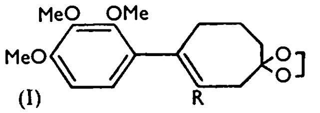
275. *Syntheses in the Colchicine Series. Part II.* Some Tricyclic Models.*

By H. J. E. Loewenthal.

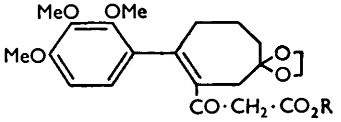
The preparation of several compounds based on dibenzo[*a,c*]*cyclo*heptatriene is described, and some aspects of their stereochemistry and of that of intermediate compounds are discussed.

In Part I the preparation of 6 : 6-ethylenedioxy-2-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hept-1-enecarboxylic acid (I; R = CO_2H), a potential intermediate for the synthesis of colchicine, was described. The primary intention was to use the carboxyl group as a starting point for constructing the elements of ring B of the alkaloid. Several ways were explored to extend a chain incorporating a potential acetamido-function while retaining the *cyclo*heptene double bond, but none of these led to a useful ring-closure product.

For example, the acid (I; R = CO_2H) was treated with methyl-lithium to give the ketone (I; R = Ac); carboxylation of this under forcing conditions with ethyl or methyl carbonate led to the keto-esters (II; R = Et or Me), which were found unsuitable for further transformations. Alternatively, the ester (I; R = CO_2Me) was reduced to the alcohol (I; R = CH_2·OH) which was smoothly oxidised with manganese dioxide to the unsaturated aldehyde (I; R = CHO). This with dimethyl malonate afforded the unsaturated diester (III); addition of nucleophilic reagents to its αβ-double bond with subsequent cyclisation to the aromatic ring also gave unpromising results. Finally, attempted decarboxylation of the ketal-acid (I; R = CO_2H) or of its derived keto-acid in order to give a 4-(2 : 3 : 4-trimethoxyphenyl)*cyclo*heptenone (IV) or its ketal (which might have been a suitable starting material for attachment of a side-chain by Michael addition) failed; the only product obtained was 7 : 8-dimethoxy-4′-oxo*cyclo*hepteno(2′ : 1′-3 : 4)-coumarin (see Part I) through elimination of methanol, even when basic conditions (copper chromite in quinoline) were used.



(I)



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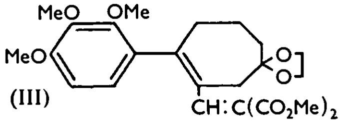

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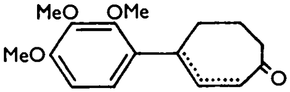

(IV)

It was decided to continue this work using a saturated system by reduction of the double bond in the alicylic ring of the acid (I), notwithstanding the ensuing stereochemical complications; the easily accessible 2-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hex-1-enecarboxylic acid (V) was taken as a model compound.

The double bond in the latter resisted catalytic reduction in non-acidic solvents, but lithium in liquid ammonia in the absence of alcohol gave in high yield a saturated acid (VI; R = CO_2H); this was believed to be the *trans*-epimer, until it was found that the methyl ester (VI; R = CO_2Me) could be epimerised in high yield (with sodium methoxide in methanol [1]) to give, after aqueous hydrolysis, the epimeric acid (VII; R = CO_2H).

Both in the lithium-ammonia reduction of acid (V) and in the epimerisation of ester (VI; R = CO_2Me) the step which determines the stereochemistry is the addition of a proton to the same carbanion, that nearest to the carboxyl group. In the epimerisation

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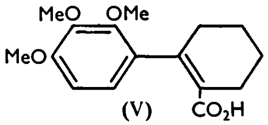
* Part I, *J.*, 1953, 3962.

[1] Compare the epimerisation of *cis*-2-phenyl*cyclo*hexanecarboxylic acid; Alder, Vagt, and Vogt, *Annalen*, 1949, **565**, 135.

this step must be thermodynamically controlled to lead to a stable *trans*-1 : 2-disubstituted *cyclo*hexane derivative. Conversely in the lithium–ammonia reduction proton addition appears to be kinetically controlled to give the unstable *cis*-epimer. This case therefore does not coincide with Barton and Robinson's views [2] on the stereochemistry of similar reductions. It must be noted that recently published work by a number of authors [3, 4, 5] on the metal–ammonia reduction of conjugated double bonds (all of them tetrasubstituted) reports the formation of an unstable *cis*-epimer as the main product. This has been explained by assuming that in the initially formed dianion the more important factor is not a favourable configuration of the anion on the carbon adjacent to the activating group (carbonyl, aryl), but greater accessability (equatorial approach) of the proton to that carbanion. In the reduction of an α-octalone a *cis*-α-decalone would then be the initial product (in the case mentioned by Birch *et al.*[3] epimerisation to the *trans*-ketone was effected simply by chromatography on alumina). Perusal of the experimental parts of the papers cited by Barton *et al.*[2] in support of their views in the steroid and triterpenoid field shows that in each case which appeared to lead to the formation of a *trans*-α-decalone the reaction product from metal–ammonia reduction was either chromatographed on alumina or subjected to more drastic alkaline treatment before being identified. Such results may therefore be misleading and perhaps should be re-investigated.



