## 1103. *The Acid-catalysed Isomerisation of Cyclopropanes.*

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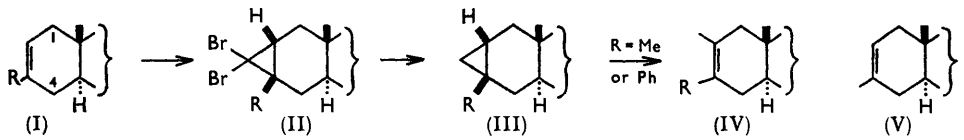
2α,3α-Methylenecholestane and its 3β-methyl and 3β-phenyl derivatives have been made by addition of carbon dibromide to the appropriate cholestene and reduction of the dibromocyclopropanes. The products of acid-catalysed cleavage of the cyclopropane ring indicate that they are derived from the methyl carbonium ions formed by addition of a proton to the ring in accordance with Markownikow's rule, and that there is no strong preference for axial opening. The slower reaction of the phenyl compound is attributed to the inductive effect.

The contrast in behaviour of epoxides and cyclopropanes in acid is due to the attachment of the proton to the unshared electrons of the oxygen atom of the former but to the C–C bond of the latter.

To compare the acid-catalysed reactions of cyclopropanes with those of related epoxides [1] and olefins [2] we made a series of 2α,3α-methylenecholestanes bearing 3-substituents of varying electronic character (H, Me, and Ph). Preliminary attempts to convert the cholestenes (I) directly into the cyclopropane derivatives (III) with methylene iodide and a zinc–copper couple [3] failed, but they were obtained without difficulty by addition of carbon dibromide [4] to form the dibromocyclopropanes (II), which were then reduced with sodium and methanol. The cyclopropanes (III; R = H and Me) showed the characteristic peaks [5] in their infrared spectra at 3050 and 1020 cm.$^{-1}$. Only one isomer (II) was isolated from each olefin, and in good yield. The attack of the bulky $CBr_2$ was assumed to occur from the α-side by analogy,[6] particularly, with the formation of the related epoxides. In fact, the cyclopropanes (III) closely paralleled the corresponding α-epoxides [1] in m. p. and rotation.

| | 2α,3α-Epoxide, | | Cyclopropane, | |
|---|---|---|---|---|
| 3-Substituent | M. p. | $[\alpha]_D$ | M. p. | $[\alpha]_D$ |
| H | 110° | 36° | 105° | 33° |
| Me | 134 | 47 | 120 | 43 |
| Ph | 133 | 63 | 124 | 73 |

Although it did not react with a 2N-sulphuric acid solution in tetrahydrofuran at 41°, the methylcyclopropane (III; R = Me) rearranged in quantitative yield to an olefin in a 0·24N-perchloric acid solution in the less basic acetic acid–chloroform. The infrared spectrum of the olefin showed that the double bond was fully substituted, and the structure




(I) (II) (III) (IV) (V)

(IV; R = Me) was confirmed by synthesis of the same substance from 2α,3α-epoxy-3β-methylcholestane by rearrangement with boron trifluoride to 3-methylcholestan-2-one, which was treated with methylmagnesium iodide and then acid.

[1] Cookson and Hudec, *Proc. Chem. Soc.*, 1957, 24; Hudec, Ph.D. Thesis, London, 1958.
[2] Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500; Cookson, Hamon, and Parker, *J.*, 1962, 5014.
[3] Simmons and Smith, *J. Amer. Chem. Soc.*, 1959, **81**, 4256; Shank and Shechter, *J. Org. Chem.*, 1959, **24**, 1825.
[4] Doering and Hoffmann, *J. Amer. Chem. Soc.*, 1954, **76**, 6162.
[5] Cole, *J.*, 1954, 3807, and refs. therein.
[6] Fieser and Fieser, "Steroids," Reinhold, New York, 1959, p. 14 and elsewhere.

