliminations to be possible ring B has to have a chair conformation in the *trans*-alcohol (XI) and a boat conformation in the *cis*-alcohol (XXXVIII).

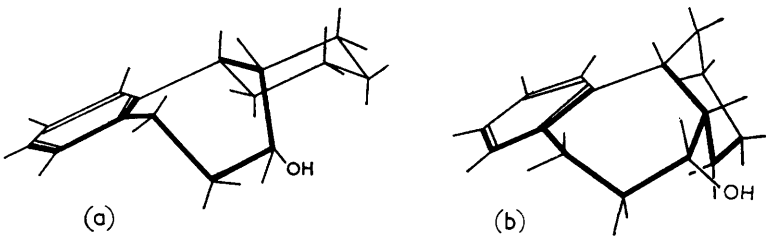
FIG. 3. *Compound* (XI): (a) *ring* B *chair*; (b) *ring* B *boat*.




These " axial " alcohols were prepared by reduction of the ketones (VIII) and (XXXVII) with complex metal hydrides. According to accepted views [16] on the steric course of such reactions, axial alcohols are formed from hindered ketones, while unhindered ketones give equatorial alcohols. Inspection of the interactions in ring B in Figs. 3a and 4a makes it clear that for reagent approach from the *unhindered* side to the *trans*-ketone (VIII) and the *cis*-ketone (XXXVII), quasi-chair and quasi-boat forms must also be assumed in these compounds.

The corresponding " equatorial " alcohols (VII) and (XXXVI) were derived from the " (quasi)equatorial " allylic alcohols (IIIb) and (XXXVb) respectively. These in turn were obtained from the olefins (IIIa) and (XXXVa) by oxidation with selenium dioxide. Not much is known about the steric course of oxidation with this reagent, since in most cases the reaction proceeds further, giving an unsaturated ketone or a conjugated diene.[17] In this work such further oxidation is probably inhibited by the solvent chosen (pyridine). Rosenblum [18] has obtained an allylic alcohol by oxidation of dicyclopentadiene with selenium dioxide, and this compound was shown by Woodward and Katz [19] to be the less hindered *exo*-epimer. In addition, a total synthesis of santonin [20] has involved formation of a quasi-equatorial unhindered hydroxyl group by allylic oxidation with the same

FIG. 4. *Compound* (XXXVIII): (a) *ring* B *boat*; (b) *ring* B *chair*.




reagent. It is probable that experiments on allylic oxidation by selenium dioxide in rigid systems, such as steroids, under the mild conditions used in the present work will show that the formation of an equatorial hydroxyl group is general. The introduction of an *axial* 4β-hydroxyl group on oxidation of cholesterol [21] by selenium dioxide may possibly involve an intermediate cyclic selenite ester.

[16] Barton, *J.*, 1953, 1026.
[17] Rabjohn, in " Organic Reactions," Wiley, New York, 1949, Vol. V, p. 331.
[18] Rosenblum, *J. Amer. Chem. Soc.*, 1957, **79**, 3179.
[19] Woodward and Katz, *Tetrahedron*, 1959, **5**, 70.
[20] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1422.
[21] Rosenheim and Starling, *J.*, 1937, 377.

The action of phosphorus oxychloride and pyridine on the "equatorial" alcohols (VII) and (XXXVI) gave phosphate esters instead of elimination. This is reminiscent of the behaviour of similarly placed equatorial hydroxyl groups in the steroid series.[22,23] The conformations assigned were confirmed, on analogy with six-membered ring systems, by measuring the relative rates of oxidation of these alcohols, and of saponification of their acetates (see Table). The results are clear-cut and in every way consistent with the above mechanistic arguments.

TABLE 1. *Comparative rates of oxidation of alcohols and of saponification of their acetates.*

(Epimeric pairs grouped together.)

| | Oxidation of alcohols | | Hydrolysis (%) of acetates | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $k$ * | half-life (min.) | 2 | 4 | 8 | 16 | 32 | 64 | 90 hr. | Probable conformn. |
| (XXXVIII) | 40 | 0·5 | | | | 6 | 12 | | | ax |
| (XXXVI) | 0·5 | 30 | | | | 30 | 51 | | | eq |
| (XI) | 54 | 3·5 | | | | | | 5 | 7 | ax |
| (VII; R=H) | 4·3 | 44 | | | | 27 | 53 | | 82 | eq |
| (XXVIII) | 7·1 | 7·5 | | | | 21 | 35 | | 74 | ? |
| (XXXIII) | 3·3 | 20 | 14 | 30 | 58 | | | | | ax |
| (XXXII) | 2·6 | 26 | 22 | 43 | 73 | | | | | eq |
| (XXX) | | | 17 | 35 | 61 | | | | | ? |

* Values relative to 5α-cholestan-3β-ol, $k = 1$.

The analogy to cyclohexane ring systems holds even when the infrared spectra of these compounds are examined. The C–O stretching region of the alcohols (9—10 μ) is unfortunately obscured by absorption due to the aromatic methoxyl groups, but the corresponding region shown by the acetates of the alcohols (VII), (XXXVI), (XI), and (XXXVIII) exhibits a striking parallel to that reported for equatorial and axial acetoxy-groups in steroids.[24] The first two compounds, both "equatorial" by the above arguments, show a single band at 8·06 μ, while the last two, both "axial," show a series of complex bands between 8·0 and 8·2 μ (measured in $CS_2$).

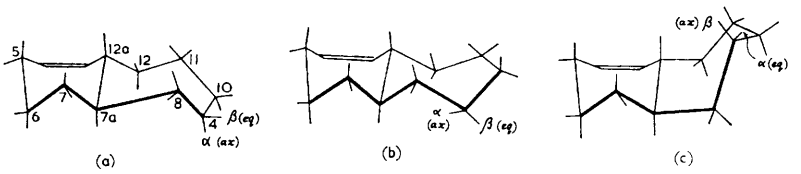
The relative configurations assigned in this paper to all the above compounds arise from the convention we have adopted, in placing the 11b-hydrogen atom in ring systems (A) and (B), and the 12a-hydrogen atom in systems (C) and (D) above the plane of the molecule (β). This atom most probably has an axial conformation relative to ring C in all these four systems.

The form of the cycloheptane ring C in systems (C) and (D) is more difficult to evaluate. As described in the preceding paper, the ketone (XXXI) is reduced stereoselectively to the epimeric alcohols (XXXII) and (XXXIII). The ratio in which these were obtained (5·5 : 1) is of the same order as that observed in reduction of unhindered steroid ketones, such as 5α-cholestan-3-one, by complex metal hydrides. In the case cited the equatorial alcohol is the preponderant product. The rates of oxidation of the alcohols (XXXII) and (XXXIII) and of saponification of their acetates were also measured (Table 1). The results are consistent in ascribing equatorial and axial character to these epimers, but they indicate that the difference in hindrance between them is rather small. The infrared spectra of these acetates both show a single band at 8·06 μ, that for the 9α-epimer being somewhat broader. If a chair form is assumed for ring C in these compounds (a boat form is shown by models to introduce an inordinate number of transannular interactions), then possible conformations for this ring are indicated in Figs. 5a, b, and c. The first two are preferable in that they best account for the small difference in hindrance between

[22] Barton and Rosenfelder, *J.*, 1951, 1048.
[23] Crawshaw, Henbest, and Jones, *J.*, 1954, 731.
[24] Cole, "Infrared Spectra of Natural Products," in Zechmeister's, "Progress in the Chemistry of Natural Products," Springer, Vienna, 1956, Vol. XIII, p. 1.

the above two alcohols and their acetates; and on this basis β- and α-configurations have been assigned provisionally. It is intended to clarify this point by establishing a steric relationship between the 7*a*-hydrogen atom and the 9-hydroxyl group in a suitable compound such as the acetoxy-ketone (XVIII) of the preceding paper.

FIG. 5 (*aromatic ring not shown*).




In the *cis*-fused system (D), the shape of the cycloheptane ring C cannot as yet be fully described. Table 1 includes data on alcohols (XXX) and (XXVIII) and their acetates. Unfortunately no epimers of these could be prepared, but the figures might indicate intermediate (equatorial-axial) character for the functional groups. This is reminiscent of results in the flexible *cis*-decalin series,[25] and the flexibility of system (D) is evident from inspection of models.

