Steroids and Walden Inversion. Part XV. The Mechanism and Stereochemical Course of Some Grignard Carboxylations and Oxygenations.*

By G. Roberts and C. W. Shoppee.

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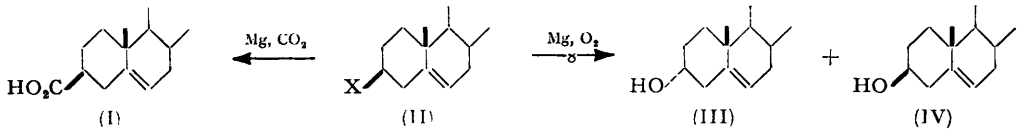
Grignard carboxylation of cholesteryl chloride or bromide has been shown to give only cholest-5-ene-3β-carboxylic acid, but, as we have confirmed, Grignard oxygenation affords approximately equimolecular quantities of *epi*-cholesterol and cholesterol. Similarly, whereas Grignard carboxylation of *epi*cholestanyl bromide or cholestanyl bromide has been shown to give uniquely cholestane-3β-carboxylic acid, Grignard oxygenation of either bromide furnishes the same approximately equimolecular mixture of *epi*-cholestanol and cholestanol.

The mechanisms of the formation of Grignard compounds and of their reactions with carbon dioxide and oxygen are discussed.

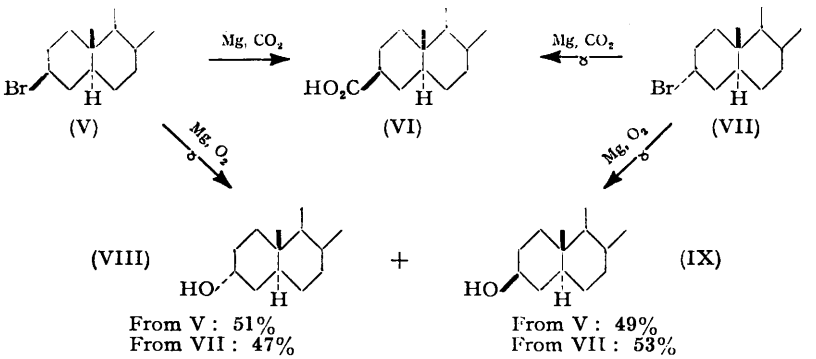
Cholesteryl chloride or bromide (II; X = Cl or Br) by treatment with magnesium and carbon dioxide gives a single acid, which we have shown to be cholest-5-ene-3β-carboxylic acid (I) (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705). Cholesteryl chloride (II; X = Cl), however, by treatment with magnesium and oxygen, gives an approximately equimolecular mixture of *epi*cholesterol (III) and cholesterol (IV) (Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 481, 1948), as we have confirmed. *epi*Cholesterol cannot arise from cholesterol in the proportion found because the latter is unaffected under the conditions of Grignard oxygenation, and the equilibrium mixture consists of ~10% of *epi*cholesterol and ~90% of cholesterol (Barnett, Heilbron, Jones, and Verrill, *J.*, 1940, 1390). Cholest-5-ene-3β-carboxylic acid could arise from the 3α-carboxylic acid since the

* Part XIV, *J.*, 1954, 3178.

equilibrium mixture consists of ~5% of 3α-carboxylic acid and ~95% of 3β-carboxylic acid, but we have found that cholest-5-ene-3α-carboxylic acid is not epimerised under the conditions of Grignard carboxylation. One reaction thus proceeds with retention of configuration at $C_{(3)}$ and the other with racemisation at $C_{(3)}$.



Cholestanyl bromide (V) and *epi*cholestanyl bromide (VII) furnish uniquely the same cholestane-3β-carboxylic acid (VI) by Grignard carboxylation (Roberts, Shoppee, and Stephenson, *loc. cit.*); we now find that both these bromides by Grignard oxygenation afford an approximately equimolecular mixture of *epi*cholestanol (VIII) and cholestanol (IX). Cholestane-3β-carboxylic acid (VI) could arise from cholestane-3α-carboxylic acid; but the equilibrium mixture contains 25—30% of the latter acid (Roberts, Shoppee, and Stephenson, *loc. cit.*), yet none could be isolated. Moreover, cholestane-3α-carboxylic acid is not epimerised under the conditions of Grignard carboxylation. *epi*Cholestanol (VIII) cannot be derived from cholestanol (IX) in the proportion found since the equilibrium



mixture consists of ~10% of (VIII) and ~90% of (IX) (Windaus and Uibrig, *Ber.*, 1914, **47**, 2384). One Grignard carboxylation (V ⟶ VI) thus proceeds with retention, and the other (VII ⟶ VI) with inversion at $C_{(3)}$, whilst both Grignard oxygenations occur with racemisation at $C_{(3)}$.