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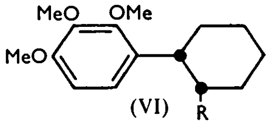

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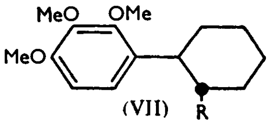

(VII)

Reduction of the *cis*-acid (VI; R = CO_2H) by lithium aluminium hydride gave the alcohol (VI; R = $CH_2{\cdot}OH$), whose toluene-*p*-sulphonate was caused to react with di-*tert.*-butyl sodiomalonate, to give after further transformations the propionic acid (VI; R = $[CH_2]_2{\cdot}CO_2H$). Cyclisation of the last acid by polyphosphoric acid gave in good yield the seven-membered ring *cis*-ketone (VIII). Application of the same reactions to the epimeric acid (VII; R = CO_2H) led to the *trans*-ketone (XIX). This was identical with the compound prepared by Gutsche and Fleming [6] and believed by them to have the *cis*-configuration, on the basis of usually accepted rules of catalytic hydrogenation, in this case of the unsaturated ester precursor of this ketone, and on the basis of melting-point relationships of similar *cis*- and *trans*-epimers. Both ketones (VIII and XIX) were easily converted into the corresponding *cyclo*alkenes (IX and XX respectively), by reduction with sodium borohydride to the corresponding alcohols which were dehydrated without purification with naphthalene-β-sulphonic acid in benzene.

Oxidation of the *cyclo*alkene (IX) with selenium dioxide in pyridine gave a mixture, separable by chromatography. The main products were the unsaturated alcohol (X) and the unsaturated ketone (XIII) which was itself obtained from (X) by oxidation with manganese dioxide. Minor products are formulated as: the ketone (XI) [possibly formed as a result of an allylic shift in (X)] since on catalytic hydrogenation it gave the original ketone (VIII), although the αβ-unsaturated ketone characteristics of both its infrared and ultraviolet spectra were abnormally weak; and a compound $C_{18}H_{22}O_5$ [possibly (XII)] whose infrared and ultraviolet spectra were similar to those of (XIII) and whose analysis showed the presence of an additional hydroxyl group.

Catalytic reduction of the unsaturated ketone (XIII) gave the saturated *cis*-ketone

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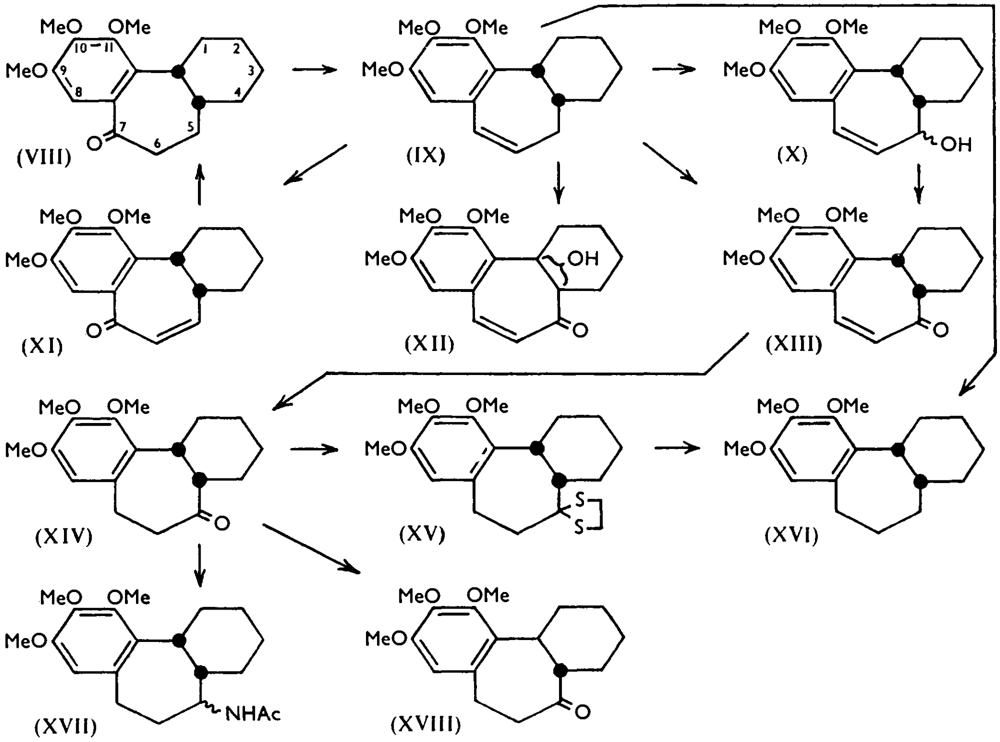
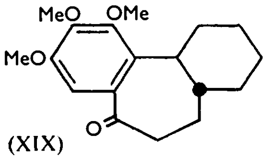
[2] Barton and Robinson, *J.*, 1954, 3045.
[3] Birch, Smith, and Thornton, *J.*, 1957, 1339.
[4] Zimmerman, *J. Amer. Chem. Soc.*, 1956, **78**, 1168.
[5] Johnson, Ackerman, Eastham, and Dewalt, *ibid.*, p. 6302.
[6] Gutsche and Fleming, *J. Amer. Chem. Soc.*, 1954, **76**, 1771.

