283. *Syntheses in the Colchicine Series. Part III.* The Disposition of the Oxygen Functions in Colchicine.*

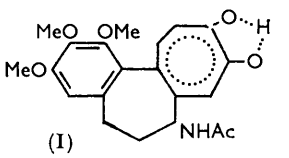
By H. J. E. Loewenthal.

The position of the carbonyl and the methoxyl groups in ring c of colchicine has been proved to be as in (II), by total synthesis of the degradation product (XXIII).

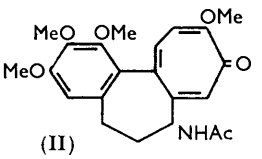
Two brilliant total syntheses of colchicine have recently been announced.[1,2] Formally, both are syntheses of the tautomeric tropolone colchiceine (I), and hence they do not differentiate between colchicine and isocolchicine which are obtained in roughly equal amounts from colchiceine by methylation with diazomethane.[3]

Confirmation of structure (II) for colchicine and hence of (III) for isocolchicine is the subject of the present paper.

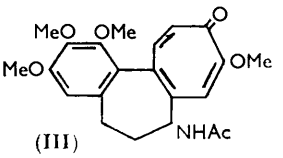
An unambiguous synthesis of the *trans*-ketal-acid (IVa) from pyrogallol and glutaric acid was described in previous Parts of this series.[4] Reaction of the toluene-*p*-sulphonate of the derived alcohol (IVb) with di-t-butyl sodiomalonate led to the keto-acid (V), which was cyclised in polyphosphoric acid to the tricyclic diketone (VI). Differentiation between the two ketonic groups in this was accomplished by partial catalytic hydrogenation to the hydroxy-ketone (VII), whose dehydration with acid led in high overall yield to the unsaturated ketone (VIII).



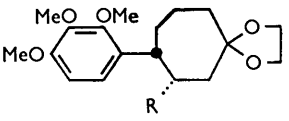
(I)



(II)

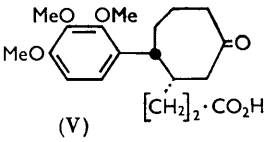


(III)

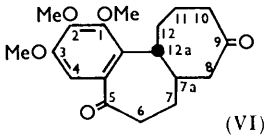


IVa: R = CO_2H

IVb: R = CH_2·OH



(V)



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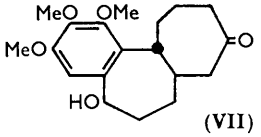

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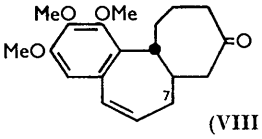

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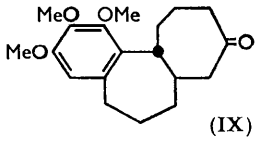

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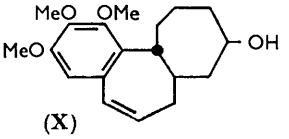
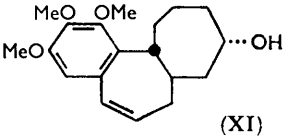


(X)



(XI)

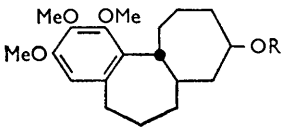
Several attempts were made to oxidise both this ketone (VIII) and its (non-crystalline) ethylene glycol ketal at the allylic 7-position. These included oxidation with selenium

* Part II, *J.*, 1958, 1367.

[1] Schreiber, Leimgruber, Pesaro, Schudel, and Eschenmoser, *Angew. Chemie*, 1959, **71**, 637.
[2] Van Tamelen, Spencer, Allen, and Orvis, *J. Amer. Chem. Soc.*, 1959, **81**, 5341.
[3] Sorkin, *Helv. Chim. Acta*, 1946, **29**, 246.
[4] *J.*, 1953, 3962; 1958, 1367.

dioxide in a variety of solvents and with t-butyl chromate, allylic bromination with *N*-bromosuccinimide and reaction of the resulting crude product with sodionitropropane [5] or with dimethyl sulphoxide.[6] They were all unsuccessful and are not described in detail.

Modification of the ketone group in (VIII) to an acyloxy-group was then considered. Reduction with lithium hydridotri-t-butoxyaluminate in tetrahydrofuran [7] was fortunately surprisingly stereoselective, giving a mixture of the non-crystalline unsaturated alcohols (X) and (XI), which, for separation and subsequent reaction, were converted into the acetates or *p*-bromobenzoates. In either case (particularly with the *p*-bromobenzoates) chromatography effected nearly sharp separation of the epimers of which one (series X) was eluted preferentially and was present in the ratio 4 : 1 to the other epimer. The probable configuration and general stereochemistry of these and following compounds will be discussed in the following paper. Similar reduction of the saturated ketone (IX) was even more stereoselective, giving the epimers (XII) and (XIII) in the ratio 5·5 : 1.