It seems of interest briefly to examine the mechanism and stereochemistry of the above Grignard carboxylations :

$$R{\cdot}X \xrightarrow{(a)} R{\cdot}MgX \xrightarrow{(b)} R{\cdot}CO_2{\cdot}MgX$$

Reaction (*a*) occurs at the magnesium surface and could, in principle, give the carbonium ion R^+, the radicle R·, or the carbanion R^-; reaction (*b*) occurs in the absence of a metallic surface, and is generally held to involve the carbanion R^- (cf. Ingold, "Structure and Mechanism in Organic Chemistry, Bell, London, 1953, 787), either free or as an ion pair, $R^-\}MgX^+$, in a non-polar solvent.

The formation of R·MgX appears to involve complete fission of the carbon–halogen bond, because (+)- and (−)-methyl-*n*-hexyl bromide both yield completely racemised methyl-*n*-hexylmagnesium bromide (Porter, *J. Amer. Chem. Soc.*, 1935, **57**, 1436). Production of a planar carbonium ion (sp^2-hybridisation with a vacant *p*-orbital) would be consistent with the formation of completely racemised Grignard derivatives from optically active halides; it apears to be excluded * by the reaction of *neo*pentyl bromide and magnesium, because treatment with carbon dioxide or phenyl *iso*cyanate yields ββ-di-

* Failure of cholesteryl bromide to give 3 : 5-*cyclo*cholestane-6β-carboxylic acid by Grignard carboxylation also tends to exclude production of the cholest-5-en-3β-yl cation.

methylbutyric acid or its anilide (Whitmore and Fleming, *ibid.*, 1933, **55**, 4161), whereas rearrangement to the *tert.*-amyl structure always occurs in reactions involving the *neo*-pentyl cation (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173). Production of a radical is known to take place in the exceptional and specially favourable case of the formation of triphenylmethylmagnesium bromide (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1930, **52**, 2435), and would be compatible with the observed racemisation of optically active halides by treatment with magnesium because the conversion of primary (+)-amyl chloride by both photochemical and peroxide-catalysed chlorination to inactive 1 : 2-dichloro-2-methylbutane (Brown, Kharasch, and Chao, *ibid.*, 1940, **62**, 3435) shows that the radical $MeEt(CH_2Cl)C\cdot$ is planar (sp^2-hybridisation with a single *p*-electron) (cf. Gilman, " Organic Chemistry, 2nd edn., Vol. I, p. 383 *et seq.*, John Wiley and Sons Inc., New York, 1943). It would also be consistent with the production from *neo*pentyl iodide in the Wurtz reaction with sodium of the unrearranged products *neo*pentane and 1 : 1-dimethyl-*cyclo*propane unaccompanied by the expected rearranged products *iso*pentane and trimethylethylene (Whitmore, Popkin, and Pfister, *ibid.*, 1939, **61**, 1616), but neither in their formation nor in their reactions do Grignard reagents generally exhibit the characteristic behaviour of radicals.* Thus, dimerisation normally leads only to unimportant by-products, but in the presence of appropriate catalysts, *e.g.*, cobaltous chloride, reactions characteristic of radicals such as dimerisation, dismutation, and abstraction of hydrogen from the medium become very prominent.

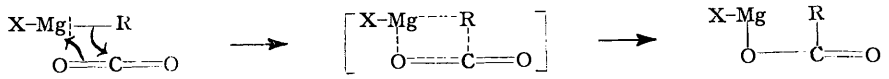
We believe that a carbanion R^-, possibly as an ion pair $R^-\}MgX^+$, is involved in both the formation and the reactions of Grignard compounds. We suggest that a carbanion has a preferred tetrahedral configuration (sp^3-hybridisation with a lone pair) separated from the inverse tetrahedral arrangement by only a low energy barrier; this would be consistent with the racemisation of optically active saturated aliphatic halides by treatment with magnesium (cf. Gilman, *op. cit.*). Sidgwick (" The Chemical Elements and their Compounds," Vol. I, xix *et seq.*, Oxford Univ. Press, 1950), and Lennard-Jones *et al.* (*Proc. Roy. Soc.*, 1949, *A*, **198**, 1, 14; 1950, *A*, **202**, 155, 166, 323, 336) have stressed the importance of lone pairs and the Cambridge authors have concluded that " lone pairs may be important factors in determining equilibrium configurations of molecules; " presumably this conclusion must extend to carbanions, in which the unshared electron pair may be expected to occupy an orbital of at least the same size as, and of possibly larger size than, a C–H bond.† It has been observed that reduction by dissolving metals of steroid polyene systems through intermediate carbanions invariably affords the thermodynamically more stable product (W. S. Johnson *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 2275); similarly, Barton (Chemical Society Symposium, Manchester, 1954) found that 5-chlorocholestane on reduction with lithium in liquid ammonia gives cholestane in quantitative yield, whilst 5 : 6α-dibromocoprostane (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066) gives cholestane, accompanied by cholest-5-ene but unaccompanied by coprostane. Thus, protonation or carboxylation affords the more thermodynamically stable arrangement at the asymmetric centre(s).