(XIV) which was epimerised to its *trans*-epimer (XVIII) to the extent of about 35—45% by either acid or base. Surprisingly, the unsaturated ketone (XIII) could not be epimerised. Further, the olefin (XX) was inert to the action of selenium dioxide under the conditions used for the oxidation of its epimer (IX). These phenomena became clearer to understand when models of these two olefins were examined. These show that only with a *cis*-fusion, such as exists in (IX), is it possible for the olefinic double bond to be coplanar with the aromatic ring. A confirming fact is the difference in light absorption between these two compounds: (IX) $\lambda_{\max.}$ 263 mμ, ε 13,100; (XX) $\lambda_{\max.}$ 260 mμ, ε 8950; and presumably coplanarity in (IX) explains the resistance of the unsaturated *cis*-ketone (XIII) to epimerisation, which would decrease the resonance of the extended conjugated system (a factor which would disappear on reduction of the double bond).





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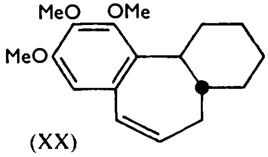

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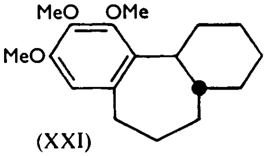


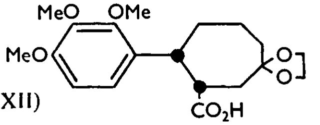
(XXI)

Reduction of the oxime of the ketone (XIV) by lithium aluminium hydride, followed by acetylation, gave the amide (XVII) as a mixture of two substances, possibly epimeric at $C_{(5)}$, thus completing the actual construction of a ring B analogue of colchicine.

In order to show that in the route (IX) ⟶ (XIV) the original *cis*-configuration at the ring junction had been retained, the ketone (XIV) was converted into the ethylene dithioketal (XV) and thence into the saturated compound (XVI) identical with the product of catalytic hydrogenation of the *cyclo*heptene (IX).

Reduction with lithium and liquid ammonia, was then applied to the unsaturated acid (I; R = CO_2H), with similar results. The main product was a low-melting saturated acid

(XXII), accompanied by a higher-melting epimer (XXIII). The ester of the latter was obtained in practically theoretical yield by epimerising the methyl ester of the former. While little is yet known of conformational preferences in a seven- as compared with a six-membered ring, the acids (XXII) and (XXIII) may be reasonably formulated as the *cis*- and the *trans*-epimer, respectively.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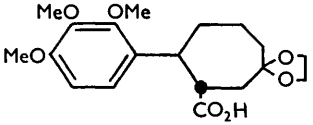
(XXIII)

EXPERIMENTAL

Infrared spectra refer to $CHCl_3$ solutions.

2-*Acetyl*-1-(2 : 3 : 4-*trimethoxyphenyl*)-4 : 4-*ethylenedioxy*cyclo*heptene* (I; R = Ac).—The acid (I; R = CO_2H) (3·65 g.), in benzene (25 ml.), was added with stirring at 0° to an ethereal N-solution of methyl-lithium (30 ml.). After several hours' stirring at room temperature water was added and the mixture was separated into neutral (2·83 g.) and recovered acid (0·88 g.) fractions. The neutral fraction was distilled at 200° (bath)/0·01 mm., to give the *ketone* as a clear oil which solidified after several months (m. p. *ca.* 70°) (Found: C, 66·4; H, 7·6. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%). The *semicarbazone*, needles from aqueous methanol, had m. p. 170—172° (Found: C, 60·2; H, 6·25; N, 9·8. $C_{21}H_{29}O_6N_3$ requires C, 60·1; H, 7·0; N, 10·0%).

Ethyl β-[6 : 6-*Ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hept*-1-*enyl*]-β-*oxopropionate* (II; R = Et).—The above ketone (2·2 g.) in ethyl carbonate (10 ml.) was added dropwise to a refluxing suspension of sodium hydride (0·16 g.) in the same solvent (10 ml.), and the mixture was refluxed for 3 hr. during which *ca.* 5 ml. of liquid were distilled off through a short column. The mixture was then cooled and diluted with light petroleum. The sodio-derivative of the product crystallised; this was filtered off and cautiously dissolved in aqueous methanol. Saturation of the solution with carbon dioxide precipitated the β-*keto-ester* (1·50 g.), m. p. 99° (from hexane) (Found: C, 64·2; H, 7·5. $C_{23}H_{30}O_8$ requires C, 63·6; H, 7·0%). The corresponding *methyl ester* (II; R = Me) was formed in the same way, though in lower yield, by using methyl carbonate; it had m. p. 85—86° after crystallisation from hexane (Found: C, 62·5; H, 6·6. $C_{22}H_{28}O_8$ requires C, 62·8; H, 6·7%).