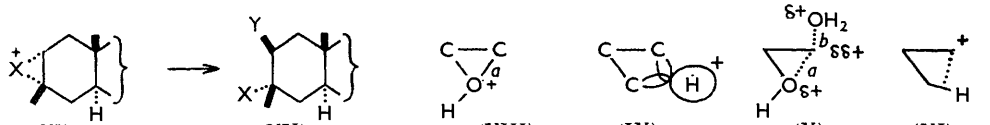
The conditions that sufficed to rearrange the methylcyclopropane (III; R = Me) completely to the olefin (IV; R = Me) left the phenylcyclopropane (III; R = Ph) unchanged. But with four times the concentration of acid and twice the time of reaction it too rearranged completely to a single olefin, recognised as 2-methyl-3-phenylcholest-2-ene (IV; R = Ph) by comparison with an authentic sample [1] made by reaction of 3-phenylcholestan-2-one with methylmagnesium iodide, followed by dehydration.

The unsubstituted cyclopropane (III; R = H) reacted under the same conditions as its methyl derivative (III; R = Me), but unlike the other two it yielded a mixture of olefins. A trace of a substance more strongly adsorbed on silica gel and having a band at 1740 cm.$^{-1}$ was also present. (Traces of a similar product, presumably a mixture of acetates, were formed from 3-methylcholest-2-ene under these conditions.) It seemed most likely that the olefinic product was an inseparable mixture of 2- and 3-methylcholest-2-ene (IV; R = H; and V). Indeed the infrared spectrum, when superimposed on those of the 2- and 3-methylcholestenes, was consistent with the product's being such a mixture, except that it had a rather strong band at 750 cm.$^{-1}$ not present in the spectrum of either pure olefin. The rotation of the olefinic product (+37°) confirmed our view that it could not consist only of 2- and 3-methylcholest-2-ene (+75° and +74°, respectively), but that at least one other olefin must be present. The reference sample of 2-methylcholest-2-ene made by addition of methylmagnesium iodide to cholestan-2-one and dehydration of the resulting mixture of epimeric alcohols, had properties identical with those of the sample synthesised earlier by another method.[7]

*Discussion.*—Unsymmetrically substituted cyclopropanes usually open according to Markownikow's rule,[8] but it has been implied [9] that the bicyclo[4,1,0]heptane system also tends to yield axial products, in analogy with the well-established diaxial opening of cyclohexene epoxides, bromonium ions, and related species.[10]

An unsymmetrical bicyclo[4,1,0]heptane can add a proton to give six different carbonium ions, according to which end of the three C–C bonds of the cyclopropane ring becomes engaged to the proton. Two will be cycloheptyl ions (*a*), two cyclohexylmethyl ions (*b*), and two 2-methylcyclohexyl ions (*c*). Of the last pair one will have the methyl group axial and one equatorial (if we assume the chair conformation), and only in that case (*c*) is it helpful to consider the analogy with acid-catalysed opening of cyclohexene epoxides or bromonium ions [which, of course, always break the bonds corresponding to case (*c*)].

In seeking a bicyclo[4,1,0]heptane in which to examine case *c*, we chose the 2α,3α-substituted cholestane system,[11] because any tendency to axial opening is opposed by Markownikow's rule when there is a 3-substituent. Even when there is a 3β-methyl group, the intermediate 2α,3α-bromonium ion (VI; X = Br$^+$) from 3-methylcholest-2-ene (I; R = Me) gives diaxial products [2] (VII; X = Br), and opening of the epoxide with acid




(VI) (VII) (VIII) (IX) (X) (XI)

(VI; X = OH) also leads only to diaxial products [1] (VII; X = OH). In these cases, then, the tendency for diaxial opening suspends Markownikow's rule. It is worth

[7] Djerassi, Finch, Cookson, and Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488.
[8] Raphael, in Rodd's " The Chemistry of Carbon Compounds," Elsevier, Amsterdam, 1953, Vol. IIa, p. 26.
[9] *Inter al.*, Büchi and White, *J. Amer. Chem. Soc.*, 1957, **79**, 750; see also ref. 19; P. de Mayo, " The Higher Triterpenoids," Interscience Publ., Inc., New York, 1959, p. 94.
[10] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 67; Barton, Kékulé Symposium, " Theoretical Organic Chemistry," Butterworths, London, 1959, p. 127, and refs. given therein.
[11] Alt and Barton, *J.*, 1954, 4284.

enquiring why, on the other hand, the cyclopropane (III; R = Me) opens entirely in accordance with the rule.