In regard to reaction (*b*), Cardwell, Cornforth, Duff, Holtermann, and Robinson (*J.*, 1953, 361) have suggested that reactions of lithium aluminium hydride, aluminium hydride, alkyl-lithiums, and alkylaluminiums with olefins and carbonyl groups proceed by electrophilic attack of aluminium on carbon or oxygen rather than by nucleophilic attack of hydrogen or alkyl on carbon, on the ground that covalent unions rather than preliminary electrovalent connections must be determinative. It seems highly probable that the reaction of alkylmagnesium halides with carbon dioxide may proceed by an analogous mechanism; Swain *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 2306; 1950, **72**, 518) have shown by kinetic studies that, in the reaction of alkylmagnesium halides and alkyl-lithiums with cyano- or carbonyl groups, the rate-determining stage is an intramolecular rearrangement of a complex. The formation of such a complex will be favoured stereochemically by the

* We are grateful to a Referee for emphasising this point.

† The atomic dipole for a tetrahedral carbon orbital is ~2 D, which suggests that the average separation of charge may be of the order of 2 Å, a value which may be compared with the C–H bond length 1·09 Å (cf. Coulson, " Valence," Oxford Univ. Press, 1952, p. 208).

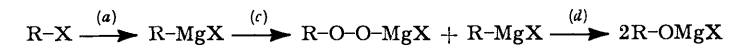
approximately rectangular configuration of the bonds from oxygen to carbon and oxygen to magnesium :



and, since the rearrangement is of S_Ni type, will occur with preservation of configuration.

We suggest that cholestanyl (V) and *epi*cholestanyl bromide (VII) on treatment with magnesium initially furnish the cholestan-3β-yl and cholestan-3α-yl anions; these at once undergo inter-conversion by passage through a planar form [sp^2-hybridisation with two *p*-orbitals each containing a single electron, and isoelectronic with the analogous form in NH_3 or NR_3 (cf. Linnett and Poë, *Trans. Faraday Soc.*, 1951, **47**, 1033)] to give exclusively the more stable cholestan-3β-yl anion (lone pair, equatorial), which by carboxylation yields only cholestane-3β-carboxylic acid [VI (CO_2H, equatorial)]. For cholesteryl (II) and *epi*cholesteryl bromide, it might be expected that the epimeric cholest-5-en-3β-yl and cholest-5-en-3α-yl anions would be formed initially and undergo equilibration to give exclusively the former (lone pair, equatorial), since apart from the greater thermodynamic stability of the equatorial conformation, the molecular geometry here will give rise to powerful repulsive forces between an unshared electron pair at $C_{(3)}$ and the π-electron cloud of the 5 : 6-double bond. It is consistent that cholesteryl bromide (II) by Grignard carboxylation gives only cholest-5-ene-3β-carboxylic acid [I (CO_2H, equatorial)], but *epi*cholesteryl bromide affords a single acid, which differs from cholest-5-ene-3α-carboxylic, and is provisionally termed cholest-5-ene-2ξ-carboxylic acid (cf. Shoppee, *Chem. and Ind.*, 1954, 759).