Attempted formation of an amino-crotonic ester, and reductive amination with hydrogen, Raney nickel catalyst, and ammonia failed with each of these esters.

2-*Hydroxymethyl*-1-(2 : 3 : 4-*trimethoxyphenyl*)-4 : 4-*ethylenedioxy*cyclo*heptene* (I; R = $CH_2{\cdot}OH$).—The ester (I; R = CO_2Me) (4·24 g.), in dry tetrahydrofuran (15 ml.), was added with stirring at −15° to a suspension of lithium aluminium hydride (0·50 g.) in ether (15 ml.). The solution was allowed to attain room temperature and then stirred for another 2 hr. The usual working-up (decomposition with Rochelle salt solution) gave the crude *alcohol* (4·20 g.) which was sufficiently pure for the next step (its infrared spectrum showed no carbonyl absorption); a sample was distilled at 200° (bath)/0·01 mm. (Found: C, 64·8; H, 8·0. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%). Crystalline derivatives could not be prepared.

4 : 4-*Ethylenedioxy*-2-*formyl*-1-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*heptene* (I; R = CHO).—The above crude alcohol (3·50 g.) was shaken in acid-free carbon tetrachloride (60 ml.) for 4 hr. with activated manganese dioxide [7] (22 g.). The mixture was filtered and the residue washed several times with acid-free chloroform. The combined filtrate and washings were concentrated *in vacuo*, to give the crude *aldehyde*, which crystallised (2·83 g.) on trituration with light petroleum. Recrystallisation from hexane gave needles, m. p. 91° (Found: C, 65·4; H, 7·2. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%). The infrared spectrum showed a strong band at 6·0 μ. The *semicarbazone* had m. p. 212—213° (from aqueous methanol) (Found: C, 59·8; H, 6·7; N, 10·3. $C_{20}H_{27}O_6N_3$ requires C, 59·2; H, 6·7; N, 10·4%).

Dimethyl α-[6 : 6-*Ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)-cyclo*hept*-1-*enylmethylene*]-*malonate* (III).—The above aldehyde (5·0 g.), dimethyl malonate (4·55 g.), piperidine (5 drops), and acetic acid (5 drops), in benzene (70 ml.), were refluxed under an azeotropic water-separator for 10 hr. The solution was cooled, washed with ice-cold dilute acetic acid, sodium hydrogen

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

carbonate solution, and water, and the solvent removed after drying. The residue was heated at 100°/0·01 mm., to remove excess of malonic ester. It then crystallised very slowly on trituration with light petroleum, to give the unsaturated *diester* (6·30 g.), m. p. 70—75°. This recrystallised with great difficulty from aqueous methanol to give prisms, m. p. 83° (Found: C, 61·9; H, 6·4; OMe, 34·2. $C_{24}H_{30}O_9$ requires C, 62·3; H, 6·5; OMe, 33·5%). The infrared spectrum showed a strong band at 5·82 μ.

Addition of cyanide ion to this unsaturated ester,[8] followed by treatment of the crude product with polyphosphoric acid under various conditions, gave mostly intractable tars from which a very small amount of a crystalline *substance*, m. p. 252° (decomp.) (from acetone), was isolated (Found: C, 66·8; H, 6·2; N, 3·9. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·5; N, 3·9%). The infrared spectrum showed a strong band at 5·87 μ and a weak band at 3·16 μ (possibly N–H frequency); this substance was not further investigated.

cis-2-(2 : 3 : 4-*Trimethoxyphenyl*)cyclo*hexanecarboxylic Acid* (VI; R = CO_2H).—The unsaturated acid [9] (V) (finely powdered; 11·0 g.) was stirred in liquid ammonia (*ca.* 600 ml.) until most of it dissolved. Lithium was added in grain-sized pieces until a blue colour persisted for more than 1 min.; the colour was then immediately discharged by addition of solid ammonium chloride. The addition took about 1 hr. and about 2—3 g.-equivs. of the metal (0·6—0·7 g.) were required. The ammonia was allowed to evaporate, finally on the steam-bath, and the solid residue was dissolved in water. The solution was saturated with sodium chloride, washed with ether, and acidified. The *acid* which separated crystallised on trituration and recrystallised from aqueous methanol as needles (8·05 g.), m. p. 127—128° (Found: C, 65·0; H, 7·65; OMe, 31·5. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5; OMe, 31·6%). The *methyl ester*, prepared with diazomethane, had m. p. 69·5—70° (needles from pentane at −10°) (Found: C, 66·2; H, 7·9. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

Hydrogenation of the acid (V) with Adams catalyst in ethanol, or reduction with Raney nickel alloy and alkali, was unsuccessful, the compound being recovered.