The most obvious difference between the reaction of an epoxide and a cyclopropane with acid is that the lone-pair electrons on oxygen can accept a proton reversibly from the solvent without direct involvement of the bonds of the three-membered ring (VIII), whereas a proton can become attached to a cyclopropane only by co-ordinating on to the electrons in the "bend" of the bent bonds,[12] as shown diagrammatically in (IX). If the C–O bond *a* in a protonated epoxide (VIII) is stretched, the developing, formally empty *p*-orbital of the $sp^2$-carbonium ion will continue to overlap the filled orbital of the oxygen atom, and, consistently with a recent re-interpretation[13] of the kinetic evidence, the participation of a nucleophilic solvent molecule is usually necessary finally to break the bond *a*. The strain in the three-membered ring would be expected to make distance *a* in the transition state (X) rather shorter than in a normal $S_N2$ displacement,* and *b* perhaps rather longer. Since it can then adopt most nearly a linear arrangement of entering group, carbon and leaving group (lines *a* and *b*), giving better orbital overlap, the transition state (X) leads to diaxial rather than diequatorial opening.[10,15]

If the C–C bond in a protonated cyclopropane (IX) † is stretched, the proton will progressively attach itself to one carbon atom ‡ which is becoming normal $sp^3$, leaving the other to become an $sp^2$-carbonium ion. A point will then be reached which can be written in an extreme form as a carbonium ion overlapping the σ-orbital of a C–H bond (XI). A hydrocarbon is much less nucleophilic than an alcohol and, unlike (X), the transition state (XI) needs no nucleophilic assistance from the solvent to complete the cleavage of the C–C bond. In other words, acid-catalysed opening of substituted cyclopropanes yields carbonium ions. The Markownikow orientation of opening is, therefore, to be expected.

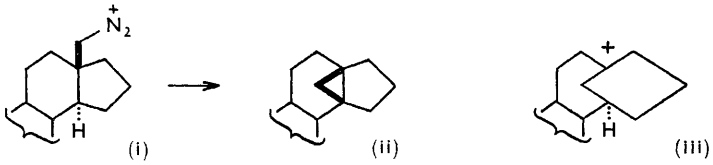
A further consequence of the absence of an entering nucleophile in the transition state (XI) must be less preference for axial opening than in the case of epoxides (X). Some preference would still be expected, owing to better overlap in the axial transition state. But bond-breaking will have progressed even less in the opening of cyclopropanes (XI) than of the epoxides (X) (they probably have roughly the same strain energy[17]), because $CH_3$–R is (as already pointed out) a much better leaving group than HO–R. The difference in orbital overlap between axial and equatorial transition states will thus be less than for epoxides (or bromonium ions), even apart from the absence of an external nucleophile.

It is, therefore, not too surprising that the "unsubstituted" cyclopropane (III;

* The opposite conclusion has been reached previously.[14]

† For our cyclopropanes there is no evidence whether a solvated form of (IX) is an intermediate in a pre-equilibrium, or whether it is represented merely by a point on a sloping valley leading to the pass on the potential-energy surface.

‡ Although it cannot be demonstrated in our compounds, this amounts to the usual electrophilic substitution with retention of configuration at this position. Cases of apparent inversion, such as i ⟶ ii,[16] can be explained by prior rearrangement (iii).




[12] Kilpatrick and Spitzer, *J. Chem. Phys.*, 1946, **14**, 463; Coulson and Moffitt, *ibid.*, 1947, **15**, 151; *Phil. Mag.*, 1949, **40**, 1; Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179.

[13] Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4978.

[14] Parker and Isaacs, *Chem. Rev.*, 1959, **59**, 737.

[15] Cookson, *Chem. and Ind.*, 1954, 223, 1512; Henbest, Smith, and Thomas, *J.*, 1958, 3293.

