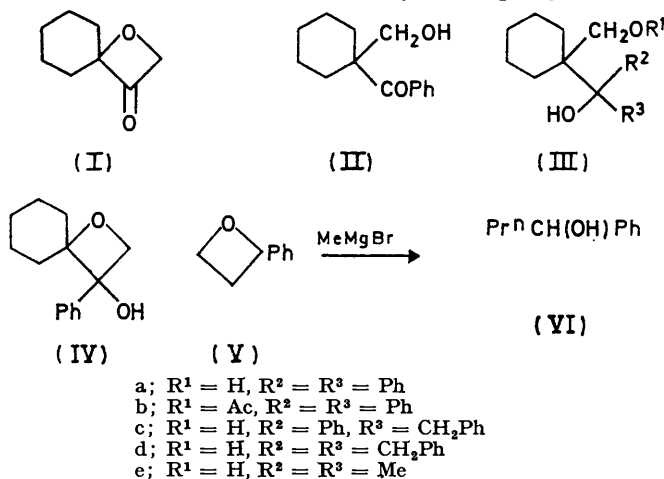# Rearrangement of an Oxetan-3-one and Related Alcohols by Grignard Reagents †

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Oxetan-3-ols, formed by the reaction of Grignard reagents with cyclohexanespiro-2'-oxetan-3'-one, rearrange under normal Grignard reaction conditions to 1-acyl-1-hydroxymethylcyclohexanes.

ALTHOUGH oxetans have considerably less ring-strain than oxirans they are, nevertheless, almost as susceptible[1] as the latter to acid catalysed ring-opening; this may be attributed to the higher electron density of the oxetan hetero-atom.[2] While successfully attempting to find

(I)   (II)   (III)

Ph OH
(IV)   (V)   (VI)

a; R^1 = H, R^2 = R^3 = Ph
b; R^1 = Ac, R^2 = R^3 = Ph
c; R^1 = H, R^2 = Ph, R^3 = CH_2Ph
d; R^1 = H, R^2 = R^3 = CH_2Ph
e; R^1 = H, R^2 = R^3 = Me

the conditions for addition, without ring-opening, of Grignard reagents to the carbonyl group of cyclohexane-spiro-2'-oxetan-3'-one (I), one of the few known[3]

tetramethyl- and tetraphenyl-oxetan-3-ones with methyl-and benzyl-magnesium bromides and Yates and Szabo[5] treated oxetan-3-one itself with phenylmagnesium bromide. In all cases simple addition to the carbonyl function was reported. When, however, we treated the spiro-oxetan-3'-one (I) with phenylmagnesium bromide under the usual Grignard reaction conditions,[6] we obtained 1-benzoyl-1-hydroxymethylcyclohexane (II) and 1-hydroxydiphenylmethyl-1-hydroxymethylcyclo-hexane (IIIa).

The diol (IIIa) is obviously formed by a secondary addition of phenylmagnesium bromide, to the benzoyl-cyclohexane (II), but the latter must arise from a re-arrangement of the initially formed 3'-phenyloxetan-3'-ol (IV). Previously reported[7] ring-openings of oxetans by Grignard reagents were uncomplicated and resulted in addition to the *less* substituted α-position, e.g. the forma-tion of 1-phenylbutan-1-ol (VI) from 2-phenyloxetan (V).

We suggest that in the present case the oxetan ring opens (Scheme) in the direction of the *more* substituted α-position to form the precursor of the cyclohexyl phenyl ketone (II). Thus the Grignard reagent, instead of attacking the unhindered 4-position, attacks the equally unhindered oxymagnesium group to allow the heterocyclic ring to open in the direction of a tertiary

SCHEME
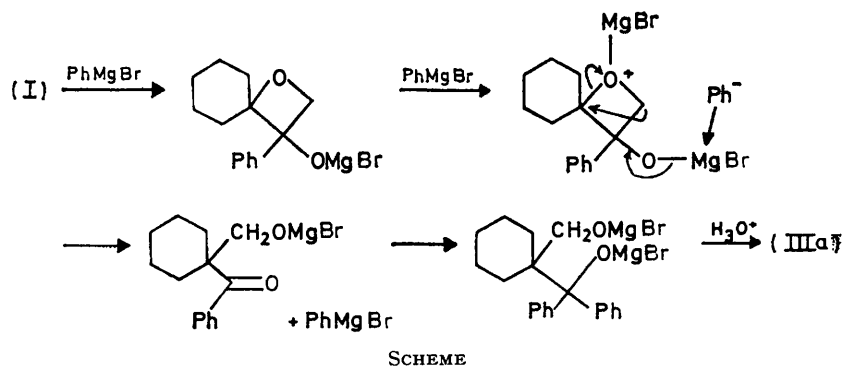
oxetan-3-ones, we observed that when ring-opening occurred the products did not have the expected struc-tures.