The stereoselective reduction of the *cis*-ketone (XXV) is somewhat puzzling. If this is hindered, as in ketones (VIII) and XXXVII), then the product (XXVIII) should have an axial 8-hydroxyl group; however, treatment with phosphorus oxychloride–pyridine gave a phosphate ester. *trans*-Diaxial elimination towards $C_{(9)}$ is theoretically possible but would proceed in an anti-Saytzeff direction.

In connection with some current views [26] on the effect of ring size and ring conformation on the infrared spectra of cycloalkanones the wavelengths of the carbonyl bands of the various seven-membered ring ketones encountered in this work have been collected in Table 2. In every case this band was at a lower wavelength for the *trans*- than for the corresponding *cis*-ketone; in the latter one of the rings is probably in the boat form.

TABLE 2. *Infrared carbonyl bands of seven-membered ring ketones.*

(Epimeric pairs grouped together.)

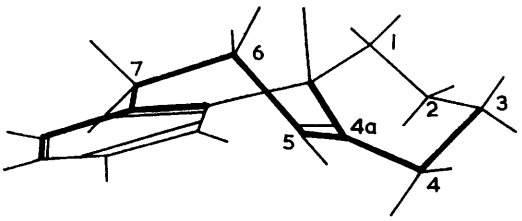
| Ketone | (XLII) | (XXXVII) | (VIII) | (XXVI) | (XXV) | (XXXI) | *cis*-Epimer of (XXXI) |
|---|---|---|---|---|---|---|---|
| Ring junction... | *trans* | *cis* | *trans* | *trans* | *cis* | *trans* | |
| ν(C:O) (μ) ..... | 5·87 | 5·90 | 5·90 | 5·91 | 5·94 | 5·90 | 5·92 |

Other stereoselective reactions open to interpretation by conformational arguments are the conversion of the olefin (XL) into the epoxide (XLIII), and the reaction of the latter with lithium aluminium hydride which gave a high yield of a tertiary alcohol. Accepted ideas [16] on the stereochemistry of these reductions demand the formation of the axial, and, if possible, the more highly substituted alcohol. When the latter condition is fulfilled, and if the hydroxyl group has a conformation axial to both rings B and C, it must have the α-configuration. This also necessitates an α configuration for the epoxide (XLIII), formed by *rear* attack of a hydroxonium ion on compound (XL); reduction of the ketone (XXXVII) to the alcohol (XXXVIII) must have proceeded by *frontal* attack by the complex-hydride ion. In other words, introduction of the 4a,5-double bond into system (B) has apparently changed the direction of most favourable approach of an ionic reaction species. On the other hand, catalytic reduction of the olefin (XL) proceeded by *frontal* adsorption on the catalyst, giving the *cis*-compound (XLVII). Indeed, catalytic reduction of the similar olefin (XII) and of the dienes (XX), (XXVII), (XXIX), and (XLVI) led in all cases to the formation of the saturated *cis*-fused ring system. We suggest that,

[25] Dauben and Pitzer, in Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 27.
[26] Prelog, *J.*, 1950, 420.

while the direction of approach of an ionic reaction species is determined more by the interactions directly affecting the point of reaction, direction of absorption on a catalyst is governed mainly by the shape of the molecule as a whole.[27] In a relatively flat molecule, such as a steroid, these two factors will in most cases overlap so that catalytic hydrogenation and, *e.g.*, epoxidation will both take place by attack on the same side. In all the above unsaturated compounds, however, the molecule is concave towards the α-side, leading to catalyst adsorption and hydrogenation on the β-side (see Fig. 6).

FIG. 6. *Compound* (XL).




Similar arguments may explain the fact that the chromatographic behaviour of the esters of the alcohol pair (XXXII) and (XXXIII) is the opposite of that expected from the results shown in Table 1, namely, that the equatorial is less strongly absorbed on alumina than the axial epimer (see preceding paper). It has been pointed out [28] that there are exceptions, even in the steroid field, to the rule that compounds containing equatorial functional groups are more strongly absorbed than the axial epimers.

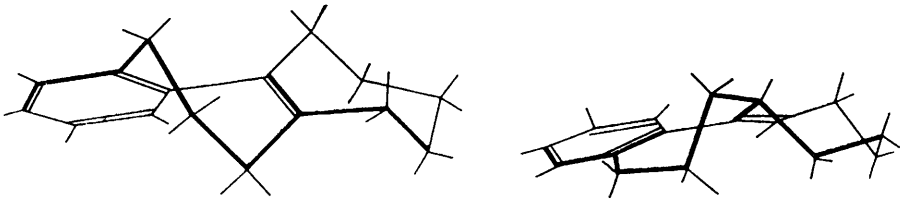
Finally we deal with an item of structural interest, namely, the positions of the double bond that resists hydrogenation in compounds (XIII) and (XLI), which were obtained from the olefins (XII) and (XL), respectively, by protonation, etc. In the 9,9-ethylenedioxy-analogue of compound (XIII) a trisubstituted position (12,12a) for this double bond is almost certain (see preceding paper). In compound (XLI) a similar position is indicated, for this would explain the reluctance of the tertiary hydroxyl group in the alcohol (XLIV) to be eliminated cleanly to give the structure where the double bond is tetrasubstituted. Another argument which could be used is based on conclusions by Henbest and his coworkers [29] on the steric requirements of hydrogen-catalyst migration of double bonds. According to these, such migration may take place if the leaving "allylic" hydrogen atom is sterically accessible to the catalyst surface. If the catalyst, in the present cases, approaches from the β-side, then the 12aβ-hydrogen atom in compound (XII) or the 11b-hydrogen atom in compound (XL) would have the required stereochemistry for such a migration, *provided that* this leads to a compound with a non-hydrogenatable tetrasubstituted double bond. Instead, no migration of the double bond took place and the olefins (XII) and (XL) were hydrogenated to the 7aβ-H and the 4aβ-H compound respectively. A case in point is that of *cis-syn*-1,2,3,4,5,6,12,13,14,15-decahydro-1,1,8-trimethoxy-4-oxochrysene described by Robins and Walker.[30] In this a trisubstituted styrene bond is partly isomerised and partly hydrogenated to give a *cis-syn-cis*-compound, depending on the conditions of the catalytic hydrogenation. Both courses of reaction are compatible with the stereochemistry of the starting material.

If the styrene bond in compounds (XIII) and (XLI) were tetrasubstituted, then it would be contained in a strained cyclohepta-1,3-diene ring in which the two double bonds cannot be in one plane. Moving the double bond to a position exocyclic to that ring would

[27] Cf. Robinson, *Tetrahedron*, 1957, **1**, 49.
[28] Fieser and Fieser, "Steroids," Reinhold Publ. Inc., New York, 1959, p. 698; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[29] Bream, Eaton, and Henbest, *J.*, 1957, 1974.
[30] Robins and Walker, *J.*, 1959, 237.

increase the coplanarity of the conjugated system, and the gain in resonance energy might well offset the loss due to decreased substitution (see Figs. 7a and b).

FIG. 7. *Compound* (XIII).



(a) (b)

Opposed to these conclusions are the results of proton magnetic resonance measurements on compound (XIII), which were kindly undertaken by Drs. Forsen and Nilsson at the Royal Institute of Technology, Stockholm. These provide no positive evidence for the presence of a vinyl proton in ring C of this compound, even though a signal due to this could possibly have overlapped that caused by the lone hydrogen atom in the aromatic ring. We cannot, therefore, at present be certain of the styrene structure shown for these compounds.

## EXPERIMENTAL

Infrared spectra are for $CHCl_3$ solutions unless otherwise stated, and ultraviolet spectra for MeOH solutions (Spectrograde).

2-(2,3,4-*Trimethoxyphenyl*)*cycloheptanecarboxylic Acid;* trans- (Ia) *and* cis-*Epimers* (IVa).—2-(2,3,4-Trimethoxyphenyl)cyclohept-1-enecarboxylic acid [5] (40 g.) was reduced in liquid ammonia (1300 ml.) with lithium (*ca.* 2 g.) as described previously for the cyclohexane analogue.[1] After isolation with ether–benzene the product was fractionally crystallised from hexane, giving as first crop the trans-*epimer* (10·7 g.) which after recrystallisation had m. p. 96—97° (Found: C, 66·0; H, 7·75. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%). The second crop consisted mainly of the cis-*epimer* (20·0 g.) which after several recrystallisations from hexane had m. p. 74—76° (Found: C, 65·8; H, 7·75%). A third crop (9·0 g.), m. p. 50—70°, also consisted mainly of the *cis*-epimer.

