POLYFLUORO-1,2-EPOXY-ALKANES AND - CYCLOALKANES.
PART II.   REACTIONS OF DECAFLUORO-1,2-EPOXYCYCLOHEXANE

PAUL L. COE, ANDREW W. MOTT and JOHN COLIN TATLOW

Chemistry Department, The University of Birmingham,
P.O. Box 363, Birmingham B15 2TT (Great Britain)

SUMMARY

The epoxy ring of the title compound has been opened by nucleophilic
attack using lithium aluminium hydride, sodium methoxide, methyl lithium,
sodium azide and potassium cyanide. The primary product incorporated the
nucleophile (N) and an alkoxy function, which was fixed by methylation
when N = CN. However, in most cases the alkoxide group decomposed to
carbonyl, and the ketone was isolated when N was OMe. More nucleophile
could be added across this carbonyl group, the resultant substituted
alkoxide being isolated as the tertiary alcohol (N = Me) or the methyl ether
(N = N_3). With lithium aluminium hydride (N = H), a secondary alcohol was
obtained, the fluorine on the ring carbon bearing the alkoxy group being
replaced by H; the pathway probably did not involve a free carbonyl group,
since the resultant alcohol was a pure stereoisomer. This was shown by nmr,
and also since the pure methoxymethyl ether made from it was dehydrofluor-
inated exclusively to 2H-octafluorocyclohexenyl methoxymethyl ether.

INTRODUCTION

Part I of this series [1] described a convenient preparation of a
series of 1,2-epoxy-polyfluorocyclohexanes. The epoxy rings of these were
reactive, but not especially so. 1,2-Epoxydecafluorocyclohexane (1), and
its 4,5-dibromo-(1A) and 4,5-dichloro-octafluoro- (1B) analogues, were
treated with potassium fluoride in acetonitrile at 50° to give alkoxides of
the type K1 (Scheme 1; N = F, M = K). These alkoxides could be isolated
as white solids from these reactions. On being heated to ca 200° they

decomposed to the corresponding cyclohexanones of type 4 (N = F) whilst treatment with methylating agents afforded ethers. 4,5-Dibromo-octafluoro-cyclohexane-1,2-epoxide (1A) was debrominated using zinc dust in propanol, with no apparent attack on the epoxy-ring, though a mixture of 1,2-epoxy octafluorocyclohex-4-ene (1C), and the 4H-4-ene (1D) was obtained. Heating of 1A to ca 400° gave some conversion to 1C but had no effect on the epoxy ring. There was an interesting selectivity of reaction between the epoxy and alkene functions of 1C and 1D. Free radical chlorination of 1C gave the dichloride 1B, leaving the epoxy ring intact, whilst KF in acetonitrile at 50° gave alkoxides from 1C and 1D, with no detectable attack on the double bonds. This paper describes further reactions of the perfluoro-epoxide (1), involving other nucleophilic reagents.

RESULTS

Reaction of epoxide (1) with lithium aluminium hydride in ether, followed by work-up after treatment with acid in the usual way, afforded a compound (2) (Scheme 2) analysing as $C_6H_3F_9O$. This had three different bands in its ^{1}H nmr spectrum, one of which disappeared on addition of deuterium oxide and one being a complex doublet, τ = 5.01, J = 47. In the ^{19}F nmr spectrum, there were 4 complex ABs or doublets corresponding to $\geq CF_2$ groups, and an isolated fluorine as a complex doublet at δ = 162.7, J = 47. Thus, 2 was a 1H,2H-nonafluorocyclohexanol, and the nmr spectra suggested that it was a pure stereoisomer.

An analogous reaction of 1 with sodium methoxide in methanol gave a product shown to be a ketone hydrate, 2-methoxynonafluorocyclohexane-1,1-diol (3), which was dehydrated by phosphorus pentoxide to 2-methoxynona-fluorocyclohexanone (4). The product from the reaction of epoxide (1) with methyl lithium in ether had two methyl substituents and was 1,2-dimethyl-nonafluorocyclohexanol (5), nmr indicating the presence of both stereo-isomers.

Epoxide (1) also reacted with sodium azide in acetonitrile in the presence of a small proportion of a crown ether. In this case, the primary product was difficult to isolate, and so dimethyl sulphate was added to the reaction mixture, to methylate the hydroxy group. The product was 1,2-di-azidononafluorocyclohexyl methyl ether (6), again both stereoisomers probably being present.