cis-1-*Hydroxymethyl*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hexane* (VI; R = $CH_2{\cdot}OH$).—The above saturated acid (17·82 g.), in dry tetrahydrofuran (50 ml.), was added with stirring to a suspension of lithium aluminium hydride (5·0 g.) in ether (50 ml.), and the mixture was refluxed for 4 hr., then worked up in the usual way; the ether and tetrahydrofuran were removed *in vacuo* and the oil taken up in benzene. The organic layer was washed with 10% sodium hydroxide solution, and then water, and dried. Removal of the solvent gave the crude *alcohol* (15·76 g.), which was used without purification. A sample was evaporatively distilled at 180° (bath)/0·01 mm. (Found: C, 68·2; H, 8·4. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%). The p-*nitrobenzoate* formed yellowish needles (from hexane), m. p. 107° (Found: C, 64·8; H, 6·2; N, 3·5. $C_{23}H_{27}O_7N$ requires C, 64·3; H, 6·3; N, 3·3%).

β-[cis-2-(2 : 3 : 4-*Trimethoxyphenyl*)cyclo*hexyl*]*propionic Acid* (VI; R = $[CH_2]_2{\cdot}CO_2H$).—The above crude alcohol (20·5 g.) was dissolved in dry pyridine (56 ml.), and the solution was distilled to remove *ca.* 5 ml. of solvent. After cooling to 0° toluene-*p*-sulphonyl chloride (14·6 g.) was added with shaking. The solution was left at 0° overnight, then water, containing the theoretical amount of potassium hydrogen carbonate, was added. The oil which separated was twice extracted with ether–benzene. The extract was washed successively with water, ice-cold dilute hydrochloric acid (twice), water, dilute sodium carbonate solution, and sodium chloride solution, and dried. Removal of the solvents in *vacuo* left the crude oily toluenesulphonate (31·3 g.). This, dissolved in the minimum amount of dry benzene, was added to a suspension of di-*tert.*-butyl sodiomalonate, prepared from the ester (31·5 g.) and sodium hydride (3·1 g.) in dry benzene (100 ml.). The mixture was refluxed for 30 hr. Water was then added to dissolve the precipitated solids, and to the dried benzene layer toluene-*p*-sulphonic acid (1·0 g.) was added. The solution was heated under reflux until gas evolution had ceased (3—4 hr.), then washed with the minimum amount of water, and dried again and the benzene was removed *in vacuo*. The residue was heated at 170—200° until no more carbon dioxide was evolved (10 min.), cooled, and taken up in ether. The ether solution was extracted several times with 10% sodium carbonate solution. Acidification of the extracts liberated the *acid* as an oil (13·5 g.) which was isolated with benzene. A sample was evaporatively distilled at 200° (bath)/0·01 mm. (Found: C, 67·3; H, 8·2. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·1%).

cis-1 : 2 : 3 : 4 : 4*a* : 5 : 6 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxy*-7-*oxodibenzo*[a,c]cyclo*heptatriene*

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[8] Allen and Johnson, *Org. Synth.*, 1950, **30**, 83.

[9] Boekelheide and Pennington, *J. Amer. Chem. Soc.*, 1952, **74**, 1558.

(VIII).—To the above crude acid (5·00 g.) polyphosphoric acid, prepared from 85% orthophosphoric acid (38 ml.) and phosphoric oxide (60 g.), was added, and the resulting red solution was heated at 75—85° for 1 hr. with occasional shaking. Ice was added and the solution was extracted several times with methylene chloride–ether. The extracts were washed with 10% sodium hydroxide solution and water. Removal of solvents from the dried extract left a residue (4·63 g.) which solidified and recrystallised from benzene–methanol, to give the *ketone* (3·85 g.), needles, m. p. 107° (Found: C, 71·2; H, 7·7. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The 2 : 4-*dinitrophenylhydrazone* formed orange-red leaflets, m. p. 222—223° (Found: C, 58·8; H, 5·8; N, 11·5. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8; N, 11·6%); this m. p. was obtained only after slow recrystallisation from benzene–*cyclo*hexane; recrystallisation from chloroform–ethanol or from ethyl acetate–ethanol always gave low-melting mixtures of polymorphic forms.

trans-2-(2 : 3 : 4-*Trimethoxyphenyl*)cyclo*hexanecarboxylic Acid* (VII; R = CO_2H).—The *cis*-epimer (VI; R = CO_2H) (10 g.) was treated with an excess of ethereal diazomethane. To the resulting methyl ester, obtained after removal of ether *in vacuo*, a 15% solution of sodium methoxide in methanol (75 ml.) was added and the whole was refluxed for 12 hr. under nitrogen. 10% Potassium hydroxide solution (80 ml.) was then added and heating under reflux was continued for another 3 hr. After addition of sodium chloride solution, washing with ether, and acidification, the liberated oil was isolated with ether. Trituration with pentane gave the trans-*acid* (8·50 g.), m. p. 87—88°. Recrystallisation from hexane gave needles, m. p. 89° (Found: C, 65·5; H, 7·7. $C_{16}H_{22}O_5$·requires C, 65·3; H, 7·5%). A further 0·7 g. of the acid of m. p. 85—87° was obtained on concentration of the mother-liquor.

trans-1-*Hydroxymethyl*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hexane* (VII; R = CH_2·OH).—The *trans*-acid (10·0 g.) was reduced with lithium aluminium hydride as described for the *cis*-epimer, to give 9·0 g. of the crude *alcohol*. A sample was distilled evaporatively at 180° (bath)/0·01 mm. (Found: C, 68·2; H, 8·4. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%). No crystalline derivatives could be prepared.