The *cis*-epimer (15·3 g.) was esterified in ether with an excess of diazomethane. The crude methyl ester obtained on removal of solvents *in vacuo* was refluxed with a 15% solution of sodium methoxide in methanol (120 ml.) under nitrogen for 12 hr. Then 10% potassium hydroxide solution (120 ml.) was added, the methanol slowly distilled off, and the remaining solution acidified after cooling. The oil which separated was isolated with benzene and crystallised from hexane, to give the above *trans*-epimer, m. p. and mixed m. p. 95—96° (11 g.). A comparable yield was obtained by subjecting the total epimer mixture obtained from the lithium–liquid ammonia reduction to the same procedure.

trans-2-(2,3,4-*Trimethoxyphenyl*)*cycloheptylmethanol* (Ib).—This was obtained by reduction of the preceding acid (Ia) (17·8 g.) with lithium aluminium hydride (5·0 g.) in ether–tetrahydrofuran, as described for the cyclohexane analogue.[1] The crude *alcohol* (16·7 g.) was used directly for the next step; a sample was distilled evaporatively at 154—156°/$10^{-1}$ mm. (Found: C, 69·15; H, 8·85. $C_{17}H_{26}O_4$ requires C, 69·35; H, 8·9%), $\nu_{max.}$ at 2·85s, 6·25 μ.

β-trans-2-(2,3,4-*Trimethoxyphenyl*)*cycloheptylpropionic Acid* (Ic).—The alcohol (Ib) (24·7 g.) was converted into its toluene-*p*-sulphonate ($\nu_{max.}$ 7·35 and 8·51 μ) by treatment with toluene-*p*-sulphonyl chloride (20·35 g.) in pyridine (116 ml.) at 0° overnight (cf. ref. 1). Condensation of this ester with di-t-butyl sodiomalonate (from 45 g. of the malonate and 4·8 g. of sodium hydride) in benzene (120 ml.) and toluene (50 ml.) also followed that described for the cyclohexane analogue. The crude condensation product was heated with acetic acid (400 ml.), water (150 ml.), and concentrated hydrochloric acid (10 ml.) under reflux for 12 hr., after which the solution was concentrated *in vacuo* and the residue heated at 180—200° until gas evolution ceased. It was then dissolved in benzene and extracted several times with 20%

potassium carbonate solution. The extracts were washed with benzene and acidified, to give the *acid* (20·2 g.) which was isolated with ether–benzene. A sample distilled evaporatively at 190—200°/$10^{-1}$ mm. as a very viscous oil (Found: C, 67·3; H, 8·45. $C_{19}H_{28}O_5$ requires C, 67·85; H, 8·4%).

5,6,7,7aα,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-5-*one* (II).—To the crude acid (Ic) (20·0 g.) was added polyphosphoric acid prepared from 85% orthophosphoric acid (150 ml.) and phosphoric oxide (240 g.), and the reaction mixture was kept at 56—58° with stirring for 25 min. It was then added to ice, and the separated oil was taken up in ether–benzene. The organic layer was washed with 20% potassium carbonate solution and water and dried ($MgSO_4$). Removal of the solvents gave a yellow oil (12·2 g.) from which by crystallisation from pentane at 0° there was obtained a first crop of the *ketone* (6·61 g.) which after further crystallisation from the same solvent had m. p. 80—81° (Found: C, 71·3; H, 8·3. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 5·92 μ.

Acidification of the alkaline extracts from this reaction gave recovered acid (6·6 g.) which was again cyclised as described above. The neutral portion from this cyclisation (3·6 g.) was combined with the mother-liquors of the first crop of the above ketone, and the whole was chromatographed in hexane on activated alumina (200 g.). Elution with hexane gave a non-ketonic fraction (3·6 g.), followed by the ketone (eluted with methylene chloride) (6·05 g.), making the total yield of ketone 65%.

From this ketone two 2,4-*dinitrophenylhydrazones* were obtained and separated by fractional crystallisation: (*a*) (red), m. p. 198—199° (from cyclohexane) (Found: C, 60·35; H, 6·1; N, 11·25. $C_{25}H_{30}N_4O_7$ requires C, 60·25; H, 6·05; N, 11·25%), and (*b*) (yellow), m. p. 128—129° (from hexane) (Found: C, 60·3; H, 6·15; N, 11·6%).

7,7aα,8,9,10,11,12,12aβ-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (IIIa).—The above ketone (5·48 g.) was reduced with sodium borohydride in methanol, and the resulting alcohol dehydrated with naphthalene-2-sulphonic acid in benzene, by the general procedure described previously.[1] The resulting *olefin* was distilled at 125—130°/$10^{-2}$ mm., to give an oil (4·46 g.) which crystallised; it recrystallised from methanol as needles, m. p. 89—90° (Found: C, 75·95; H, 8·65. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·65%), $\lambda_{max.}$ 258 mμ (ε 10,800), $\nu_{max.}$ 6·26 and 6·40 μ.

5,6,7,7aα,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (C).—(*a*) The foregoing olefin was catalytically hydrogenated in methanol over 10% palladium–carbon, to give the saturated trans-*compound*, m. p. 86—87° (from methanol) (Found: C, 74·95; H, 9·4. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%), $\lambda_{max.}$ 280 mμ (ε 1050).

(*b*) The ketone (XXXI) (see preceding paper) (140 mg.) was dissolved in ethanedithiol (0·14 ml.) and dioxan (0·3 ml.) in the presence of fused zinc chloride (17 mg.) and anhydrous magnesium sulphate (15 mg.). Next morning water and ether were added and the mixture was worked up in the usual manner. The crude thioketal (125 mg.) was heated in dry ethanol (6 ml.) with Raney nickel (*ca.* 2 g.) under reflux for 3 hr., and the mixture then filtered and evaporated. The residue was extracted several times with hot hexane, and the extracts were filtered, concentrated, and cooled. The product which separated recrystallised from methanol, to give the *trans*-compound, m. p. 86°, undepressed on admixture with the product from experiment (*a*).

7,7aα,8,9,10,11,12,12aβ-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene*-7α-*ol* (IIIb).—To the olefin (IIIa) (4·46 g.) in boiling dry pyridine (30 ml.), selenium dioxide (freshly sublimed; 2·30 g.) was added in small portions during 3 hr., after which heating was continued for another 1·5 hr. The suspension was cooled, diluted with ether–benzene, and filtered. The filtrate was washed with cold 3N-hydrochloric acid, water, 20% potassium carbonate solution, and again water, and dried ($MgSO_4$). Removal of solvents left a dark residue which was chromatographed in methylene chloride–hexane on activated alumina (100 g.) above a short column (4·5 g.) of a mixture of alumina and precipitated silver (1 : 1). Early fractions consisted of unchanged starting material (1·84 g.); after this methylene chloride–chloroform eluted the unsaturated *alcohol* (1·45 g.) which crystallised from cyclohexane in needles, m. p. 154° (Found: C, 71·65; H, 8·15. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 2·86—2·90 (broad), 6·25 and 6·27 μ. Chromatography of the mother-liquors failed to reveal an epimer.

*Oxidation of the Alcohol* (IIIb) *with Manganese Dioxide*.—The unsaturated alcohol (0·25 g.) was dissolved in carbon tetrachloride (12 ml.) and active manganese dioxide [31] (3 g.) was added. The suspension was shaken for 8 hr. at room temperature, then filtered, and the manganese

[31] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

dioxide was washed with hot chloroform. The filtrate and washings were combined and the solvents removed. The residue was chromatographed in hexane–methylene chloride (3 : 1) on neutral active alumina. The initial solvent mixture eluted 7,7aα,8,9,10,11,12,12aβ-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7-*one* (IX) (35 mg.), m. p. 87—88° (from pentane) (Found: C, 72·35; H, 7·65. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\lambda_{max.}$ 252, 310 mμ (ε 11,300, 10,500), $\nu_{max.}$ 6·02, 6·26, and 6·40 μ. Chloroform eluted a yellow *substance* (X), m. p. 123—124° (from ether) (Found: C, 64·85; H, 6·0; O, 29·0; active H, 0·3. $C_{18}H_{20}O_6$ requires C, 65·05; H, 6·05; O, 28·9; 1H, 0·3%), $\lambda_{max.}$ 266, 351 mμ (ε 36,600, 19,300), $\nu_{max.}$ 6·01—6·10s (broad), 6·23, and 6·34 μ.