1   i →

K1

ii →

4 N = OCH₃

iii ↙

7 + 8

i ↓

i ↙

6 ← iii

K2

iv →

$\left[\begin{array}{c} 2 \\ 5 \end{array}\right.$
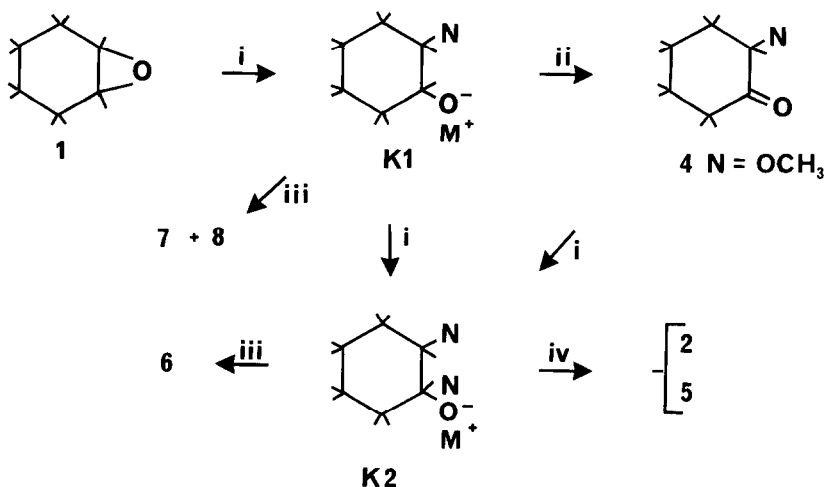
Reagents   i $\overset{-}{N}\overset{+}{M}$ ii   Loss of $\overset{-}{F}\overset{+}{M}$ iii   MeX   iv $\overset{+}{H}$ – H_2O

All unmarked bonds are to fluorine

Scheme 1

2 : R = -H
9 : R = -CH₂OCH₃

3

4

5

6

7

8 A

8 B

10

11 : R = -H
12 : R =
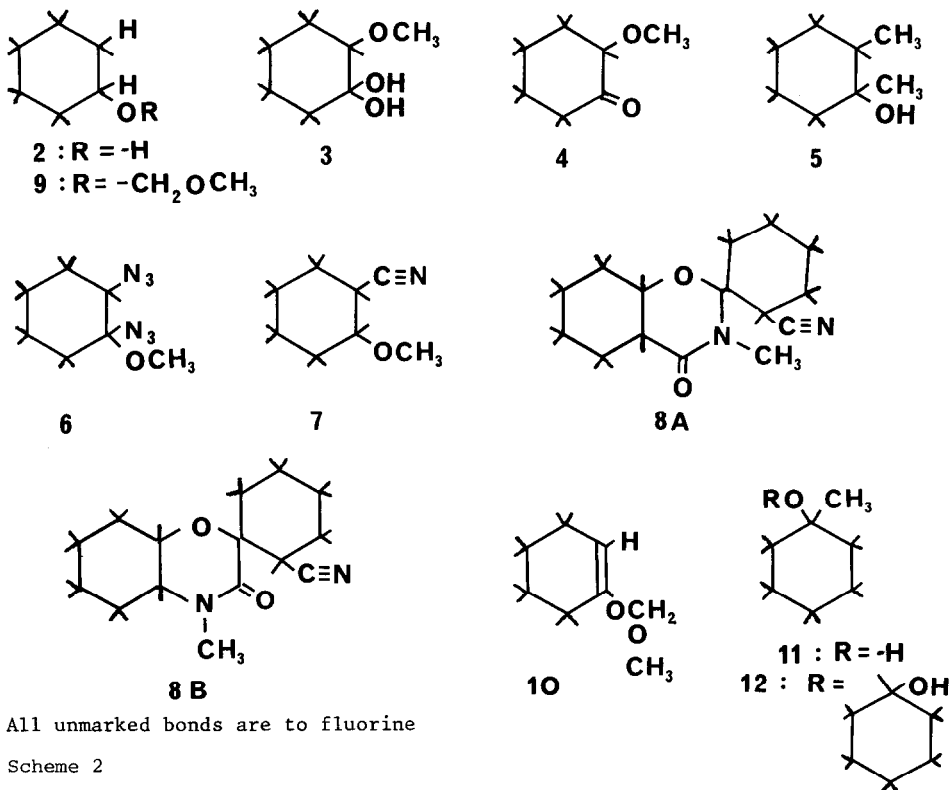
All unmarked bonds are to fluorine