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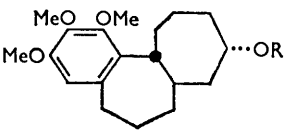

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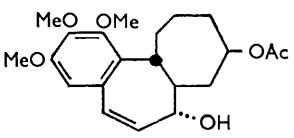

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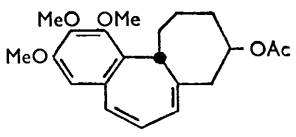
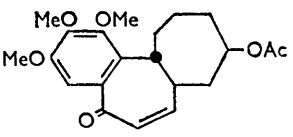


(XV)



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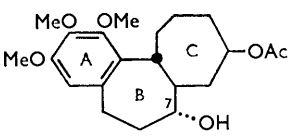
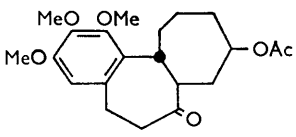
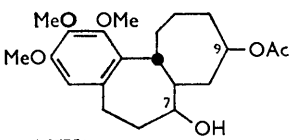


(XVII)



(XVIII)



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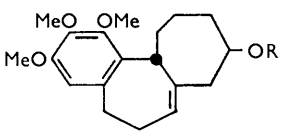


XXa: R = Ac

XXb: R = H

Oxidation of the unsaturated acetoxy-compound (Xb) with selenium dioxide in pyridine gave mainly three products: the unsaturated acetoxy-alcohol (XIV) and -diene (XV) and what appears to be the unsaturated acetoxy-ketone (XVI) (cf. Part II [4]). The alcohol was catalytically reduced and the " equatorial " conformation of the free hydroxyl group in the product (XVII) was assumed by analogy with the corresponding compound without a substituent in ring c (see following paper). Oxidation of this product (XVII) with chromic oxide in pyridine gave the saturated acetoxy-ketone (XVIII) in which the *trans*-junction between the two seven-membered rings appeared to be stable in attempted epimerisation at position 7a. Reduction of this ketone with lithium hydridotri-t-butoxyaluminate gave in turn the epimeric acetoxy-alcohol (XIX) which was dehydrated to the acetoxy-monoene (XXa) by means of phosphorus oxychloride in pyridine or (preferably) by the action of collidine on the 9-acetate-7-methanesulphonate.[8] The product from the former reaction was contaminated by the derived 7-chloride.

Treatment with hydrogen chloride in chloroform failed to rearrange the double bond

[5] Montavan, Lindlar, Marbet, Ruegg, Ryser, Saucy, Zeller, and Isler, *Helv. Chim. Acta*, 1957, **40**, 1250.

[6] Kornblum, Powers, Anderson, Jones, Larson, Levand, and Weaver, *J. Amer. Chem. Soc.*, 1957, **79**, 6562.

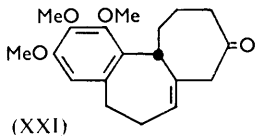
[7] Brown and McFarlin, *J. Amer. Chem. Soc.*, 1958, **80**, 5372.

[8] Cf. Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284.

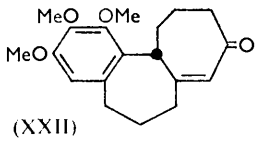
of the unsaturated acetate (XXa) to a position conjugated to the aromatic ring, and the compound was recovered unchanged. This was surprising in view of the successful prototropic rearrangement of the ring-c unsubstituted analogue.[9] Possibly the acetoxy-group prevents access of a proton to the double bond, as does the spirostan or 20-oxopregnane side chain in certain $\Delta^{8,14}$-steroids.[10]

On the other hand, the $\beta\gamma$-unsaturated ketone (XXI), obtained by oxidation of the alcohol (XXb) with chromic oxide in pyridine, isomerised smoothly to the non-crystalline ketone (XXIII) on treatment with toluene-*p*-sulphonic acid in acetone. By following this isomerisation in chloroform containing hydrogen chloride in the infrared spectrograph it was clear that it did not proceed *via* the $\alpha\beta$-unsaturated ketone (XXII). The ketone (XXIII) gave a crystalline ethylene ketal which was kindly compared by Professor Rapoport (University of California) with the corresponding product of degradation of colchicine [11] and found to be identical with it.

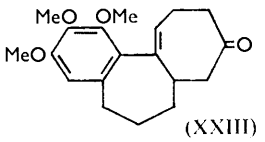
The unambiguity of the degradation of colchicine (II) to this ketal *via* *NN*-dimethyl-aminocolchicide (XXIV) and the keto-amide (XXV) has been discussed in detail by Rapoport and his co-workers.[11,12] As they point out, the ketone group in colchicine (II) and in the ketone (XXV) is undoubtedly at the same position in ring c, since both compounds on hydrogenation give the same hydroxy-amide (XXVI); and the conversion [11] of the amide (XXV) into the ethylene ketal of ketone (XXIII) cannot introduce a further element of uncertainty on this point. The only problem remaining is that of the position of the non-reducible styrene double bond in compounds (XXIII) and (XXV). The



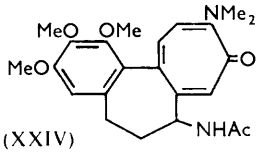
(XXI)



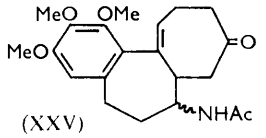
(XXII)