There are at least four recorded Grignard reactions of oxetan-3-ones. Lester and his co-workers[4] treated

carbocation. If this interpretation is correct then it is surprising that the previously mentioned Grignard reactions[4] of tetramethyl- and tetraphenyl-oxetan-3-ones were uncomplicated by molecular rearrangement.

[1] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1958, **80**, 4162.

[2] H. S. Gutowsky, R. L. Rutledge, M. Tamres, and S. Searles, *J. Amer. Chem. Soc.*, 1954, **76**, 4242.

[3] A. T. Rowland, P. J. Bennett, and T. S. Shoupe, *J. Org. Chem.*, 1968, **33**, 2426, and references therein.

[4] J. L. Harper and C. T. Lester, *J. Org. Chem.*, 1961, **26**, 1294; G. B. Hoey, D. O. Dean, and C. T. Lester, *J. Amer. Chem. Soc.*, 1955, **77**, 391.

[5] P. Yates and A. G. Szabo, *Tetrahedron Letters*, 1965, 485.

[6] L. F. Fieser, ' Organic Experiments,' Heath and Co., Boston, 1966, p. 92.

[7] S. Searles, in ' Heterocyclic Compounds with Three- and Four-Membered Rings,' ed. A. Weissberger, Interscience, New York, 1964, p. 1007.

A similar mechanism has recently been proposed by Kagan and Przybytek[8] for the acid catalysed conversion of

(VII)   (VIII)
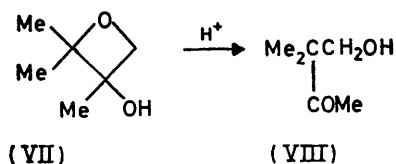
2,2,3-trimethyloxetan-3-ol (VII) into 3-hydroxymethyl-3-methylbutan-2-one (VIII). They also proposed, as
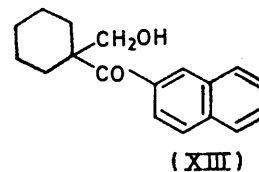

(IX)
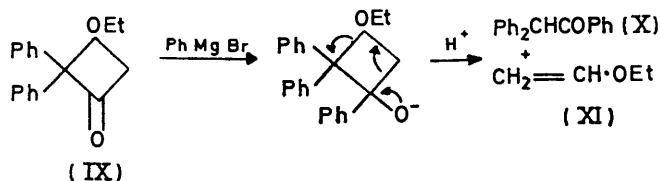
equally likely, a mechanism involving an epoxide intermediate (their Mechanism 3). An unattractive feature is that, as applied to the present rearrangement, it involves the contraction[9] of a four-membered ring to a
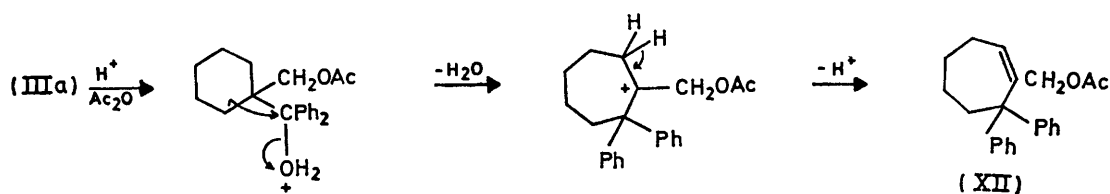
three-membered ring with the simultaneous formation of a tertiary carbocation at the expense of a benzyl tertiary carbocation.