The crude alcohol (19·0 g.) was converted into the toluene-*p*-sulphonate, which (28·6 g.) was added to di-*tert*.-butyl sodiomalonate, as described for the *cis*-epimer. The resulting β-[*trans*-2-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hexyl]propionic acid (VII; R = $[CH_2]_2$·CO_2H) crystallised on trituration with pentane, to give 15·64 g. of solid, m. p. 82·5—83° (Gutsche *et al.*[6] give m. p. 82·5—83° for the compound to which they ascribe the *cis*-configuration). Polyphosphoric acid cyclisation of this acid gave *trans*-1 : 2 : 3 : 4 : 4a : 5 : 6 : 11b-octahydro-9 : 10 : 11-trimethoxydibenzo[*a,c*]*cyclo*heptatrien-7-one (XIX), needles (from methanol), m. p. 113°. The 2 : 4-dinitrophenylhydrazone had m. p. 247—248°. Gutsche *et al.* report m. p.s 112·5—113·5° and 249—251° for the corresponding "*cis*"-compounds. A mixed m. p. determination, kindly undertaken by Professor C. D. Gutsche, was 112·5—114·5° for the ketone and 247—248·5° for the 2 : 4-dinitrophenylhydrazone.

In the cyclisation of acid (VII; R = $[CH_2]_2$·CO_2H) the best yield of product (XIX) was obtained by adhering closely to the conditions quoted [6] (65—70° for 25 min.); conducting the cyclisation under the conditions found optimal for the *cis*-epimer (see above; 75—85° for 1 hr.) led to a considerable amount of non-polar oils.

cis-1 : 2 : 3 : 4 : 4*a* : 11*b*-*Hexahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatriene* (IX).—To the ketone (VIII) (3·50 g.), suspended in methanol (10 ml.) and tetrahydrofuran (10 ml.), sodium borohydride (1 g.) was added at room temperature. After several hours the mixture was warmed on the steam-bath for 10 min. and most of the solvents were then removed *in vacuo*. Water was added and the oily alcohol was isolated with ether. The residue obtained on removal of the solvent was treated in benzene (40 ml.) with naphthalene-β-sulphonic acid (0·10 g.). The solution was refluxed under an azeotropic water-separator for 45 min. The cooled solution was washed, dried, and concentrated. The remaining *product* crystallised immediately on cooling and recrystallised from benzene–methanol as needles, m. p. 98° (2·92 g.) (Found: C, 74·35; H, 8·31. $C_{18}H_{24}O_3$ requires C, 74·97; H, 8·38%), $\lambda_{max.}$ 263 mμ (ε 13,100).

Oxidation of Compound (IX) *by Selenium Dioxide*.—The compound (IX) (7·42 g.) was dissolved in pyridine (28 ml.) and heated to 100°. Selenium dioxide (resublimed; 3·64 g.) was added with stirring in small portions during 4 hr. The mixture was cooled and diluted with ether–benzene, and the precipitated selenium filtered off. The filtrate was washed several times with ice-cold dilute hydrochloric acid, then with water, dilute sodium carbonate solution, and again with water, and dried. The crude product obtained after removal of solvents *in vacuo* (7·85 g.) was chromatographed on activated alumina (Fisher; 140 g.), starting with hexane–methylene chloride (6 : 1) as solvent and eluant. The first fractions contained unchanged material (*ca.* 0·4 g.); later fractions contained a mixture of the unsaturated ketone (XIII) and substance A (see below) from which A (0·10 g.) was separated by trituration with ether. Methylene chloride and methylene chloride–chloroform (2 : 1) eluted cis-1 : 2 : 3 : 4 : 4*a* : 11*b*-*hexahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatrien*-5-*ol* (X) (4·0 g.; m. p. 80—82° after trituration with pentane) mixed with some of substance B (see below) which was not separated at this stage; after several recrystallisations from hexane the alcohol had m. p. 83° (Found: C, 70·9; H, 8·1. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%).