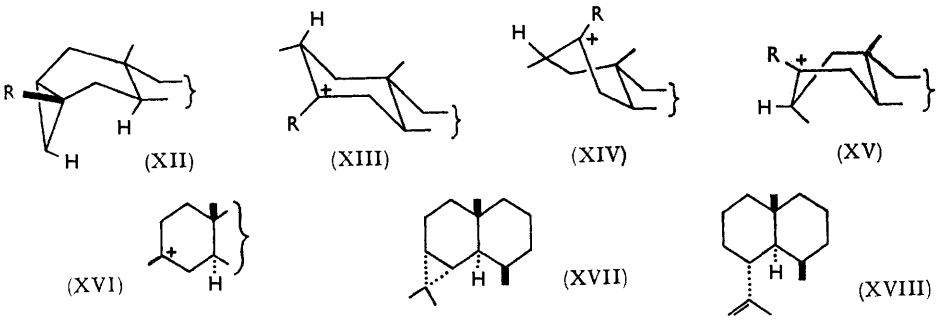
[16] Hora, Cerny, and Šorm, *Tetrahedron Letters*, 1962, 501; Dauben and Long, *ibid.*, p. 453.

[17] Benson, *J. Chem. Phys.*, 1961, **34**, 521; see also Nelson and Jessup, *J. Res. Nat. Bur. Stand.*, 1952, **48**, 206; Knowlton and Rossini, *ibid.*, 1949, **43**, 113.

R = H) gives a mixture of both 2- and 3-methylcholest-2-ene. The additional component is probably an olefin, or olefins, formed by cleavage of the third bond of the cyclopropane ring (the one fused to ring A), which would also give a secondary carbonium ion [case (*a*)]. Whether the olefins were formed entirely by loss of a proton from the original secondary carbonium ions, or partly by subsequent elimination from the alcohols or acetates produced by reaction with the solvent, is uncertain. 3β-Acetoxycholestane is stable under the conditions of the experiment, so perhaps the former alternative is rather more likely.

In the conformation (XII) of the cyclopropanes (III) having least deformation of bond angles the 5α-hydrogen atom would be only about 1·4 Å away from the α-hydrogen of the cyclopropane's methylene group. This distance can be increased by twisting,[18] which involves rotating the cyclopropane ring upwards about the axis C-1—C-4. There is probably only one conformation for ring A that represents a potential-energy minimum: C-10 is in the same plane as C-1, -2, -3, and -4, and C-5 is below it, the H–H distance (XII) is still only about 1·7 Å. The ring could undergo direct equatorial opening to the chair carbonium ion (XIII), or axial opening, if that is sufficiently favoured, to either of the boat conformations (XIV) or (XV), or to a twisted conformation [18] intermediate between the last two. The family of boat conformations of the ion could then lose an equatorial 2β-proton, or an axial one after inversion to the chair form (XIII). We have recently shown [2] that the closely related carbonium ion (XVI) in a similar solvent loses the 2α- in preference to the 2β-proton.

Büchi and his colleagues [19] have already demonstrated that rearrangement of maaliane (XVII) to the olefin (XVIII) is the result of overall equatorial opening, in obedience to Markownikow's rule. The situation there, however, is different from that in the methylenecholestanes just discussed [case (*c*)], for in maaliane and similar tetrasubstituted cyclopropanes the proton becomes attached to the cyclohexane ring, leaving the tertiary carbonium ion on the former [1]-bridge of the bicyclo[4,1,0]hexane [case (*b*)]. The overlap then is equal for axial and equatorial opening and no stereoelectronic preference for axial




opening is to be expected. Another factor that may be important, however, where the carbonium ion is not held in a ring, is the energy required to hold the developing tertiary carbonium ion in the conformation for maximum overlap with the new C–H bond (XI), against the forces of repulsion tending to rotate it into a less strained conformation. The repulsion of the substituent on the inside of the [1]-bridge in the alternative transition states will usually be dominant, and will control the direction of cleavage, as in maaliane.

The anomaly that still has to be explained is the much slower reaction of the 3-phenyl derivative (III; R = Ph) than of the other two cyclopropanes (III; R = H or Me). If the transition state for its opening is on the way to a tertiary benzylcarbonium ion a faster

[18] Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4357; Johnson, Bauer, Margrave, Frisch, Dreger, and Hubbard, *ibid.*, p. 606.
[19] Büchi, Wittenau, and White, *J. Amer. Chem. Soc.*, 1959, **81**, 1968.

rate might have been expected. Possible explanations are: (1) The phenyl group is constrained in the conformation where it is in the plane of the C–C bond to be broken, and energy is required to rotate it into the conformation at right angles to the axis of the developing empty *p*-orbital of C-3 in the transition state. (2*a*) The phenyl group causes hindrance to proton transfer from the solvent if that is the slow step, or (2*b*) an unfavourable pre-equilibrium constant by hindrance to solvation.[20] (3*a*) If a slow proton-transfer is involved, the transition state is so near the reactants that little carbonium-ion character has developed and electromeric release of electrons by the phenyl group cannot overcome its opposing inductive effect (cf. nitration of halogenobenzenes [21]), or (3*b*) the inductive removal of electrons reduces the basicity of the ring in a pre-equilibrium.