Like Kagan and Przybytek,[8] we had also considered that the rearrangement might be a *trans*-hydroxy-methylation reaction[10] occurring by loss of formaldehyde from the 3'-phenyloxetan-3'-ol precursor, followed by an aldol condensation. This was suggested by the work of Kimbrough and Hancock[11] who found that phenylmagnesium bromide reacted with a substituted cyclobutanone (IX) to give a ketone (X) and a vinyl ether (XI). However, several attempts to condense formaldehyde with cyclohexyl phenyl ketone failed to yield 1-benzoyl-1-hydroxymethylcyclohexane (II).

The addition of phenylmagnesium bromide to the spiro-oxetan-3'-one (I) to give the unrearranged product, the 3'-phenyloxetan-3'-ol (IV), was carried out at $-50°$. The oxetanol (IV), on reaction with this Grignard reagent under normal conditions,[6] gave the rearrangement products (II) and (IIIa). The diol (IIIa) was also formed by a similar reaction on the cyclohexyl phenyl ketone (II). The diol (IIIa) readily gave the mono-acetate (IIIb). On treatment with toluene-*p*-sulphonic acid in acetic anhydride (IIIa) was converted into a

8 J. Kagan and J. T. Przybytek, *Tetrahedron*, 1973, **29**, 1163.
9 See, however, R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1959, **81**, 4390; J. Conia and J. Ripoli, *Compt. rend.*, 1960, **251**, 1071.

product tentatively assigned as 2-acetoxymethyl-3,3-diphenylcycloheptene (XII). When oxidised with chromium trioxide in pyridine the diol (IIIa) gave benzophenone. A related diol (IIIc) was obtained from the 3'-phenyloxetan-3'-ol (IV) by reaction with benzyl-magnesium bromide.

Although mechanistically a phenyl substituent on the 3-position of the oxetanol—leading to the formation of a phenyl ketone—might seem necessary for the rearrangement, this is not the case. The oxetan-3-one (I) readily reacted with methyl- and benzyl-magnesium halides to give the diols (IIIe) and (IIId), respectively. In a similar reaction using 2-naphthylmagnesium bromide, the product was the ketone (XIII). The failure of this ketone to undergo the usual further addition of Grignard reagent is probably due to intramolecular overcrowding of the carbonyl group.

EXPERIMENTAL

N.m.r. spectra were measured at 60 MHz with a Varian HR 60A or a Perkin-Elmer R12 spectrometer, in deuterio-chloroform with tetramethylsilane as internal reference; signals due to hydroxy-groups were removed with deuterium

(XII)

oxide. M.p.s were obtained with a Kofler hot-stage apparatus.

Grignard Reactions.—These were carried out in typical fashion[6] in dry, refluxing (unless otherwise stated) ether. For work-up, saturated aqueous ammonium chloride was added and the resulting mixture was extracted with ether.

(XIII)

The extract was dried (Na_2SO_4) and fractionated by preparative layer chromatography (p.l.c.) on silica gel.

(a) Cyclohexanespiro-2'-oxetan-3'-one[12] (I) (1·3 g) in ether (10 ml), was added to phenylmagnesium bromide [from bromobenzene (2·25 ml) and magnesium (0·54 g)] in ether (15 ml) at $-50°$, to give 3'-phenylcyclohexanespiro-2'-oxetan-3'-ol (IV), m.p. 105°, as prisms (1·3 g) from benzene–light petroleum (b.p. 60—80°) (Found: C, 76·7; H, 8·2. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%), τ 7·07 (OH), 5·53 (d, 4'-H), and 5·03 (d, $J_{4',4'}$ 9 Hz, 4'-H).

(b) The spiro-oxetan-3'-one (I) (2·6 g) in ether (10 ml), was added to phenylmagnesium bromide [from bromo-benzene (4·5 ml) and magnesium (1 g)] in ether (10 ml), to give 1-benzoyl-1-hydroxymethylcyclohexane (II) (0·8 g)

10 S. Olsen, *Acta Chem. Scand.*, 1955, **9**, 955.
11 R. D. Kimbrough and R. D. Hancock, *Chem. and Ind.*, 1965, 1180.
12 J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1952, 467.

(Found: C, 77·0; H, 8·4. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%), τ 7·15 (OH) and 6·15 (s, OCH_2R), i.r. 5·98 μm (PhCOR), m/e 218. Also obtained was 1-hydroxy(diphenyl)methyl-1-hydroxymethylcyclohexane (IIIa), m.p. 129—131°, as crystals (2·4 g) from ethanol (Found: C, 81·1; H, 8·3. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%), τ 6·6br (s, 2 OH) and 6·22 (s, OCH_2R).