The mechanism of Grignard oxygenation appears to involve three stages :



since Walling and Buckler (*J. Amer. Chem. Soc.*, 1953, **75**, 4372) have isolated alkyl hydroperoxides formed in stage (*c*) in high yield, and have shown that treatment of alkylperoxymagnesium halide with additional Grignard reagent in stage (*d*) gives alcohols in high yield (personal communication). The stereochemical course of these reactions is obscure but in cyclic systems appears always to lead to racemisation with production of pairs of epimeric alcohols. We have not attempted to isolate the steroid hydroperoxide(s), but from the ultimate production of *epi*cholesterol (III) and cholesterol (IV), and of *epi*cholestanol (VIII) and cholestanol (IX) as described above, we infer that the racemisation process probably occurs in stage (*c*) and may be connected with the electronic structure of the oxygen molecule, because for stage (*d*) we postulate a four-centre transition state of S_Ni type (*A*) leading to retention of configuration in both the residues R. Campbell, Burney, and Jacobs

(*J. Amer. Chem. Soc.*, 1950, **72**, 2735) in a discussion of the reaction of di-*tert.*-butyl peroxide with Grignard reagents other than methylmagnesium halides have, however, proposed a six-centre transition state involving hydrogen bonding (*B*).

Experimental

For general directions see *J.*, 1954, 3178.

Cholesterol and epi*Cholesterol.*—A solution of cholesteryl bromide (1·17 g.), in ether (20 c.c.) was added to a solution of methylmagnesium iodide prepared from magnesium (0·25 g.), during 5 hr. During a total reflux period of 22 hr. a further quantity of methyl iodide (0·5 c.c.) in ether (5 c.c.) was added. Oxygen was then passed into the solution at 0° for 2 hr.; ice-cold 2*N*-sulphuric acid was added and the product extracted with ether. Washing, drying, and removal of solvent gave a product, which was chromatographed on a column of aluminium oxide (30 g.) prepared in pentane. Use of pentane (300 c.c.) as eluant furnished a mixture of

3β : 3β-dicholesteryl, other hydrocarbons, and unchanged cholesteryl bromide (630 mg.), whilst ether (200 c.c.) gave a mixture of alcohols (350 mg.) which was rechromatographed. Benzene–pentane (1 : 4; 6 × 30 c.c.) gave an oil (31 mg.), but use of benzene (6 × 30 c.c.) gave a solid (162 mg.), which was crystallised from methanol and had m. p. and mixed m. p. with authentic *epi*cholesterol 141°. Further elution with ether–benzene (1 : 1; 4 × 30 c.c.) gave a solid (166 mg.), which was crystallised from methanol to give cholesterol, m. p. and mixed m. p. 146—147°.

Cholestanol and epi*Cholestanol.*—(*a*) To a solution of methylmagnesium iodide prepared from magnesium (0·25 g.), ether (10 c.c.), and methyl iodide (0·1 c.c.) was added a solution of pure cholestan-3α-yl bromide (Roberts, Shoppee, and Stephenson, *loc. cit.*) (1 g.) in ether (10 c.c.). A further quantity of methyl iodide (0·4 c.c.) was added during the first 6 hr. of the total reflux period of 25 hr. The solution was then oxygenated at 0° during 4·5 hr. and the product isolated as in the previous experiment. Some ether-insoluble 3β : 3β-dicholestanyl (81 mg.) was removed, and the residue chromatographed on a column of aluminium oxide (24 g.) prepared in pentane. Use of pentane (3 × 80 c.c.) furnished a solid (651 mg.) consisting mainly of unchanged cholestan-3α-yl bromide; benzene–pentane (1 : 1, 3 × 80 c.c.) gave a solid (48 mg.) which, was crystallised from methanol, had m. p. 188°, and was identical with authentic *epi*cholestanol and characterised as the acetate, m. p. 96°. Further elution with benzene (80 c.c.) and with ether (80 c.c.) gave a solid (53 mg.) which, crystallised from methanol, had m. p. and mixed m. p. with cholestanol 144°, and was characterised as the acetate, m. p. 108°.

(*b*) A reaction was carried out on a similar scale and under similar conditions but with pure cholestan-3β-yl bromide (Roberts, Shoppee, and Stephenson, *loc. cit.*). The product was chromatographed on a column of aluminium oxide (24 g.). Use of pentane (4 × 80 c.c.) gave an oil (495 mg.), and benzene–pentane (1 : 4) again gave an oil (2 mg.); benzene–pentane (1 : 1; 3 × 80 c.c.) furnished a solid (108 mg.), which was crystallised from methanol and identified as *epi*cholestanol, m. p. 188° (acetate, m. p. 96°). Further elution with benzene (80 c.c.) and ether (80 c.c.) gave a solid (112 mg.), which was crystallised from methanol and identified as cholestanol, m. p. 144° (acetate, m. p. 109°).

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UNIVERSITY OF WALES, UNIVERSITY COLLEGE OF SWANSEA. [*Received, June 12th,* 1954.]