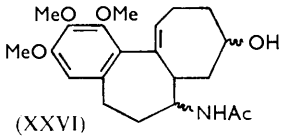
(XXIII)



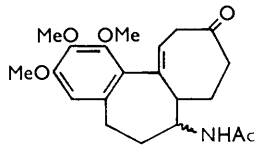
(XXIV)



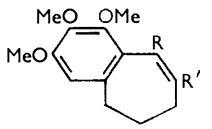
(XXV)



(XXVI)



(XXVII)



XXVIIIa: R = R' = H
XXVIIIb: R = Me, R' = H
XXVIIIc: R = R' = Me

ultraviolet spectra of these two compounds are very similar.[11] Muller and Velluz [13] have shown that the cyano-diene obtained from (XXV) by conversion into the cyanohydrin and subsequent dehydration has ultraviolet absorption similar to that of (XXV) ($\lambda_{max.}$ 251 mμ), while the corresponding compound obtained from the keto-amide derived from isocolchicine (XXVII) showed evidence of extended conjugation ($\lambda_{max.}$ 268 mμ). On the assumption that the styrene double bond in (XXV) and (XXVII) is tetra-substituted they concluded that the carbonyl groups in colchicine and isocolchicine should be placed at positions 10 and 9 respectively. Against this, Forbes [14] suggested placing the double

[9] Loewenthal and Rona, *Proc. Chem. Soc.*, 1958, 114, and the following paper.
[10] Mancera, Barton, Rosenkranz, and Djerassi, *J.*, 1952, 1021.
[11] Rapoport, Campion, and Gordon, *J. Amer. Chem. Soc.*, 1955, **77**, 2389.
[12] Rapoport, Williams, Campion, and Pack, *J. Amer. Chem. Soc.*, 1954, **76**, 3693.
[13] Muller and Velluz, *Bull. Soc. chim., France*, 1955, 1452.
[14] Forbes, *Chem. and Ind.*, 1956, 192.

bond at the trisubstituted 12,12a-position,[15] and this would correlate the position now established for the carbonyl group in the ketone (XXIII) with Muller and Velluz's results and with our conclusions (see following paper) that owing to the strained nature of the cycloheptadiene ring one of the double bonds in such a system would tend to move to an exocyclic position if this is structurally and energetically possible.

Gardner and his co-workers [16] have commented that the ultraviolet absorption of the ketal (as XXIII) and the amide (XXV) ($\lambda_{max.}$ 256 $\pm$ 3 mμ) violates Woodward's rules regarding the effect of substitution on a conjugated double bond, when compared with that of the trimethoxybenzocyclohepta-1,3-diene (XXVIIIa) ($\lambda_{max.}$ 264 mμ). The methyl-substituted homologues (XXVIIIb and c) were prepared; and examination of their ultraviolet spectra shows that here, too, substitution at the double bond leads to a hypsochromic shift. Clearly this is due to steric interference by the neighbouring aromatic methoxyl group.

Experimental

Infrared spectra refer to $CHCl_3$ solutions, and ultraviolet spectra to MeOH (Spectrograde) solutions.

β-trans-2-(2,3,4-*Trimethoxyphenyl*-6-*oxo*)*cycloheptylpropionic Acid* (V).—*trans*-6,6-Ethylenedioxy-2-(2,3,4-trimethoxyphenyl)cycloheptanecarboxylic acid (IVa) (20 g.), dissolved in dry tetrahydrofuran (50 ml.), was added dropwise with stirring to a solution of lithium aluminium hydride (5·5 g.) in boiling ether (150 ml.). Heating under reflux was continued for another 4 hr. and the mixture then decomposed with Rochelle salt solution. After addition of benzene the organic layer was washed with 10% sodium hydroxide solution and water, dried ($MgSO_4$), and evaporated *in vacuo*. The remaining crude trans-6,6-*ethylenedioxy*-2-(2,3,4-*trimethoxyphenyl*)*cycloheptylmethanol* (IVb) (18·0 g.) was used directly for the next step; a sample distilled evaporatively at 200—210° (bath)/10^{-2} mm. as a colourless very viscous oil (Found: C, 64·45; H, 8·05. $C_{19}H_{28}O_6$ requires C, 64·75; H, 8·0%), $\nu_{max.}$ 2·82 and 6·24 μ.