8,9,10,11,12,12a-*Hexahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (XX).—The unsaturated alcohol (IIIb) (1.38 g.) was refluxed in ethanol (100 ml.) containing concentrated hydrochloric acid (5 ml.) for 1·5 hr. The solvents were removed *in vacuo* and the residue, isolated with ether–benzene, was purified by chromatography and crystallisation from hexane, giving the *diene* (1·13 g.), m. p. 118—119° (Found: C, 75·65; H, 7·85. $C_{19}H_{24}O_3$ requires C, 75·95; H, 8·05%), $\lambda_{max.}$ 302 mμ (ε 8500), $\nu_{max.}$ 6·25 and 6·37 μ.

Catalytic hydrogenation of this diene (100 mg.) in ethanol in the presence of 10% palladium–carbon (25 mg.) gave in nearly theoretical yield the *cis*-compound (D) (see below), m. p. 86—87°, mixed m. p. 87—89°.

5,6,7,7aα,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7α-*ol* (VII; R=H).—The unsaturated alcohol (IIIb) (0·50 g.) was hydrogenated in methanol over prehydrogenated 5% palladium–calcium carbonate (50 mg.). After the theoretical amount of hydrogen was absorbed (0·5 hr.) the solution was filtered, the solvent removed, and the residue crystallised from cyclohexane, to give the 7α-*alcohol*, m. p. 151—152° (Found: C, 71·7; H, 8·8. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%), $\nu_{max.}$ 2·76 and 6·26 μ. The *acetate*, formed with acetic anhydride–pyridine at 100° (15 min.), had m. p. 106—107° (from pentane) (Found: C, 70·1; H, 8·4. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·35%). The *toluene*-p-*sulphonate*, formed from the alcohol (0·70 g.) and toluene-*p*-sulphonyl chloride (0·60 g.) in pyridine (7 ml.) at 0° overnight, had m. p. 130—131° (from ether–hexane) (Found: C, 65·9; H, 7·55; S, 6·65. $C_{25}H_{34}O_6S$ requires C, 65·8; H, 7·2; S, 6·75%), $\nu_{max.}$ 7·36 and 8·51 μ.

The alcohol (20 mg.), dissolved in dry pyridine (1 ml.), was treated at 0° with phosphorus oxychloride (0·1 ml.), and the mixture was kept for several hours at 0°, then decomposed with ice. Ether was added and the ether layer washed with dilute potassium hydrogen carbonate solution. Evaporation of the dried organic layer gave only a trace of neutral material. Acidification of the alkaline extract followed by isolation with ether gave an oil which showed a strong test for phosphorus on sodium fusion.

5,6,7,7aα,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7-*one* (VIII).—The above 7α-alcohol (0·87 g.), dissolved in dry pyridine (9 ml.), was added to chromic oxide–pyridine complex (from 0·95 g. of the oxide). Next morning benzene–ether was added and the suspension filtered. The filtrate was washed with dilute hydrochloric acid containing 10% of ferrous sulphate, then with water, 20% potassium carbonate solution, and again with water, and dried ($MgSO_4$). Removal of solvents and crystallisation of the residue from hexane gave the *ketone* (0·76 g.), m. p. 109° (Found: C, 71·45; H, 8·4. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 5·90 μ. The yellow 2,4-*dinitrophenylhydrazone* had m. p. 196—197° (from ethanol–chloroform) (Found: C, 60·35; H, 6·1; N, 11·65. $C_{25}H_{30}N_4O_7$ requires C, 60·25; H, 6·05; N, 11·25%).

Attempted epimerisation of this ketone (180 mg.) with boiling 1% sodium methoxide solution (15 ml.) for 2 hr. led to recovery of starting material, identified by its infrared spectrum and mixed m. p.

β-cis-2-(2,3,4-*Trimethoxyphenyl*)*cycloheptylpropionic Acid* (IVc).—This was prepared, starting from the acid (IVa), in the same was as the *trans*-acid (Ic), through the intermediate cis-2-(2,3,4-*trimethoxyphenyl*)*cycloheptylmethanol* (IVb) (Found, on an evaporatively distilled sample: C, 69·15; H, 8·85. $C_{17}H_{26}O_4$ requires C, 69·35; H, 8·9%), and in comparable yield. The cis-*acid* (IVc) distilled evaporatively at 190—200°/$10^{-1}$ mm. as a very viscous oil (Found: C, 67·3; H, 8·45. $C_{19}H_{28}O_5$ requires C, 67·85; H, 8·4%).

5,6,7,7aβ,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-5-*one* (V).—The *cis*-acid (IVc) (13 g.) was cyclised with polyphosphoric acid in the same manner as the *trans*-acid (Ic), except that the temperature during the cyclisation was kept at 65—67°. The neutral product (9·88 g.) was chromatographed in hexane on alumina (200 g.). All fractions shown

to be homogeneous by infrared spectra were combined and distilled at 169°/0·1 mm., giving the cis-*ketone* (8·4 g.) as an oil (Found: C, 71·15; H, 8·25. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 5·96 μ. From this ketone two 2,4-*dinitrophenylhydrazones* were obtained: (*a*) (red), m. p. 200—201° (from cyclohexane) (Found: C, 60·2; H, 6·15; N, 11·25. $C_{25}H_{30}N_4O_7$ requires C, 60·2; H, 6·2; N, 11·2%), and (*b*) (yellow), m. p. 174° (from benzene–cyclohexane) (Found: N, 11·25%).

7,7aβ,8,9,10,11,12,12aβ-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (VIa).—The above *cis*-ketone (8·84 g.) was reduced with sodium borohydride, and the product dehydrated, as indicated for the *trans*-ketone (IIa), to the cis-*olefin* which distilled at 163°/$10^{-1}$ mm. (7·0 g.) and had m. p. 74·5—75° (from pentane at −20°) (Found: C, 75·2; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·65%), $\lambda_{max.}$ 262 mμ (ε 14,000), $\nu_{max.}$ 6·26 and 6·40 μ.

Catalytic hydrogenation of this gave 5,6,7,7aβ,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (D), m. p. 88—89° (from methanol), strongly depressed on admixture with the *trans*-compound (C) (Found: C, 74·6; H, 9·4. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%).

*Oxidation of Compound* (VIa) *with Selenium Dioxide*.—To the olefin (7·3 g.) in pyridine (40 ml.) at 85—90°, freshly sublimed selenium dioxide (3·3 g.) was added, with stirring, in small portions during 12 hr. After working up as described for the analogous oxidation of (IIIa) the crude product was chromatographed in hexane on active alumina (140 g.). Elution with hexane gave the diene (XX) (3·7 g.), identified by m. p. and mixed m. p. Chloroform–methylene chloride eluted a mixture of alcohols which were fractionally crystallised from hexane. The first crop, m. p. 150—151° (0·15 g.), was identified with the *trans*-unsaturated alcohol (IIIb) by m. p. and mixed m. p. From the mother-liquor 7,7aβ,8,9,10,11,12,12aβ-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7ξ-*ol* (VIb) (0·49 g.) was obtained, with m. p. 110—111° (from hexane) (Found: C, 71·5; H, 8·2. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%).

5,6,7,7aβ,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7ξ-*ol* (XXI).—This *alcohol* was obtained by catalytic hydrogenation of the *cis*-unsaturated alcohol (VIb) in methanol with 5% palladium–calcium carbonate; it had m. p. 138—139° (from hexane) (Found: C, 71·2; H, 9·1. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%), $\nu_{max.}$ 2·79—2·90 (broad) and 6·26 μ.