Examination of models gives no support to suggestion (1), and the ultraviolet spectrum is very similar to that of phenylcyclopropane [22] ($\lambda_{max.}$ 220 mμ). The most economical explanation would be in terms of (3*a*), perhaps reinforced by (2*a*): in the conformation needed for conjugation the *o*-hydrogen atom of the phenyl group might interfere somewhat with the solvent molecule delivering the proton.

## Experimental

Rotations were measured for chloroform solutions (0·8—1·2%). Infrared spectra of Nujol mulls were measured on a Unicam S.P. 100, and ultraviolet spectra of ethanol solutions on an S.P. 700 spectrophotometer. Identity of samples was established by mixed m. p.s and infrared spectra.

2α,3α-(*Dibromomethylene*)-3β-*phenylcholestane* (II; R = Ph).—Potassium t-butoxide (5 g.) was added to a solution of 3-phenylcholest-2-ene (2·3 g.) in benzene (50 ml.). Bromoform was then run into the stirred mixture during 0·5 hr. After 12 hr. the solution was filtered and evaporated and the resulting oil was chromatographed on silica in light petroleum. Unchanged olefin (0·56 g.) was followed off the column by the *dibromocyclopropane* (II; R = Ph) (1·2 g.), m. p. 145—147° (from methanol–ethyl acetate), $[\alpha]_D$ +34° (Found: C, 66·3; H, 7·8; Br, 25·9. $C_{34}H_{50}Br_2$ requires C, 66·2; H, 8·0; Br, 25·9%).

2α,3α-(*Dibromomethylene*)-3β-*methylcholestane* (II; R = Me) was made in the same way from 3-methylcholest-2-ene (2·8 g.) with potassium t-butoxide (4 g.) and bromoform in boiling benzene (50 ml.). Chromatography on silica gave the dibromocyclopropane (1·8 g.), m. p. 116—118° (from methanol–ethyl acetate), $[\alpha]_D$ +25°.

2α,3α-(*Dibromomethylene*)*cholestane* (II; R = H) (1·1 g.), m. p. 84—86° (from methanol–ethyl acetate), $[\alpha]_D$ +43°, was made similarly from cholest-2-ene (2·5 g.).

2α,3α-*Methylene*-3β-*phenylcholestane* (III; R = Ph).—Small pellets of sodium were added to a solution of the dibromo-derivative (1·2 g.) in dioxan–ether, and methanol containing 3% of water was allowed to drip slowly into the stirred mixture. After 24 hours' treatment, more sodium being added as required, the product was isolated and chromatographed on silica. The *cyclopropane* (III; R = Ph) (0·45 g.), m. p. 123—124° (thermochromic) (from methanol–ethyl acetate), $[\alpha]_D$ +73°, had a weak band at 1030 cm.$^{-1}$ and $\lambda_{max.}$ 220 (ε 7100) and 264 mμ (ε 267, fine structure) (Found: C, 88·7; H, 11·2. $C_{34}H_{52}$ requires C, 88·7; H, 11·3%). Further elution with light petroleum gave unchanged dibromide.

3β-*Methyl*-2α,3α-*methylenecholestane* (III; R = Me).—Reduction of the dibromo-derivative (1·7 g.) in the same way, followed by chromatography, led to the *methylcyclopropane* (0·64 g.) and unchanged dibromide. After crystallisation from ethyl acetate, the former had m. p. 120°, $[\alpha]_D$ +43°, $\nu_{max.}$ 3050 and 1020 cm.$^{-1}$ (Found: C, 87·6; H, 12·5. $C_{29}H_{50}$ requires C, 87·4; H, 12·6%).