This crude alcohol (18·0 g.) was dissolved in dry pyridine (55 ml.) and cooled to −10°. Toluene-*p*-sulphonyl chloride (12·4 g.) was added and the resulting solution kept at −5° overnight, after which it was decomposed by cautious addition of 10% potassium hydrogen carbonate solution. The oil which separated was extracted with ether–benzene; the extract was washed several times with water, then with ice-cold 10% acetic acid (300 ml.), again with water, with 10% potassium hydrogen carbonate solution, and finally with saturated sodium chloride solution. The dried ($MgSO_4$) extract was concentrated *in vacuo* below 40°. The remaining oil (no OH band; bands at 7·35 and 8·53 μ) was dissolved in toluene (30 ml.) and added to a suspension of di-t-butyl sodiomalonate, prepared from the ester (23 g.) and sodium hydride (2·1 g.) in benzene (30 ml.) and toluene (30 ml.). After 30 hours' refluxing, water was added; the organic layer was separated and dried and the solvents were removed *in vacuo*. The residue was heated under reflux with acetic acid (200 ml.) and 4% hydrochloric acid (80 ml.) for 15 hr., after which the solvents were removed *in vacuo* at 100°. The residue was heated for 15 min. at 200°, cooled, and taken up in ether–benzene. The organic layer was extracted several times with 5% potassium carbonate solution; acidification of the extracts gave the crude *keto-acid* (13·9 g.) which was isolated with ether. Trituration with ether–cyclohexane (2 : 1) gave needles (8·8 g.), m. p. 110—112°; further crystallisation from ether raised the m. p. to 114·5—115·5° (Found: C, 65·05; H, 7·4. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%); it had infrared band with inflections at 5·80 and 5·85 μ.

5,6,7,7aα,8,9,10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene*-5,9-*dione* (VI).—The above keto-acid (16·0 g.) was melted by heating to 120°; the melt was cooled and polyphosphoric acid, prepared from 85% orthophosphoric acid (140 ml.) and phosphoric oxide (260 g.), was added. The red solution was heated with stirring at 75—80° for 1 hr., after which it was added to ice. The gum which separated was extracted with ether–benzene, and the organic extract washed with water, 5% sodium hydroxide solution, again with water, dried ($MgSO_4$), and concentrated. The residue was passed in benzene through a short column of activated alumina, the solvent was removed from the eluate, and the residue crystallised from cyclohexane to

[15] Vaterlaus and Muller (*Bull. Soc. chim. France*, 1957, 1329) later came to the same conclusion on more indirect evidence.

[16] Gardner, Brandon, and Haynes, *J. Amer. Chem. Soc.*, 1957, **79**, 6334.

give the *diketone* (8·1 g.) which after recrystallisation from the same solvent was obtained as needles, m. p. 110—110·5° (Found: C, 68·3; H, 7·4; MeO, 27·5. $C_{19}H_{24}O_5$ requires C, 68·65; H, 7·3; 3MeO, 28%), $\nu_{max.}$ 5·90—5·95 (broad) and 6·26 μ. Chromatography of the mother-liquors gave another 1·0 g. of the diketone.

7,7aα,8,9,10,11,12,12aβ-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9-*one* (VIII).—The above diketone (1·62 g.) was catalytically reduced in methanol, with a prehydrogenated mixture of 10% palladium–carbon (110 mg.) and 4% palladium–strontium carbonate (110 mg.). Hydrogen absorption was slow and practically ceased after uptake of one mol. The residue of the keto-alcohol (VII), obtained after filtration and removal of solvent (bands at 2·77 and 5·91s μ), was heated for 2 hr. in benzene (50 ml.) with naphthalene-2-sulphonic acid (100 mg.) with azeotropic removal of water. The cooled solution was washed with 5% sodium hydroxide solution and water, then dried ($MgSO_4$), and the solvent was removed. The residue, which crystallised, was purified by chromatography and crystallisation from hexane to give the unsaturated *ketone* (1·46 g.), m. p. 82—83°. Further recrystallisation gave needles, m. p. 87·5—88° (Found: C, 72·3; H, 7·7. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\lambda_{max.}$ 259 mμ (ε 11,000), $\lambda_{min.}$ 243 mμ (ε 7400), $\nu_{max.}$ 5·90, 6·26, and 6·40 μ. The *semicarbazone* formed needles (from dilute ethanol), m. p. 187·5—188° (Found: C, 64·5; H, 7·2; N, 11·45. $C_{20}H_{27}N_3O_4$ requires C, 64·3; H, 7·3; N, 11·25%).

Catalytic hydrogenation of the above unsaturated ketone in methanol in the presence of 4% palladium–strontium carbonate was rapid, giving 5,6,7,7aα,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9-*one* (IX), which formed needles, m. p. 118·5—119·0°, from methanol (Found: C, 72·0; H, 8·25. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%), bands at 5·90 μ and 6·25 μ. The 2,4-*dinitrophenylhydrazone*, orange needles from chloroform–ethanol, had m. p. 207—207·5° (Found: C, 59·9; H, 6·05; N, 11·25. $C_{25}H_{30}N_4O_7$ requires C, 60·25; H, 6·05; N, 11·25%).

Esters of 7,7aα,8,9,10,11,12,12aβ-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9-*ols* [β(X)- and α(XI)-*Epimers*).—The unsaturated ketone (VIII) (3·50 g.) was added at 0° to a solution of lithium hydridotri-t-butoxyaluminate (10 g.) in tetrahydrofuran (150 ml.). After being stirred overnight at room temperature the mixture was decomposed by ice-cold 5% hydrochloric acid and the tetrahydrofuran removed *in vacuo*. The crude mixture of epimeric unsaturated alcohols, isolated with ether–benzene, could not be separated into crystalline fractions even after chromatography. It (4·0 g.) was therefore heated with acetic anhydride (7·0 ml.) in pyridine (15·0 ml.) at 100° for 2 hr. The crude mixture of acetates obtained after the usual working-up was chromatographed on activated alumina (Alcoa; 10 g.), with hexane as solvent and methylene chloride–hexane as eluant, giving first the 9β-*acetate* (as X), needles (from hexane), m. p. 98—99° (Found: C, 70·1; H, 7·7. $C_{21}H_{28}O_5$ requires C, 69·95; H, 7·85%), $\nu_{max.}$ 5·81, 6·26, and 6·40 μ, followed by the 9α-*epimer* (as XI), prisms (from hexane), m. p. 78·5—79·5° (Found: C, 70·2; H, 7·75%), $\nu_{max.}$ 5·81, 6·25, and 6·40 μ.