5,6,7,7aα,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7β-*ol* (XI).—The ketone (VIII) (1·05 g.) was dissolved in dry tetrahydrofuran (40 ml.) and lithium hydridotri-t-butoxyaluminate (3·0 g.) was added. The solution was left at room temperature overnight, after which acetone (5 ml.) was added and most of the solvents were then removed *in vacuo* at room temperature. Water was added; the crude product was isolated with ether–benzene and crystallised from pentane, to give the 7β-*alcohol* (0·94 g.), m. p. 105—106° (Found: C, 71·25; H, 8·75. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%). The *acetate*, formed with acetic anhydride–pyridine at 100° in 15 min., had m. p. 94·5—95° (from pentane) (Found: C, 69·85; H, 8·35. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·35%).

The mother-liquors from the alcohol were chromatographed. At first more of the same compound was obtained, but later a small amount of the more strongly absorbed 7α-alcohol (VII) (*ca.* 20 mg.), identified by m. p. and mixed m. p.

5,6,8,9,10,11,12,12a-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (XII).—(*a*) The above 7β-alcohol (0·77 g.) was dissolved in dry pyridine (5·0 ml.), and phosphorus oxychloride (0·8 ml.) was added at 0°. The mixture was kept at room temperature for 3 hr. and then decomposed by ice. The product was extracted with ether–benzene, washed with dilute hydrochloric acid, water, dilute potassium carbonate solution, and again water, and dried ($MgSO_4$). Removal of solvent and crystallisation from methanol gave the *olefin*, m. p. 102—102·5° (Found: C, 75·3; H, 8·7. $C_{19}H_{26}O_3$ requires C, 75·45; H, 8·65%).

(*b*) The toluene-*p*-sulphonate of the 7α-alcohol (VII; R = H) (1·04 g.) was heated in 2,4,6-trimethylpyridine (3·5 ml.) for 1·5 hr. Water and ether–hexane were added; the organic layer was washed with 3N-sulphuric acid and water and dried ($MgSO_4$). The residue obtained on removal of solvents was chromatographed in hexane on activated alumina (15 ml.). Elution with hexane and hexane–methylene chloride gave the (impure) olefin (0·43 g.), m. p. 90—92° (from methanol), raised on admixture with the product described under (*a*).

(*c*) The *cis*-alcohol (XXI) (0·16 g.) was treated in pyridine (1·5 ml.) with toluene-*p*-sulphonyl chloride (0·11 g.) at 0° overnight. The usual working-up gave an oil which was refluxed with 2,4,6-trimethylpyridine (1 ml.) for 1 hr. Working up as under (*b*) gave the (impure) olefin (0·06 g.), m. p. 95—97°, raised on admixture with the product described under (*a*).

Catalytic hydrogenation of the olefin obtained as under (*a*) (50 mg.) in acetic acid in the

presence of platinum oxide (10 mg.) gave in practically theoretical yield the *cis*-compound (D), m. p. 85—86°, mixed m. p. 88—89°.

5,6,7,7a,8,9,10,11-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (XIII) (*Deacetamidotetrahydrodemethoxydeoxocolchicine*).—(*a*) Colchicine was degraded as described by Rapoport *et al.*[4] The product had m. p. 76—77° (lit.,[4] 76·4—77·5°).

(*b*) A solution of the olefin (XII) (100 mg.; m. p. 95—97°) in chloroform (4 ml.) was saturated with dry hydrogen chloride at −10° and left at this temperature overnight. The chloroform was then removed *in vacuo* and the residue crystallised from methanol to give the olefin (XIII), m. p. 72—74° (52 mg.). Further crystallisation from methanol gave needles, m. p. 78—78·5°, undepressed on admixture with the degradation product. The infrared spectra of the two compounds (in $CHCl_3$ and $CS_2$) were identical.

This method gave a purer product than treatment with the boron trifluoride–ether complex in benzene, as previously described.[2]

The synthetic product (20 mg.) with ethereal monoperphthalic acid gave the epoxide, m. p. 116·5° (from hexane) (lit.,[4] m. p. 116—117°).

4 - *Bromo* - 5,6,7,7aα,8,9,10,11,12,12aβ - *decahydro* - 1,2,3 - *trimethoxybenzo*[a]*heptalen* - 7 - *one* (XIV).—To the ketone (VIII) (0·58 g.) and sodium acetate (0·31 g.) in acetic acid (5 ml.) and ether (4 ml.), 0·5M-bromine in acetic acid (4·26 ml.) was added dropwise with stirring at room temperature, and the suspension was stirred for another 0·5 hr. More ether and 5% sodium sulphite solution were added; the organic layer was washed with sodium hydrogen carbonate solution, then with water, and dried ($MgSO_4$) Removal of solvent and crystallisation from pentane gave the *bromo-ketone* (0·62 g.), m. p. 121—122° (Found: C, 57·15; H, 6·25; Br, 20·2. $C_{19}H_{25}BrO_4$ requires C, 57·45; H, 6·35; Br, 20·1%); it showed the ketone band at 5·86 μ, but the aromatic band at 6·25 μ was very weak. The 2,4-*dinitrophenylhydrazone* had m. p. 176° (from ethanol) (Found: N, 9·75; Br, 13·85. $C_{25}H_{29}BrN_4O_7$ requires N, 9·7; Br, 13·85%).

Dehalogenation of this bromo-ketone (44 mg.) by shaking it in hydrogen in methanol (4 ml.) in the presence of pre-reduced 5% palladium–calcium carbonate (20 mg.) gave an oil (31 mg.) which, crystallised from hexane, had m. p. 104—105°, raised on admixture with the ketone (VIII). The infrared spectra were identical.

4 - *Bromo* - 5,6,7,7aα,8,9,10,11,12,12aβ - *decahydro* - 1,2,3 - *trimethoxybenzo*[a]*heptalen* - 7β - *ol* (XVI).—The above bromo-ketone (0·60 g.) was reduced with lithium hydridotri-t-butoxyaluminate in tetrahydrofuran, as described for reduction of the ketone (VIII), giving the 4-*bromo*-7β-*alcohol* (0·49 g.), m. p. 99—100° (from pentane) (Found: C, 57·3; H, 7·1; Br, 20·0. $C_{19}H_{27}BrO_4$ requires C, 57·2; H, 6·8; Br, 20·05%), $\nu_{max.}$ 2·79 μ (sharp).

Treatment of this alcohol (0·35 g.) with phosphorus oxychloride in pyridine at 0° as described for formation of the olefin (XII) from the alcohol (XI) gave a product (0·30 g.) which was chromatographically homogeneous but did not crystallise; it was evidently the bromo-olefin (XVII). The aromatic band at 6·25 μ was absent.

4-*Bromo*-5,6,7,7aα,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7α-*ol* (VII; R = Br).—The acetate of the alcohol (VII) (0·24 g.), and sodium acetate (0·11 g.), dissolved in acetic acid (1·75 ml.) and ether (3·4 ml.), were treated dropwise with 0·5M-bromine in acetic acid (1·5 ml.). Working-up as described for the bromo-ketone (XIV) gave an oil which was hydrolysed by boiling 5% methanolic sodium hydroxide (15 ml.) in 15 min. Addition of water and isolation with ether–benzene gave the 4-*bromo*-7α-*alcohol* (0·20 g.), m. p. 90—91° (from ether–pentane) (Found: C, 57·35; H, 6·5; Br, 20·45%).

4-*Bromo*-5,6,7,9,10,11,12,12a-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7-*one* (?) (XV).—The bromo-ketone (XIV) (1·09 g.) was dissolved in acetic acid (18 ml.) and ether (15 ml.), and a few drops of hydrogen bromide in acetic acid were added. 0·5M-Bromine in acetic acid (6·4 ml.) was added dropwise with stirring, excess of bromine being avoided. Sodium acetate (0·24 g.) was then added and the solvents were removed *in vacuo* at room temperature. After addition of water the product was taken up in ether–benzene, washed with potassium hydrogen carbonate solution and water, and dried ($MgSO_4$). The residue obtained on removal of solvents *in vacuo* was heated in dry pyridine (6 ml.) at 120—130° during 1·25 hr. After cooling, ether–benzene was added and the organic layer washed with dilute hydrochloric acid and water and dried ($MgSO_4$). The oily product (1·08 g.) was chromatographed in hexane on neutral activated alumina. Elution with methylene chloride and crystallisation from pentane gave the unsaturated *bromo-ketone* (0·46 g.), m. p. 141—142° (Found: C, 57·9; H, 6·1; Br, 20·2. $C_{19}H_{23}O_4Br$ requires C, 57·75; H, 5·85; Br, 20·2%), $\nu_{max.}$ 5·99 (unsaturated ketone), 5·85w,

6·19s μ (no aromatic band at 6·25 or styrene band at 6·40 μ), with no selective absorption in the range 220—300 mμ.