(c) The spiro-oxetan-3'-ol (IV) (0·3 g) in ether (20 ml), was added to benzylmagnesium chloride [from benzyl chloride (0·5 g) and magnesium (0·1 g)] in ether (10 ml), to give 1-(1-hydroxy-1,2-diphenylethyl)-1-hydroxymethylcyclohexane (IIIc), m.p. 92—93°, as crystals (298 mg) from ethanol (Found: C, 80·8; H, 8·4. $C_{21}H_{26}O_2$ requires C, 81·2; H, 8·4%), τ 6·9br (s, 2 OH), 6·58 (s, OCH_2R), and 6·45 (d) and 6·12 (d) (RCH_2Ph).

(d) The spiro-oxetan-3'-ol (IV) (1·1 g) in ether (25 ml), was added to phenylmagnesium bromide [from bromobenzene (1·1 ml) and magnesium (0·26 g)] in ether (10 ml), to give the ketone (II) (0·4 g) and the diol (IIIa) (0·4 g), m.p. 129°.

(e) The ketone (II) (279 mg) in ether (10 ml), was added to phenylmagnesium bromide [from bromobenzene (1·1 ml) and magnesium (0·25 g)] in ether (10 ml), to give the diol (IIIa) (161 mg), m.p. 129° (from ethanol).

(f) The spiro-oxetan-3'-one (I) (415 mg) in ether (25 ml), was added to methylmagnesium bromide [from methyl bromide (0·4 g) and magnesium (0·1 g)] in ether (25 ml), to give 1-hydroxymethyl-1-(1-hydroxy-1-methylethyl)cyclohexane (IIIe), m.p. 44—45°, as crystals (398 mg) from aqueous ethanol (Found: C, 69·7; H, 11·9. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%), τ 8·75 (s, 2 Me), 6·1 (s, OCH_2R), and 6·3 (s, 2 OH).

(g) The spiro-oxetan-3'-one (I) (750 mg) in ether (20 ml),

was added to benzylmagnesium chloride [from benzyl chloride (2·6 g) and magnesium (0·5 g)] in ether (25 ml), to give 1-(1,1-dibenzyl-1-hydroxymethyl)-1-hydroxymethylcyclohexane (IIId), m.p. 115—116°, as crystals (430 mg) from ethanol (Found: C, 80·8; H, 8·7. $C_{22}H_{28}O_2$ requires C, 81·4; H, 8·7%), τ 7·19 (d) and 6·84 (d) $(CH_2Ph)_2$, and 6·00 (s, OCH_2R).

(h) The spiro-oxetan-3'-one (I) (540 mg) in ether (20 ml), was added to 2-naphthylmagnesium bromide [from 2-naphthyl bromide (1·7 g) and magnesium (0·2 g)] in ether (15 ml), to give 1-hydroxymethyl-1-(2-naphthoyl)cyclohexane (XIII), m.p. 119—120°, as crystals (335 mg) from ethanol (Found: C, 80·5; H, 7·6. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%), τ 7·5br (s, OH), and 6·06 (s, OCH_2R).

Reactions of the Diol (IIIa).—Acetylation of the diol (0·5 g), under reflux, with acetic anhydride (20 ml) and sodium acetate (1 g) gave 1-acetoxymethyl-1-hydroxy(diphenyl)methylcyclohexane (IIIb), m.p. 115—117° (Found: C, 78·5; H, 7·5. $C_{22}H_{26}O_3$ requires C, 78·1; H, 7·7%), τ 8·05 (s, Ac), 6·53 (s, OH), and 5·50 (s, CH_2OAc).

The diol (0·6 g) in pyridine (10 ml) was added to a mixture of chromium trioxide (0·6 g) and pyridine (10 ml) maintained at 15—20°. After 20 h the solution was diluted with ether, filtered, poured into water, and extracted with ether. The extract was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water. The residue, after removal of the solvent, was purified by p.l.c. on silica gel and gave benzophenone (0·15 g), m.p. 48° (lit.,[13] 49°).

[13] I. Heilbron, A. H Cook, H. M. Bunburry, and D. H. Hey, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965, vol. 1, p. 348.