Alternatively, and for a sharper chromatographic separation, the crude alcohol mixture (3·30 g.) was heated at 50—60° for 1 hr. with *p*-bromobenzoyl chloride (2·50 g.) in pyridine (17·0 ml.). The crude product obtained after the usual working-up was likewise chromatographed in hexane on alumina (Alcoa; 100 g.), giving first the 9β-p-*bromobenzoate* (as X), which after several recrystallisations from hexane formed needles, m. p. 106—106·5° (Found: C, 62·25; H, 5·85. $C_{26}H_{29}BrO_5$ requires C, 62·3; H, 5·85%), $\nu_{max.}$ 5·85, 6·40, and 6·70 μ, followed by the 9α-*epimer* (as XI), leaflets (from cyclohexane), m. p. 125—125·5° (Found: C, 62·15; H, 5·8%), infrared spectrum very similar to that of the 9β-ester except for absence of strong band at 7·60 μ.

Rechromatography of mother-liquors and intermediate fractions from both the acetates and the *p*-bromobenzoates established that in both cases the ratio of 9β- to 9α-epimer was 4 : 1.

Alkaline hydrolysis of both 9β- and 9α-bromobenzoates, followed by acetylation, gave the corresponding acetates, identified by m. p. and mixed m. p.

5,6,7,7aα,8,9 10,11,12,12aβ-*Decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9-*ols* [β- (as XII) and α- (as XIII) *Epimers*], *and their Esters*.—The saturated ketone (IX) (1·00 g.) was reduced with lithium hydridotri-t-butoxyaluminate in tetrahydrofuran, as described for the unsaturated ketone (VIII). The crude product (1·10 g.) was heated at 50—60° for 2 hr. with *p*-bromobenzoyl chloride (0·85 g.) in pyridine (5·0 ml.). The crude mixture of *p*-bromobenzoates obtained after the usual working-up was chromatographed on alumina (Alcoa; 35 g.) with hexane as solvent and methylene chloride–hexane as eluant, giving first the 9β-p-*bromobenzoate* (as XII), leaflets (from cyclohexane), double m. p. 112—112·5°, 122—123°, $\nu_{max.}$ 5·85 and 6·26 μ

(Found: C, 62·0; H, 6·3; Br, 16·0. $C_{26}H_{31}BrO_5$ requires C, 62·05; H, 6·2; Br, 15·9%), followed by the 9α-*epimer* (as XIII), needles (from cyclohexane), m. p. 126—126·5° (depressed on admixture with the 9β-epimer), $\nu_{max.}$ 5·85, 6·27 μ (Found: C, 62·1; H, 6·1; Br, 15·9%).

Alkaline hydrolysis of the 9β-*p*-bromobenzoate gave the 9β-*alcohol*, leaflets (from cyclohexane) which retained solvent tenaciously; after intensive drying *in vacuo* they had m. p. 103—104° (Found: C, 71·45; H, 8·95. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%). Acetylation of this alcohol with acetic anhydride–pyridine at 100° for 0·5 hr. gave the 9β-*acetate*, prisms (from hexane), m. p. 102—103°, $\nu_{max.}$ 5·81 and 6·26 μ (Found: C, 69·5; H, 8·4. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·25%). The same product was also obtained by catalytic hydrogenation of the unsaturated acetoxy-compound (from X) in methanol with palladium–strontium carbonate and identified by m. p. and mixed m. p.

Catalytic hydrogenation of the unsaturated 9α-acetoxy-compound (from XI) with palladium–strontium carbonate in methanol gave the 9α-*acetate* (as XIII), needles (from cyclohexane), m. p. 125·5—126°, $\nu_{max.}$ 5·82 and 6·26 μ (Found: C, 69·25; H, 8·2%). Alkaline hydrolysis of this gave the 9α-*alcohol* needles (from cyclohexane), m. p. 117·5—118° (Found: C, 71·25; H, 8·7. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%). Acylation of this with *p*-bromobenzoyl chloride in pyridine gave the 9α-*p*-bromobenzoate (as XIII) identified by m. p. and mixed m. p.