Shaking this bromo-ketone (0·13 g.) under hydrogen in methanol over pre-reduced 5% palladium–calcium carbonate (0·13 g.) gave an oil (0·10 g.) (negative Beilstein test) which after chromatography on active alumina (Woelm; activity I; 2·5 g.) and crystallisation from hexane gave the ketone (VIII), m. p. 103—104°, raised on admixture (correct infrared spectrum).

*Oxidation of Compound* (XII) *with Selenious Acid.*—To the olefin (0·64 g.), dissolved in ether (21 ml.), acetic acid (17 ml.), and water (3·4 ml.), was added a 0·1N-solution of selenious acid in acetic acid (16·2 ml.). The whole was kept at room temperature for 2 days, after which the precipitate of selenium was filtered off. To the filtrate a 50% solution of potassium hydroxide (60 ml.) was added, with cooling to 0°, and the product was extracted with ether–benzene. The extract was washed, dried ($MgSO_4$), and evaporated. The residue was dissolved in 5% methanolic potassium hydroxide (30 ml.) and left at room temperature overnight. Water was added and the product extracted with ether–benzene. The extract was washed and dried ($MgSO_4$) and the residue obtained on removal of solvents chromatographed in hexane on active alumina (12 mg.) above a short column (1·6 g.) of 1 : 1 alumina–precipitated silver. Hexane eluted the diene (XX) (110 mg.), identified by m. p. and mixed m. p. Methylene chloride, chloroform, and chloroform–methanol (96 : 4) eluted a mixture of alcohols which were separated by fractional crystallisation from ether–hexane, giving (*a*): 5,6,7,7a,8,9,10,11-*hexahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7ξ-*ol* (XXII) (?) (30 mg.), feathery needles (from hexane), m. p. 160—161° (Found: C, 71·55; H, 8·32. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\lambda_{max.}$ 258 mμ (ε 10,400), $\nu_{max.}$ 2·76 (sharp), 6·25, and 6·39 μ; and (*b*) 5,6,8,9,10,11,12,12aβ-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-8ξ-*ol* (XXIII) (120 mg.), prisms (from ether–hexane), m. p. 135—136° (Found: C, 71·5; H, 8·35%), $\lambda_{max.}$ 279 mμ (ε 2500), $\nu_{max.}$ 2·79 and 6·26 μ.

5,6,8,9,10,11,12,12a-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-8-*one* (XXIV).—The unsaturated alcohol (XXIII) (50 mg.) in pyridine (0·5 ml.) was added at 0° to chromic oxide–pyridine complex (from 55 mg. of the oxide and 0·5 ml. of pyridine), and the mixture was left overnight at room temperature. Working up as described for the oxidation of (VII), chromatography, and crystallisation from hexane gave the unsaturated *ketone* (20 mg.), m. p. 128—129° (Found: C, 72·4; H, 7·7. $C_{19}H_{24}O_4$ requires C, 72·4; H, 7·65%), which had no selective absorption at 220—300 mμ, and $\nu_{max.}$ 5·95, 6·15, and 6·25 μ.

8,9,10,11,12,12a-*Hexahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-8ξ-*ol* (XXVII).—The diene (XX) (1·15 g.) was dissolved in pyridine (20 ml.), and selenium dioxide (freshly sublimed, 0·51 g.) was added to the refluxing solution in small portions during 2·5 hr., after which heating was continued for another 2·5 hr. The mixture was worked up as described for the oxidation of compound (IIIa) (see above), and the product chromatographed in hexane on active alumina. After elution of unchanged starting material (0·38 g.) with hexane, methylene chloride–chloroform eluted the unsaturated *alcohol* (0·30 g.) which after crystallisation from ether–hexane and intensive drying had m. p. 130—131° (Found: C, 72·25; H, 7·75. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·56%), $\lambda_{max.}$ 304 mμ (ε 6600), $\nu_{max.}$ at 2·77 (sharp), 6·25, and 6·40 μ.

5,6,7,7aβ,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-8ξ-*ol* (XXVIII).—The alcohol (XXVII) (0·30 g.) was hydrogenated in methanol in the presence of pre-reduced 5% palladium–calcium carbonate (50 mg.). Two mol. of hydrogen were rapidly absorbed, giving, after filtration and removal of solvent, the cis-*alcohol*, which after crystallisation from cyclohexane had double m. p. 118—119°, 125—126° (0·25 g.) (Found: C, 71·2; H, 8·65. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%), $\nu_{max.}$ 2·75 (sharp) and 6·25 μ.

Treatment of this alcohol with phosphorus oxychloride–pyridine as described for the alcohol (VII) led to a phosphate.

The *acetate*, prepared by use of acetic anhydride–pyridine at 100° for 25 min., had m. p. 94·5—95° (from pentane), strongly depressed on admixture with the acetate of alcohol (XI) (Found: C, 69·8; H, 8·45. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·35%).

5,6,7,7aβ,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-8-*one* (XXV).—(*a*) The *cis*-alcohol (XXVIII) (142 mg.) was oxidised with chromic oxide–pyridine complex, and the product worked up as described for the oxidation of compound (VII), chromatographed, and crystallised from ether–hexane, to give the cis-*ketone*, m. p. 130—131° (Found: C, 71·5; H, 8·1. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 5·94 and 6·25 μ (no band at 6·15 μ). The 2,4-*dinitrophenylhydrazone* had m. p. 215—216° (from ethanol–chloroform) (Found: C, 60·35; H, 6·05; N, 11·45. $C_{25}H_{30}N_4O_7$ requires C, 60·25; H, 6·05; N, 11·25%).

(*b*) The unsaturated ketone (XXIV) (40 mg.) was catalytically hydrogenated in methanol over 5% palladium–barium sulphate (30 mg.). The product, after filtration, removal of solvent, and crystallisation from hexane, had m. p. 126—127°, raised to 128—129° on admixture with the product obtained as under (*a*), but depressed to 119—120° on admixture with starting material.

*Conversion of Ketone* (XXV) *into Compound* (D).—The ketone (40 mg.) was dissolved in ethane-1,2-dithiol (0·04 ml.) in the presence of fused zinc chloride (5 mg.) and anhydrous magnesium sulphate (4 mg.). After the mixture had been left overnight at room temperature water was added and the product extracted with chloroform, washed with 15% potassium hydroxide solution and water, and dried ($MgSO_4$). Removal of the solvent left a residue whose infrared spectrum showed no carbonyl band. It was refluxed in ethanol (5 ml.) with Raney nickel (*ca.* 2 g.) for 3 hr. After filtration, the ethanol was removed from the filtrate and the residue dissolved in hot hexane. The hexane solution was filtered, concentrated, and cooled. The product which crystallised (25 mg.) had m. p. 80—82°, raised to 84—85° on admixture with the *cis*-compound (D). Comparison of infrared spectra also confirmed the identity.

*Reconversion of Ketone* (XXV) *into Alcohol* (XXVIII).—To the ketone (0·20 g.) in dry tetrahydrofuran (4 ml.) was added lithium hydridotri-t-butoxyaluminate (0·30 g.). The mixture was left at room temperature overnight, and acetone (2 ml.) was added, whereafter the working up followed the usual procedure. The product (0·18 g.), after recrystallisation from hexane, had m. p. 119—121°, undepressed on admixture with alcohol (XXVIII). The infrared spectra of the two alcohols and of their acetates were identical.

*Epimerisation of Ketone* (XXV).—The ketone (74 mg.) was refluxed under nitrogen for 2 hr. with 1% methanolic sodium methoxide (6 ml.). The usual working up gave 5,6,7,7aα,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-8-*one* (XXVI), which after crystallisation from hexane had m. p. 149·5—150° (Found: C, 71·85; H, 8·15. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 5·91 μ.