Scheme 2

Potassium cyanide in acetonitrile reacted with epoxide (1) to give two products. As before, because of isolation difficulties, the reaction mixture was treated with dimethyl sulphate to methylate hydroxy groups and permit separation by glc. The more volatile product, present in slightly higher proportion, showed an ir band corresponding to a cyano group and was 1 cyano-2-methoxydecafluorocyclohexane (7), and analysis of the nmr spectrum indicated one stereoisomer only. The other product (8) had elemental analysis, ir, and nmr spectra indicating the presence of two fluorocyclohexane rings, and cyano, N-Me, and C=O functions. It was probably formed by attack of an alkoxide intermediate of type K1 (N=CN) on the ketone (4, N=CN) formed from it by loss of fluoride ion, though an alternative pathway would be attack of an intermediate of type K2 (N=CN) on the epoxide (1). Subsequent stabilization of intermediates to give 8 would probably involve stages analogous to those postulated [2] for the reaction of hexafluoroacetone with cyanide ion. The most likely formulae for 8 are 8A and 8B, but it is not possible on present evidence to distinguish between them or perhaps even other isomeric structures.

The epoxide (1) reacted with cobalt fluoride at 250° but not very readily and not in a useful way, the product being perfluoro-n-pentane. This presumably arises via degradation of an alkoxide K1 involving formation of carbonyl fluoride, or by direct loss of CO from decafluorocyclohexanone [cf. 3].

The cyclohexanol (2) was converted into its methoxymethyl ether (9) by formation of a sodio-derivative with sodium hydride in dry benzene, followed by reaction with chloromethyl methyl ether. Ether 9, like alcohol 2, appeared to be a pure stereoisomer, from its nmr spectra. It was dehydrofluorinated with aqueous potassium hydroxide to give only one product, 2H-octafluorocyclohex-1 ene-1-yl methoxymethyl ether (10). This showed that ether 9 was the 1H,2H/-stereoisomer, which from earlier results [4] would lose HF in only one way to give only one alkene. The 1H/2H-stereoisomer of 9, having two axial hydrogens, and an equatorial F at the > CHF position, would have given two other alkene ethers, the 6H-1-ene-1-yl and the 1H-2-ene-1-yl isomers, each distinguishable from 10.

Decafluorocyclohexanone is a rearrangement product of the epoxide (1) and a check was made that the reactions were not proceeding via its intermediacy. It was treated with methyl lithium and two products were obtained neither of which was compound 5. One was the expected carbonyl addition

product, the tertiary alcohol 1-methyldecafluorocyclohexan-1-ol (11), and the second (12) was the hemi-ketal of (11) with decafluorocyclohexanone.

DISCUSSION

The pathway that seems to operate in the nucleophilic ring-opening of these epoxides is summarised in Scheme 1. There is no evidence to suggest that the stereochemistry of opening of oxirane rings in fluorocyclohexane-1,2-epoxides differs from normal. Therefore, their nucleophilic reactions should give diaxial products, i.e. the attacking nucleophile and the ultimate alkoxide both occupying axial positions, at first. The cyano-ether (7) was a pure steroisomer, as was the cyclohexanol (2). This expected stereochemistry persisted in product 2, though it had two groups inserted by the attacking nucleophile, the fluorine on the alkoxy position having been replaced by H, to give a secondary alcohol. Clearly, this did not occur via random reduction of a carbonyl group. Either a stereo-selective reduction took place, or the fluorine on the alkoxide-bearing carbon (K1, N=H) was replaced by attack from the same side as the H. It could for example have had H substituted for it by the same alumino-hydride moiety as had originally attacked the epoxy ring carbon, and was still held close to the face of the cyclohexane ring in some way. The methoxy-product (4) had only one methoxy group and was a carbonyl compound, whilst the products of reactions involving methyl lithium and azide ion each had two groups inserted by the nucleophile and each consisted of two stereo-isomers. This would be expected from random addition of further nucleophile to the analogous carbonyl compounds, to give tertiary alcohols.