Oxidation of the Acetate of Compound (X) *by Selenium Dioxide.*—The unsaturated acetate (2·83 g.) was heated in pyridine (20 ml.) under reflux. Freshly sublimed selenium dioxide (1·20 g.) was added in small portions during 10 hr., together with further portions of pyridine (total 15 ml). The dark suspension was cooled and most of the pyridine removed *in vacuo* below 50°. Ether was added to the residue and the suspension was filtered. The filtrate was washed with ice-cold 5% hydrochloric acid, water, 5% potassium carbonate solution, and again with water and dried ($MgSO_4$). Removal of solvent *in vacuo* below 40° left a residue which was chromatographed in hexane–methylene chloride (4 : 1) on neutral activated alumina (60 g.) above a short column (3 g.) of a 3 : 1 mixture of alumina and precipitated silver.[17] The initial solvent eluted unchanged starting material (1·0 g.), followed by a mixture of (probably) (XVI) (see below) and the acetoxy-diene (XV) (see below) while methylene chloride and chloroform eluted 9β-*acetoxy*-7,7aα,8,9,10,11,12,12aβ-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-7α-*ol* (XIV) which after recrystallisation from cyclohexane formed needles, m. p. 117·5—118° (Found: C, 67·2; H, 7·45. $C_{21}H_{28}O_6$ requires C, 67·0; H, 7·5%), $\lambda_{max.}$ 259 mμ (ε 11,000), $\lambda_{min.}$ 243 mμ (ε 7100). After rechromatography of mother-liquors and adjacent chromatographic fractions the total yield of this compound was 35% based on unrecovered starting material.

The fractions preceding this product were twice rechromatographed, giving (in order of elution): (a) 9β-*acetoxy*-8,9,10,11,12,12aβ-*hexahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (XV), needles (from hexane), m. p. 102·5—103·5° (Found: C, 70·4; H, 7·25. $C_{21}H_{26}O_5$ requires C, 70·35; H, 7·3%), $\lambda_{max.}$ 303 (ε 9700), $\lambda_{min.}$ 261 mμ (ε 2400), $\nu_{max.}$ 5·80, 6·26, and 6·40 μ; (b) a *substance* [probably (XVI)], which after recrystallisation from hexane had double m. p. 98—98·5° (needles), 104·5—105° (prisms) (Found: C, 67·25; H, 6·8. $C_{21}H_{26}O_6$ requires C, 67·35; H, 7·0%), $\lambda_{max.}$ 226 mμ (ε 29,000), $\nu_{max.}$ 5·80, 5·95, 6·21, and 6·45 μ.

9β - *Acetoxy* - 5,6,7,7aα,8,9,10,11,12aβ - *decahydro* - 1,2,3 - *trimethoxybenzo*[a]*heptalen* - 7α - *ol* (XVII).—The unsaturated acetoxy-alcohol (XIV) (360 mg.) was catalytically hydrogenated in methanol over 4% palladium–strontium carbonate (150 mg.). Usually this hydrogenation succeeded only after shaking with pre-reduced catalyst, filtration, and addition of fresh catalyst. The product was obtained by filtration, removal of solvent, and crystallisation from chloroform–cyclohexane as prisms of the *acetoxy*-7α-*alcohol* (330 mg.), m. p. 116·5—117·5°, depressed on admixture with starting material. The analytical sample had m. p. 120·5—121°, $\nu_{max.}$ 2·80—2·90 (broad), 5·82, and 6·26 μ (Found: C, 66·9; H, 8·0. $C_{21}H_{30}O_6$ requires C, 66·65; H, 8·0%).

9β - *Acetoxy* - 5,6,7,7aα,8,9,10,11,12,12aβ - *decahydro* - 1,2,3 - *trimethoxybenzo*[a]*heptalen* - 7 - *one* (XVIII).—The acetoxy-alcohol (XVII) (400 mg.) was added to the chromic oxide–pyridine complex (from 0·4 g. of chromic oxide and 4 ml. of pyridine) and the mixture left at room temperature overnight. Ether and benzene were added and the suspension was filtered, washed with 5% hydrochloric acid containing ferrous sulphate, then with water, 5% sodium carbonate solution, again with water, and dried ($MgSO_4$). Removal of solvent and crystallisation of the residue from chloroform–cyclohexane gave the *acetoxy-ketone* (356 mg.), m. p. 155—155·5° (Found: C, 67·25; H, 7·65. $C_{21}H_{28}O_6$ requires C, 67·0; H, 7·5%), $\nu_{max.}$ 5·80—5·85s and 6·25 μ.

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

Hydrolysis of this compound with 5% methanolic potassium hydroxide, followed by re-acetylation of the product, returned the starting material in high yield.

9β - *Acetoxy* - 5,6,7aα,8,9,10,11,12,12aβ - *decahydro* - 1,2,3 - *trimethoxybenzo*[a]*heptalen* - 7β - *ol* (XIX).—The acetoxy-ketone (XVIII) (434 mg.) was added at 0° to a solution of lithium hydridotri-t-butoxyaluminate (1·3 g.) in tetrahydrofuran (15 ml.), and the solution was left at room temperature overnight. Working-up as described for the reduction of the unsaturated ketone (VIII), followed by crystallisation of the product from cyclohexane, gave the *acetoxy-7β-alcohol* (374 mg.), m. p. 123·5—124·5° depressed by admixture with the 7α-epimer (Found: C, 67·05; H, 8·05. $C_{21}H_{30}O_6$ requires C, 66·65; H, 8·0%), $\nu_{max.}$ 2·80 (sharp), 5·82, and 6·25 μ.