This alcohol (4·0 g.) was shaken with activated manganese dioxide [7] (40 g.) in carbon tetrachloride (40 ml.) for 4 hr. The filtrate and washings therefrom were combined with the ether filtrate from substance A, and the solvents were removed *in vacuo*. The residue was chromatographed on activated alumina (Fisher; 70 g.) starting with hexane as solvent and hexane–methylene chloride as eluant. These solvents eluted cis-1 : 2 : 3 : 4 : 4*a* : 11*b*-*hexahydro*-9 : 10 : 11-*trimethoxy*-5-*oxodibenzo*[a,c]cyclo*heptatriene* (XIII) which, recrystallised from hexane, gave very pale yellow needles (2·75 g.), m. p. 97—99° (Found: C, 71·6; H, 7·5. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%), $\lambda_{max.}$ 251, 310 mμ (ε 11,000, 10,000), strong infrared band at 6·09 μ. The 2 : 4-*dinitrophenylhydrazone*, red leaflets from chloroform–ethanol, had m. p. 193° (Found: C, 60·1; H, 5·6; N, 11·7. $C_{24}H_{26}O_7N_4$ requires C, 59·7; H, 5·4; N, 11·6%). On further elution of this chromatogram with chloroform and chloroform–methanol there was obtained, after trituration with ether–hexane, *substance B* [probably (XII)] (0·20 g.), which after recrystallisation from chloroform–*cyclo*hexane formed yellowish needles, m. p. 144° (Found: C, 68·0; H, 7·0; active H, 0·31. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·95; 1 active H, 0·31%), $\lambda_{max.}$ 251,317 mμ (ε 13,000, 12,000), strong band at 6·06 μ.

Substance A [probably (XI)] on recrystallisation from chloroform–*cyclo*hexane formed stout yellowish needles, m. p. 156° (Found: C, 71·7; H, 8·2. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%), $\lambda_{max.}$ 255, 289 mμ (ε 13,000, 5500), medium infrared band at 6·05 μ. This substance gave no 2 : 4-dinitrophenylhydrazone. On catalytic hydrogenation, with 5% palladium–carbon, 1 mol. of hydrogen was rapidly absorbed. The product was purified by chromatography and recrystallised from methanol to give the ketone (VIII), m. p. and mixed m. p. 107°.

trans-1 : 2 : 3 : 4 : 4*a* : 11*b*-*Hexahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatriene* (XX).—The *trans*-ketone (XIX) (5·50 g.) was reduced with sodium borohydride, and the product was dehydrated with naphthalene-β-sulphonic acid in benzene, as described for the *cis*-epimer. The *product* distilled at 160° (bath)/0·01 mm. (4·25 g.) but did not crystallise (Found: C, 75·0; H, 8·3. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·4%), $\lambda_{max.}$ 260 mμ (ε 8950).

On attempted oxidation by selenium dioxide under the conditions described for the *cis*-epimer practically no selenium was precipitated and the starting material was recovered unchanged.

cis-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxy*-5-*oxodibenzo*[a,c]cyclo*heptatriene* (XIV).—The unsaturated ketone (XIII) (1·23 g.) was hydrogenated in ethanol (20 ml.) with 5% palladium–calcium carbonate (0·10 g.). Absorption was slow; after about 8 hr. *ca.* 110% of the theoretical amount was taken up. Filtration, evaporation, and crystallisation of the residue from hexane gave the *ketone* (XIV) (0·93 g.), m. p. 113—115°. Further recrystallisation from the same solvent gave needles, m. p. 115·5°, showing the ketone band at 5·90 μ (Found: C, 70·7; H, 8·05. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 184—185° (orange-yellow needles from benzene–*cyclo*hexane) (Found: C, 59·7; H, 6·0. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8%).

cis-5 : 5-*Ethylenedithio*-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*octahydro*-9 : 10 : 11-*trimethoxydibenzo*[a,c]-cyclo*heptatriene* (XV).—The preceding saturated ketone (0·5 g.), zinc chloride (fused *in vacuo*; 0·6 g.), anhydrous sodium sulphate (0·7 g.), and ethanedithiol (0·5 ml.) were mixed by shaking and left at room temperature for 24 hr. Dilute sodium hydroxide solution and ether–benzene were added; the organic layer was washed repeatedly with water and dried. Removal of solvents left a residue which on trituration with ether–hexane gave the *thioketal* (0·42 g.), m. p. 164—165°. Recrystallisation from benzene–*cyclo*hexane gave needles, m. p. 166° (Found: C, 62·9; H, 7·4. $C_{20}H_{28}O_3S_2$ requires C, 63·1; H, 7·4%).

cis-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxydibenzo*[a,c]cyclo*heptatriene* (XVI).—(*a*) Catalytic reduction, in ethanol, of the compound (IX), in presence of 5% palladium–carbon, was very rapid; the theoretical amount of hydrogen was absorbed in 3 min. Filtration and concentration of the filtrate gave the *product*, which crystallised from benzene–methanol in needles, m. p. 102·5—103° (Found: C, 73·92; H, 8·97. $C_{18}H_{26}O_3$ requires C, 74·44; H, 9·03%).