*Addition of Bromine to Compounds* (XII) *and* (XVII), *and Amination of the Products.*—(*a*) The olefin (XII) (0·30 g.) in carbon tetrachloride (4 ml.) was treated dropwise during 20 min. with a 0·5M-solution of bromine in the same solvent (1·98 ml.). The mixture was kept at room temperature for 1 hr., water was added, the organic layer was dried ($MgSO_4$), and the solvent removed, giving an oil (0·45 g.) which still showed the aromatic 6·25 μ band in its infrared spectrum. This was dissolved in dioxan (4 ml.), and liquid ammonia (10 ml.) was added. The mixture was left in a sealed tube at room temperature for 18 hr. during which a precipitate of ammonium bromide separated. After removal of the ammonia, ether–benzene was added, and the solution was washed with water and then extracted with 3N-hydrochloric acid (3 × 15 ml.). The acidic extracts were basified with potassium carbonate solution, and the product isolated with ether, as an oil (122 mg.). This was dissolved in dry ether, and pyridine (0·3 ml.) and benzoyl chloride (0·15 ml.) were added. After the mixture had been left overnight at room temperature ice was added and the mixture was worked up in the usual manner. The product was twice chromatographed on hexane, giving eventually 17 mg. of material, m. p. 131—134°, which gave a negative Beilstein test for halogen. This was apparently the *amide* (XVIII) (Found: N, 3·4. $C_{26}H_{31}NO_4$ requires N, 3·3%); it showed no selective ultraviolet absorption (220—300 mμ), and no styrene band at 6·40 μ.

(*b*) The crude bromo-olefin (XVII) (0·14 g.), in carbon tetrachloride (4 ml.), was treated dropwise during 20 min. with a 0·5M-solution of bromine in the same solvent (1·05 ml.). The product was isolated and treated with ammoniacal dioxan under pressure as described above. The basic product from this reaction (116 mg.) was left in pyridine (2 ml.) and acetic anhydride (0·7 ml.) at room temperature overnight. The neutral portion of product was then chromatographed on alumina and eluted with hexane–methylene chloride, giving an oil (77 mg.), showing an amide band at 6·0 μ. This (73 mg.) and dry sodium acetate (21 mg.) were dissolved in acetic anhydride (3 ml.), and the solution catalytically hydrogenated in the presence of 5% palladium–carbon (30 mg.) and platinum oxide (15 mg.). One mol. of hydrogen was absorbed but the oily product (72 mg.) still showed a positive Beilstein test for halogen, showing that only the double bond had been reduced. It (68 mg.) was dissolved in methanol (4 ml.) and shaken under hydrogen with pre-reduced 5% palladium–calcium carbonate (20 mg.), giving after the usual working up a *substance*, presumably the saturated *acetamide* corresponding to (XVIII) (35 mg.), m. p. 158—161° (from ether–hexane) (Found: C, 69·2; H, 8·8; N, 4·0.

$C_{21}H_{31}O_4N$ requires C, 69·75; H, 8·65; N, 3·9%), $\lambda_{max.}$ 281 mμ (ε 880), amide band at 6·05 μ, Beilstein test for halogen negative.

7-*Acetamido*-5,6,7,7a,8,9,10,11-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (XIX) (*hexahydrodemethoxydeoxocolchicine*).—This was prepared by degradation of colchicine as described by Rapoport and his co-workers;[3] it had m. p. 183° (lit.,[3] m. p. 183·5—184°).

9β-*Acetoxy*-5,6,7,7aβ,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene*.—9β-Acetoxy-8,9,10,11,12,12aβ-hexahydro-1,2,3-trimethoxybenzo[*a*]heptalene (XXIX) (see preceding paper) (100 mg.) was catalytically hydrogenated in methanol over pre-reduced 4% palladium–strontium carbonate (13 mg.). Filtration, removal of solvent, and crystallisation of the residue from hexane gave the *acetate* of the *cis*-alcohol (XXX), m. p. 113·5—114° (Found: C, 69·3; H, 8·2. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·35%).

Alkaline hydrolysis of this gave 5,6,7,7aβ,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9β-*ol* (XXX), m. p. 119—119·5° (from cyclohexane) (Found: C, 71·35; H, 8·7. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

5,6,7,7aβ,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9-*one*.—The above alcohol (62 mg.) was oxidised with the chromic oxide–pyridine complex (from 65 mg. of the oxide). The usual working up gave the cis-*ketone*, m. p. 150·5—151° (from hexane) (Found: C, 71·45; H, 8·2. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), $\nu_{max.}$ 5·92 μ.

*Oxidation of Compound* (XXXIV) *with Manganese Dioxide*.—9β-Acetoxy-7,7aα,8,9,10,11,12,12aβ-octahydro-7α-hydroxybenzo[*a*]heptalene (see preceding paper) (0·13 g.) was shaken in carbon tetrachloride (3 ml.) with active manganese dioxide (1·1 g.), and the mixture worked up as described for the analogous oxidation of compound (IIIb). The product was chromatographed on active alumina (3 g.). Elution with hexane gave a small amount of non-crystalline material, followed by a yellow *substance* (65 mg.), eluted with methylene chloride–chloroform. This had m. p. 150—152° (decomp.) (from isopropyl ether) (Found: C, 61·85; H, 5·65. $C_{20}H_{22}O_8$ requires C, 61·55; H, 5·7%), $\lambda_{max.}$ 263, 351 mμ (ε 36,400, 19,200).

1,2,3,4,4aβ,6,7,11bβ-*Octahydro*-9,10,11-*trimethoxy*-5H-*dibenzo*[a,c]*cycloheptatrien*-5β-*ol* (XXXVI).—1,2,3,4,4aβ,11bβ-Hexahydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptatrien-5β-ol[1] (1·90 g.) was catalytically hydrogenated in ethanol over 4% palladium–strontium carbonate (220 mg.). Concentration of the filtered solution and crystallisation of the product from cyclohexane gave the saturated 5β-*alcohol*, needles, m. p. 132° (Found: C, 70·6; H, 8·5. $C_{18}H_{26}O_4$ requires C, 70·55; H, 8·55%), $\nu_{max.}$ 2·76—2·90 μ (broad). The *acetate* formed with acetic anhydride–pyridine at room temperature had double m. p. 112—113° (needles), 129° (prisms) (from hexane); crystallisation from methanol gave only the high-melting form (Found: C, 68·85; H, 8·15. $C_{20}H_{28}O_5$ requires C, 68·95; H, 8·1%).

Treatment of the alcohol (1·0 g.) with toluene-*p*-sulphonyl chloride (0·74 g.) in pyridine (4 ml.) at room temperature for 4 hr. gave, after the usual working up, the *toluene*-p-*sulphonate* (1·45 g.), which crystallised from methanol as needles, m. p. 150° (Found: S, 7·0. $C_{25}H_{32}O_6S$ requires S, 6·95%), $\nu_{max.}$ 7·36, 8·51 μ.

Oxidation of the alcohol (120 mg.) with chromic oxide–pyridine complex (from 0·15 g. of the oxide) gave 1,2,3,4,4aβ,6,7,11bβ-octahydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptatrien-5-one[1] (XXXVII) (80 mg.), m. p. and mixed m. p. 115° (from hexane).

Reaction of the alcohol (0·30 g.) with phosphorus oxychloride (0·3 mg.) in pyridine (3 ml.) at room temperature for 3 hr., followed by addition of ice, ether-extraction, and washing of the ether layer with dilute acid and 10% sodium carbonate solution, gave only traces of neutral material. Acidification of the alkaline extract and ether-extraction gave a semicrystalline product which gave a strong test for phosphorus on sodium fusion.

1,2,3,4,4aβ,6,7,11bβ-*Octahydro*-9,10,11-*trimethoxy*-5H-*dibenzo*[a,c]*cycloheptatrien*-5α-*ol* (XXXVIII).—The ketone (XXXVII) (270 mg.) was refluxed in ether (10 ml.) with lithium aluminium hydride (0·12 g.) for 2 hr. After the usual working up the crude product was crystallised from cyclohexane, to give the 5α-*alcohol* (247 mg.), needles, m. p. 163·5—164° (Found: C, 70·15; H, 8·45. $C_{18}H_{26}O_4$ requires C, 70·55; H, 8·55%), $\nu_{max.}$ 2·78 μ (sharp). The *acetate*, formed by acetic anhydride–pyridine at 100° for 2 hr., crystallised as needles (from cyclohexane), m. p. 161° strongly depressed on admixture with starting material (Found: C, 68·55; H, 8·0. $C_{20}H_{28}O_5$ requires C, 68·95; H, 8·1%). Attempted acetylation at room temperature returned mostly unchanged material.