2α,3α-*Methylenecholestane* (III; R = H) (0·47 g.), made similarly from the corresponding dibromide (1 g.), had m. p. 104—105° (from ethyl acetate), $[\alpha]_D$ +33°, $\nu_{max.}$ 3050 and 1020 cm.$^{-1}$ (Found: C, 87·2; H, 12·3. $C_{28}H_{48}$ requires C, 87·5; H, 12·5%).

[20] Bird and Cookson, *J.*, 1960, 2343.
[21] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 246.
[22] Rogers, *J. Amer. Chem. Soc.*, 1947, **69**, 2544.

*Reaction of Cyclopropanes with Acid.*—No detectable reaction occurred when 3β-methyl-2α,3α-methylenecholestane (III; R = Me), dissolved in 2·08N-sulphuric acid in tetrahydrofuran containing 5% of water, was kept at 41° for 18 hr.

Water (10 ml.) and 12·2N-perchloric acid (10 ml.) were separately made up to 100 ml. with acetic acid. In the standard procedure the acid solution (5 ml.) was added to the cyclopropane which had been dissolved in chloroform (10 ml.) and " 90% " acetic acid (10 ml.). The solution was then kept at 41° before being poured into water and extracted with chloroform, which was washed with sodium hydrogen carbonate solution and then with water. After being dried ($Na_2SO_4$) the extract was evaporated to give the crude product.

The crude product from 3β-methyl-2α,3α-methylenecholestane (III; R = Me) (61 mg.) after 24 hr. under the standard conditions had m. p. 78—81° and lacked the bands at 3050 and 1020 cm.$^{-1}$. Chromatography on silica with light petroleum gave 2,3-*dimethylcholest*-2-*ene* (IV; R = Me), m. p. 84—85° (from methanol–ethyl acetate), $[\alpha]_D$ +83°, as the sole product (Found: C, 87·6; H, 12·3. $C_{29}H_{50}$ requires C, 87·4; H, 12·6%), identical with the sample synthesised below.

After 24 hr. under the standard conditions, the crude product from 2α,3α-methylene-3β-phenylcholestane (III; R = Ph) had m. p. 115° and an infrared spectrum identical with the starting material's. Only the pure cyclopropane resulted from chromatography. After 48 hr. under the standard conditions, but with four times the concentration of perchloric acid, a crude product was obtained, having m. p. 144—145°, raised to 147—148° by recrystallisation from methanol–ethyl acetate. It was identical with an authentic sample of 2-methyl-3-phenylcholest-2-ene (IV; R = Ph).

After 24 hr. under the standard conditions, 2α,3α-methylenecholestane (III; R = H) yielded a crude product that solidified (with difficulty), then having m. p. 40—50°. The infrared spectrum, which differed from that of the cyclopropane, included a peak at 1740 cm.$^{-1}$. On chromatography on silica, light petroleum eluted a mixture of hydrocarbons melting over a range at about 50°, not improved by recrystallisation, $[\alpha]_D$ +37°, $\nu_{max.}$ 790w and 750s cm.$^{-1}$. Ethyl acetate eluted a small gummy fraction, $\nu_{max.}$ 1740 cm.$^{-1}$, presumably a mixture of acetates.

After 96 hr. under the standard conditions, 3-methylcholest-2-ene (I; R = H) formed a product that was separated by chromatography into unchanged olefin and a gum with $\nu_{max.}$ 1740 cm.$^{-1}$, also present in the spectrum of the crude product.

2,3-*Dimethylcholest*-2-*ene* (IV; R = Me).—The product of reaction of 3α-methylcholestan-2-one (70 mg.) (kindly supplied by Mr. M. Nye) with methylmagnesium iodide in ether was heated in acetic acid containing a few drops of perchloric acid at 90° for 1 hr. Chromatography of the product in light petroleum on alumina gave 2,3-dimethylcholest-2-ene (IV; R = Me) (50 mg.), m. p. 83—84° (from methanol–ethyl acetate), $[\alpha]_D$ +83°.

2-*Methylcholest*-2-*ene* (IV; R = H).—Reaction of cholestan-2-one (0·2 g.) with methylmagnesium iodide in ether, followed by dehydration of the product with perchloric acid in acetic acid, gave, after chromatography, 2-methylcholest-2-ene (0·12 g.), m. p. 95—97° (from methanol–ethyl acetate), $[\alpha]_D$ +75°.

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