9β-*Acetoxy*-5,6,8,9,10,11,12,12aβ-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene* (XXa).—(*a*) The acetoxy-7β-alcohol (XIX) (92 mg.) was dissolved in dry pyridine (0·3 ml.), and freshly distilled methanesulphonyl chloride (0·06 ml.) was added at −10°. After being kept overnight at room temperature the red suspension was decomposed with ice, the product was isolated with ether, and the ether layer washed with 5% hydrochloric acid, water, 5% sodium carbonate, again with water, and dried ($MgSO_4$). The ether was removed *in vacuo* at room temperature and the oily residue refluxed under nitrogen with toluene (0·3 ml.) and 2,4,6-trimethylpyridine (0·3 ml.) for 3 hr. Water and ether were added and the ether layer was washed several times with ice-cold 5% hydrochloric acid and water and dried ($MgSO_4$). The residue (88 mg.) obtained on removal of solvent was purified by chromatography on neutral active alumina and crystallisation from pentane to give the unsaturated *acetate* (54 mg.), needles, m. p. 99—99·5° (Found: C, 70·05; H, 7·75. $C_{21}H_{28}O_5$ requires C, 69·95; H, 7·85%), $\nu_{max.}$ 5·81 and 6·25 μ.

(*b*) The acetoxy-7β-alcohol (XIX) (69 mg.) was dissolved in pyridine (0·2 ml.), and phosphorus oxychloride (0·03 ml.) was added. The suspension was heated at 60° for 4 hr., after which it was decomposed with ice. The usual working-up gave a residue which showed a positive Beilstein test. It was still inhomogeneous after chromatography and was separated by fractional crystallisation from pentane into the above unsaturated acetate, m. p. and mixed m. p. 97—99°, and 9β-*acetoxy*-7α-*chloro*-5,6,7,7aα,8,9,10,11,12,12aβ-*decahydro*-1,2,3-*trimethoxybenzo*[a]*heptalene*, which after repeated crystallisation from hexane had m. p. 135—136° (Found: Cl, 8·7. $C_{21}H_{29}ClO_5$ requires Cl, 8·95%).

Hydrolysis of the above unsaturated acetate (109 mg.) under reflux in methanol (4 ml.) with 15% sodium hydroxide solution (1·3 ml.) for 15 min. gave 5,6,8,9,10,11,12,12aβ-*octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9β-*ol* (XXb) (88 mg.), needles (from chloroform–cyclohexane), m. p. 128—128·5° (Found: C, 71·5; H, 8·3. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%).

5,6,8,9,10,11,12,12aβ-*Octahydro*-1,2,3-*trimethoxybenzo*[a]*heptalen*-9-*one* (XXI).—The alcohol (XXb) (70 mg.) was oxidised with the chromic oxide–pyridine complex as described for preparation of the acetoxy-ketone (XVIII), to give the *ketone* (60 mg.), needles (from cyclohexane), m. p. 128·5—129° (Found: C, 71·95; H, 7·75. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\nu_{max.}$ 5·90 and 6·25 μ.

9,9 - *Ethylenedioxy* - 5,6,7,7a,8,9,10,11 - *octahydro* - 1,2,3 - *trimethoxybenzo*[a]*heptalene* (cf. XXIII).—The preceding ketone (33 mg.) was heated under reflux with toluene-*p*-sulphonic acid (10 mg.) in acetone (1 ml.) for 1 hr. Removal of the acetone and isolation with ether gave a residue which was absorbed in hexane on active acidic alumina (Woelm; activity I) (1 g.) and eluted with methylene chloride. Removal of solvent from the eluate gave an oil (22 mg.) [probably the ketone (XXIII)] which had $\lambda_{max.}$ 255 mμ (log ε 3·92), $\lambda_{min.}$ 243 mμ (log ε 3·86), $\nu_{max.}$ 5·89, 6·25, 6·40 μ, and a small band at 6·06 μ (trace of αβ-unsaturated ketone). This (20 mg.) was heated in benzene (1·5 ml.) with ethylene glycol (0·06 ml.) and toluene-*p*-sulphonic acid (5 mg.) for 4 hr. under a small condenser containing silica gel. The product obtained after the customary working-up was chromatographed in hexane on alumina (1 g.). The same solvent eluted the *ketal* which after crystallisation from pentane formed prisms (11·5 mg.), m. p. 96·5—97° (Fisher block), $\lambda_{max.}$ 256 mμ (ε 13,500), $\lambda_{min.}$ 240 mμ (ε 9400) [reported [11] for the degradation product from colchicine: m. p. 95—96°; $\lambda_{max.}$ 256 ± 2 mμ (log ε 4·1), $\lambda_{min.}$ 243 ± 2 mμ (log ε 3·95)]. A sample of the above synthetic product was found by Professor Rapoport to be identical with his degradation product by mixed m. p. determination and in infrared spectrum.