Oxidation of the alcohol with chromic oxide–pyridine complex returned the ketone (XXXVII), identified by mixed m. p.

1,2,3,4,6,7-*Hexahydro*-9,10,11-*trimethoxy*-11bH-*dibenzo*[a,c]*cycloheptatriene* (XL).—To the alcohol (XXXVIII) (147 mg.) in pyridine (0·6 ml.) was added phosphorus oxychloride (0·18 ml.) at −10°. The suspension was then kept at room temperature for 3 hr. After decomposition with ice, the product was isolated with ether and crystallised from methanol, to give the *olefin* (90 mg.) as prisms, m. p. 116·5—117° (Found: C, 75·0; H, 8·35. $C_{18}H_{24}O_3$ requires C, 74·85; H, 8·4%), $\lambda_{max.}$ 279 mμ (ε 1070, $\nu_{max.}$ 12·25s μ (in $CS_2$).

4aα,5α-*Epoxy*-1,2,3,4,4a,6,7,11bβ-*Octahydro*-9,10,11-*trimethoxy*-5H-*dibenzo*[a,c]*cycloheptatriene* (XVIII).—The olefin (XL) (0·73 g.) in chloroform (1 ml.) was treated overnight at 5° with ethereal monoperphthalic acid (0·3 mmole/ml.; 10·0 ml.). The usual working up gave a product which was recrystallised from cyclohexane, to give the *epoxide* (0·65 g.), m. p. 160·5—161·5°. The analytical sample had m. p. 164° (Found: C, 70·85; H, 8·05. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%).

After this epoxide had been heated for 3 hr. at 120° in a sealed tube in dioxan previously saturated at 0° with ammonia, only unchanged starting material, identified by m. p. and mixed m. p., was obtained.

1,2,3,4,4aβ,11bβ-*Hexahydro*-9,10,11-*trimethoxy*-7H-*dibenzo*[a,c]*cycloheptatriene* (XXXIX).—The toluene-*p*-sulphonate of the alcohol (XXXVI) (1·0 g.) was heated under reflux with 2,4,6-trimethylpyridine (5 ml.) for 2 hr. The neutral product, isolated with ether, was once crystallised from methanol, to give a mixture, m. p. 102—105°, whose infrared spectrum (in $CS_2$) was the sum of those of (XL) and (XXXIX) (see below).

This mixture (0·54 g.) in chloroform (1·0 ml.) was treated with ethereal monoperphthalic acid (0·17 mmole/ml.; 7·15 ml., 15% excess), and the solution was left at 0° for 2 days. The usual working up gave a crude product which was once crystallised from cyclohexane, giving the epoxide (XLIII) (210 mg.), m. p. and mixed m. p. 161—162°. The mother-liquors were evaporated to a gum (330 mg.), which was chromatographed in hexane on active alumina (Fisher; 7 g.). The initial solvent eluted the *olefin* (239 mg.), m. p. 102—103° (from methanol). Recrystallisation from methanol until there was no further change in the fingerprint region of the infrared spectrum (in $CS_2$, see below) gave needles, m. p. 105—105·5° (Found: C, 74·5; H, 8·8. $C_{18}H_{24}O_3$ requires C, 74·95; H, 8·4%), $\lambda_{max.}$ 279 mμ (ε 1200), no pronounced absorption in 12—13 μ region (in $CS_2$).

Catalytic hydrogenation of the olefins (XL) and (XXXIX), over platinum in acetic acid, or palladium–calcium carbonate, in methanol gave in both cases and in practically quantitative yield 1,2,3,4,4aβ,6,7,11bβ-octahydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptatriene [1] (XLVII), identified by m. p. and mixed m. p.

1,2,3,4a,6,7,11bβ-*Octahydro*-9,10,11-*trimethoxy*-5H-*dibenzo*[a,c]*cycloheptatrien*-4aα-*ol* (XLIV).—The epoxide (XLIII) (0·59 g.) was refluxed with lithium aluminium hydride (0·35 g.) in ether (4 ml.) and tetrahydrofuran (4 ml.) for 7 hr. The product obtained in the usual way crystallised from cyclohexane, giving the tertiary *alcohol* (0·44 g.), m. p. 128·5—129°. The analytical sample (needles from methanol) had m. p. 132—132·5° (Found: C, 70·45; H, 8·6. $C_{18}H_{26}O_4$ requires C, 70·55; H, 8·55%), $\nu_{max.}$ 2·79 μ. This compound was recovered unchanged after treatment with excess of chromic oxide–pyridine complex or acetic anhydride–pyridine for 2 days at room temperature.

2,3,4,4a,6,7-*Hexahydro*-9,10,11-*trimethoxy*-5H-*dibenzo*[a,c]*cycloheptatriene* (XLI).—A solution of the olefin (XL) (0·27 g.) in chloroform (5 ml.) was saturated at −10° with dry hydrogen chloride and left overnight at this temperature. The chloroform was then removed *in vacuo* and the residue distilled at 160° (bath)/$10^{-2}$ mm. The distillate of the isomeric *olefin* crystallised spontaneously; it had m. p. 62—63° (Found: C, 75·1; H, 8·15. $C_{18}H_{24}O_3$ requires C, 74·95; H, 8·4%), $\lambda_{max.}$ 252 (ε 9500), $\lambda_{min.}$ 238 mμ (ε 7600).

*Dehydration of the Alcohol* (XLIV).—The tertiary alcohol (94 mg.) was heated in pyridine (0·25 ml.) with phosphorus oxychloride (0·10 ml.) at 100° for 1 hr. The customary working up gave a solid which after crystallisation from methanol had m. p. 69—73° unchanged by further crystallisation and sublimation at 65°/$10^{-4}$ mm. (Found: C, 75·1; H, 8·4%), $\lambda_{max.}$ 251 mμ (ε 5550), $\lambda_{min.}$ 244 mμ (ε 5320).

1,2,3,4-*Tetrahydro*-9,10,11-*trimethoxy*-11bH-*dibenzo*[a,c]*cycloheptatriene* (XLVI).—The unsaturated alcohol (XXXV) (65 mg.) was heated under reflux in ethanol containing 3% hydrochloric acid (3 ml.) during 1 hr. The solvents were removed and the residue crystallised from methanol, giving the *diene* as prisms, m. p. 107·5—108° (Found: C, 75·85; H, 7·7. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·75%), $\lambda_{max.}$ 293 (ε 6150), $\lambda_{min.}$ 265 mμ (ε 3650), $\nu_{max.}$ 6·26, 6·45 μ.

Catalytic hydrogenation of this diene in ethyl acetate in the presence of palladium–strontium carbonate led to the *cis*-compound (XLVII), m. p. and mixed m. p. 99—102°.

*Measurement of Relative Oxidation Rates of Alcohols.*—These were kindly determined by Professor A. Eschenmoser and Mr. L. Moldovanyi at the Eidgenössische Technische Hochschule, Zurich. The concentrations used were: $6 \times 10^{-4}$ mole/l. for the alcohols and $8 \times 10^{-4}$ mole/l. for chromic oxide, in 90·5% acetic acid at 20° ± 1°. The rate constants (see Table 1) were calculated as previously described.[32]

*Measurement of Relative Rates of Hydrolysis of Acetates.*—The acetate (0·066 mmole) was dissolved in 95% ethanol (3 ml.). To the solution was added N/30-sodium hydroxide in 67% aqueous ethanol (5·00 ml.), and the volume was made up to 10·00 ml. with 95% ethanol. The solution was kept at 25·0° ± 1°, and 1·00 ml. portions were withdrawn at intervals and titrated against 0·01N-hydrochloric acid (phenolphthalein). The results, which were checked against a control solution, are shown in Table 1.

We are indebted to Dr. M. Tischler (Merck, Sharp, and Dohme) for a generous gift of colchicine, to Drs. Forsen and Nilsson for proton magnetic resonance measurements on compound (XIII), to Professor A. Eschenmoser and Mr. L. Moldovanyi for measurements of oxidation rates, and to Professor D. Ginsburg for his interest.

CHEMISTRY DEPARTMENT, ISRAEL INSTITUTE OF TECHNOLOGY,
HAIFA, ISRAEL.

[*Received, June 10th,* 1960.]

[32] Schreiber and Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1529.