(*b*) The thioketal (XV) (0·20 g.) was refluxed in ethanol (20 ml.) with Raney nickel catalyst (W 2; teaspoonful) for 5 hr. The mixture was filtered and the residue washed with benzene. The combined filtrate and washings were concentrated in *vacuo* and the residue was taken up in hot hexane. The hexane solution was filtered, the hexane removed, and the residue crystallised from methanol to give product (XVI), m. p. 100—102°, mixed m. p. with the product from (*a*) 102—103°.

trans-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b-Octahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatriene* (XXI).—This was obtained by catalytic reduction of the compound (XX) as described above for the *cis*-epimer; after distillation at 160° (bath)/0·01 mm. the *product* crystallised (m. p. 72·5—73°) (Found: C, 74·1; H, 9·0%).

trans-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b-Octahydro*-9 : 10 : 11-*trimethoxy*-5-*oxodibenzo*[a,c]cyclo*heptatriene* (XVIII).—The *cis*-epimer (XIV) was recovered unchanged after passage in hexane through active basic alumina (Woelm; activity I). It was, however, partially epimerised under the following conditions: (*a*) The ketone (0·3 g.) in ethanol (30 ml.) and 6N-hydrochloric acid (9 ml.) was refluxed for 2½ hr. (*b*) The same compound (0·5 g.) in dry methanol (15 ml.) containing 10% sodium methoxide solution (0·5 ml.) was refluxed for 2 hr. (*c*) The ketone (0·3 g.) in methanol (35 ml.) containing potassium hydroxide (0·4 g.) was refluxed for 45 min.

Quantitative examination of the infrared spectra of the crude products (for estimation method see Zimmerman [4]) obtained by adding sodium chloride solution and ether-extraction showed that in each case between 35 and 45% of the trans-*epimer* had been formed. The latter was obtained pure by fractional crystallisation of the mixture of epimers from hexane; it had m. p. 101·5—102°, and showed the ketone band at 5·87 μ and a band at 7·60 μ not shown by the *cis*-epimer (Found: C, 71·0; H, 8·0. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The 2 : 4-*dinitrophenylhydrazone* formed orange-yellow leaflets (from chloroform–ethanol), m. p. 213—214° (Found: C, 59·2; H, 5·7; N, 11·4. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8; N, 11·6%).

cis-5-*Acetamido*-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b-octahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]-cyclo*heptatriene* (XVII).—The ketone (XIV) was converted in practically quantitative yield into the *oxime*, by hydroxylamine acetate in aqueous ethanol at pH 7. This formed leaflets, m. p. 215—217° (decomp.) from aqueous dioxan (Found: C, 67·65; H, 7·85. $C_{18}H_{25}O_4N$ requires C, 67·7; H, 7·9%). It (0·8 g.) was reduced by lithium aluminium hydride (0·7 g.) in dry refluxing tetrahydrofuran (20 ml.) for 6 hr. The product obtained after working-up with ice and sodium hydroxide solution, followed by ether-extraction, was treated with acetic anhydride (1 ml.) in pyridine (5 ml.) on the steam-bath for 1 hr. The mixture was treated with ice and extracted with ether. After being washed with dilute hydrochloric acid, water, and sodium carbonate solution the ether layer was dried and the solvent removed. The residue was chromatographed on acid-washed alumina (12 g.) with hexane–methylene chloride as eluant. The crystalline eluates were triturated with ether–hexane, to give the *amide* (0·3 g.), m. p. 143—152°, which exhibited a typical amide infrared spectrum (bands at 6·00 and 2·90 μ). Recrystallisation from *cyclo*hexane gave needles, m. p. 162—178° (Found: N, 4·3. $C_{20}H_{29}O_4N$ requires N, 4·0%). Further recrystallisation from the same solvent failed to improve the m. p. of what was evidently a mixture of 5-epimers.

6 : 6-*Ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*heptanecarboxylic Acid* [trans (XXIII) *and* cis (XXII) *Epimers*].—The acid (I; R = CO_2H) (8·90 g.) was reduced with lithium (*ca.* 0·4 g.) in liquid ammonia, as described above for the reduction of the unsaturated acid (V). The residue obtained after removal of ammonia on the steam-bath was dissolved in water; the solution was saturated with sodium chloride, washed with ether, and acidified at 0° under a layer of benzene–ether. The organic layer was thoroughly washed with water, dried, and evaporated *in vacuo*. The remaining oil was dissolved in ether (30 ml.) and the trans-*epimer* was allowed to crystallise at room temperature after seeding, to give 1·0 g. (11%) of material, m. p. 148—150°. Further recrystallisation from benzene–*cyclo*hexane gave prisms, m. p. 152·5—153° (Found: C, 62·4; H, 7·3; OMe 26·5%; equiv., 364. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·15; OMe, 25·4%; equiv., 366).

The ether filtrate from this *trans*-epimer was concentrated and the remaining oil triturated with hexane. The crude cis-*epimer* slowly separated and was recrystallised from aqueous methanol (in which the *trans*-epimer was much more soluble), to give 6·35 g. (71%) of material, m. p. 126·5—130°. Further recrystallisation from the same solvent gave prisms, m. p. 130—131° (Found: C, 62·0; H, 7·0%; equiv., 363).

The *cis*-epimer (3·0 g.) was treated with diazomethane in ether, and the product refluxed with sodium methoxide in methanol, then hydrolysed by aqueous alkali, as described for the epimerisation of the saturated acid (VI; R = CO_2H). This gave the *trans*-epimer (2·7 g.), m. p. 148—150°, mixed m. p. 148—151°.

The *trans*-epimer was recovered unchanged after being subjected to the same treatment.

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