This isomerisation was investigated by following the change in the infrared spectrum of the ketone (XXI) in chloroform containing *ca.* 1% of hydrogen chloride. After 6 hr. an inflexion at 6·39 μ developed to a distinct band (styrene double bond); after 24 hr. a small band

at 6·05 μ (trace of αβ-unsaturated ketone) appeared. The carbonyl band at 5·90 μ remained unchanged throughout.

2,3,4-Trimethoxybenzosuber-5-one (*2′,3′,4′-Trimethoxy-1,2-benzocyclohept-1-en-3-one*) (*Improved Procedure*).[18]—3,4,5-Trimethoxybenzaldehyde (5·0 g.) and methyl crotonate (5·1 g.) were added at room temperature with cooling to a solution of potassium (2·1 g.) in dry t-butyl alcohol (80 ml.). The mixture became orange and a solid separated. After being kept overnight it was acidified with acetic acid and water was added. The oil which separated was extracted with ether; the extract was washed with water and dried ($MgSO_4$) and the ether removed. The remaining oil was dissolved in ethyl acetate and hydrogenated at 55 lb./sq. in. over 5% palladium–barium sulphate. The crude product obtained on filtration and removal of solvent was hydrolysed by refluxing 10% sodium hydroxide solution. The acid obtained after the usual working-up was purified by distillation in a high vacuum and crystallisation from hexane, to give δ-(3,4,5-trimethoxyphenyl)valeric acid (5·6 g.), m. p. 68—69° (reported,[19] m. p. 66—68°).

Cyclisation of this acid (5·5 g.) with polyphosphoric acid, prepared from 85% orthophosphoric acid (42 ml.) and phosphoric oxide (75 g.), at 95° for 0·5 hr., followed by crystallisation of the crude product from methanol gave the *ketone* (3·24 g.), m. p. 100° (reported,[19] m. p. 99—100°), $\nu_{max.}$ 5·95 and 6·26 μ.

Methylation. The ketone (2·25 g.) in benzene (50 ml.) was added to a suspension of dry potassium t-butoxide (from 327 mg. of potassium) in benzene (50 ml.). The alkoxide immediately dissolved giving a red solution. About half of the solvent was distilled off and, after cooling, methyl iodide (14 ml.) was added. The mixture was refluxed overnight, water was added, the organic layer was dried ($MgSO_4$), and the solvent removed. The remaining oil was chromatographed in hexane successively on two columns of active alkaline alumina (Woelm; activity I; 30 g. each), and the products were eluted with methylene chloride–hexane in ascending proportions of the former, giving first *2′,3′,4′-trimethoxy-4,4-dimethyl-* (0·21 g.), needles (from hexane), m. p. 78—79° (Found: C, 69·1; H, 7·9. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·95%), bands at 5·91 and 6·26 μ, followed by *2′,3′,4′-trimethoxy-4-methyl-1,2-benzocyclohept-1-en-4-one* (1·09 g.), prisms (from hexane), m. p. 90—90·5: (Found: C, 67·95; H, 7·45. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%), $\nu_{max.}$ 5·91, 6·26 μ, and finally by unchanged starting ketone (0·61 g.).

2′,3′,4′-Trimethoxy-3-methyl-1,2-benzocyclohepta-1,3-diene (XXVIIIb).—2′,3′,4′-Trimethoxy-1,2-benzocyclohept-1-en-3-one (500 mg.) was added in benzene (5 ml.) to a solution of methylmagnesium iodide, prepared from magnesium (100 mg.) and methyl iodide (0·9 ml.) in ether (10 ml.). After 5 hours' heating under reflux the mixture was worked up in the usual manner, a small amount of phenolic material being removed by extraction with sodium hydroxide solution. The crude product was refluxed in benzene (20 ml.) with naphthalene-2-sulphonic acid (30 mg.) until azeotropic removal of water was complete. The crude oily product from this dehydration was passed in hexane through alumina and distilled at *ca.* $110°/10^{-2}$ mm., to give the oily colourless *product* which crystallised at 0° (Found: C, 72·45; H, 8·05. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%), $\lambda_{max.}$ 248 (ε 9750), $\lambda_{min.}$ 238 mμ (ε 7450), $\nu_{max.}$ 5·95, 6·10 (small), 6·25 and 6·40 μ.

2′,3′,4′-Trimethoxy-3,4-dimethyl-1,2-benzocyclohepta-1,3-diene (XXVIIIc).—The 4-methyl-ketone (500 mg.) was caused to react with methylmagnesium iodide as described above, except that most of the ether was distilled off during the reaction. The crude neutral product was dehydrated and the dehydration product purified as described for (XXVIIIb), giving the *dimethyl derivative* as a slightly coloured oil (Found: C, 73·25; H, 8·45. $C_{16}H_{22}O_3$ requires C, 73·25; H, 8·45%), $\lambda_{max.}$ 251 (ε 10,300), $\lambda_{min.}$ 238 mμ (ε 8100), $\nu_{max.}$ 6·25 and 6·37 μ.

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[18] General method kindly communicated by Dr. A. Dreiding before publication.
[19] Gardner, Horton, Thompson, and Twelves, *J. Amer. Chem. Soc.*, 1952, **74**, 5527.