EXPERIMENTAL

General conditions and spectroscopy were as in Part I [1]. Nmr results are given in the order chemical shift, relative intensity of peak, coupling; ir frequencies are cm^{-1}.

Reactions of Decafluoro-1,2-epoxycyclohexane (1)

(a) <u>With lithium aluminium hydride</u>. A solution of epoxide (1) (5.0 g) in dry diethyl ether (10 cm^3) was added during 1 h to a stirred suspension of lithium aluminium hydride (0.5 g) in ether (30 cm^3). The mixture was stirred for 4 h at 15°, and diethyl ether saturated with water added

carefully, followed by sulphuric acid (50 ml; 2 $\underline{M}$). The ether layer and two further ether extracts (10 cm^3 each) of the aqueous layer were dried (Mg SO_4) and the ether evaporated through a fractionating column 15 cm long packed with Dixon gauzes to give an orange solid residue. Sublimation at 35°/20 mm gave 1H,2H/-nonafluorocyclohexanol (2) (2.4 g) m.p. 77-79° (Found: C, 27.7; H, 1.1; F, 65.3. $C_6H_3F_9O$ requires C, 27.5; H, 1.1; F, 65.3%) : ν (OH) 3100-3500 b : nmr (100 MHz), τ 3.06, 1, s (collapses on shaking with D_2O); 4.30, 1, bm; 5.01, 1, cd, J=47 : δ F 125.6, 2, cAB, J=290, $\Delta\nu$ = 908; 127.7, 2, cd, J=80; 132.6, 2, cAB, J=280, $\Delta\nu$ = 1220; 134.8, 2, cAB, J=290, $\Delta\nu$ = 1330, 162.7, 1, cd, J=47: analysis of the nmr spectra showed that only 1 compound was present.

(b) <u>With sodium methoxide</u>. A solution of (1) (5.0 g) in dry ether (5 cm^3) was added to a stirred solution of sodium methoxide [made by dissolving sodium metal (2.0 g) in dry methanol (30 cm^3)]. After being stirred for 12 h at 15°, most of the solvents were evaporated, and the residue was acidified with sulphuric acid (50 ml; 2 $\underline{M}$). After extraction with ether (2 x 50 cm^3), the extracts were dried (Mg SO_4), and evaporated as above to leave an oily residue. Transference in vacuo gave a colourless oil (3.2 g) which solidified on being kept. Sublimation (30°/20 mm) gave 2-methoxy-nonafluorocyclohexane-1,1-diol (3) m.p. 37° (Found: C, 27.1; H, 1.8, F, 55.0. $C_7H_5F_9O_3$ requires C, 27.3; H, 1.6; F, 55.5%): ν (OH) 3100-3540 b: nmr (in CD_3COCD_3), τ 3.79, 3, cs: 4.5-6.4, 2, b : δ F 118.5-141.1, complex series of peaks.

The crude solid residue above (5.0 g) was mixed with phosphoric oxide (5.0 g), the volatile part transferred in vacuo onto further phosphoric oxide (1.0 g) and then distilled off to give 2-methoxynonafluorocyclohex-anone (4) (3.9 g), b.p. 109° (Found: C, 28.3; H, 1.0; F, 59.2. $C_7H_3F_9O_2$ requires C, 29.0; H, 1.0; F, 58.9%) : ν (C=O) 1790 : τ 3.63, bs : δ F 125.2, 2, cAB, J=282, $\Delta\nu$ = 949; 132.3, 2, cAB, J=276, $\Delta\nu$ = 950; 132.6, 4, cAB, J=293, $\Delta\nu$ = 681; 144.7, 1, cm.

(c) <u>With methyl lithium</u>. To a stirred solution of (1) (5.0 g) in dry ether (30 cm^3) at 0° in a flask flushed with a stream of dry nitrogen, was added methyl lithium in ether (1.5 $\underline{M}$; 24 cm^3). The solution was allowed to warm to 15° and stirred for a further 12 h. Water (30 cm^3) was then added, cautiously, followed by sulphuric acid (50 cm^3; 2 $\underline{M}$), The organic layer was combined with 2 further ether extracts and dried (Mg SO_4). Evaporation gave

a brown oil (1.7 g) which was purified by glc [Pye 104; silicone gum (SE 30)/Supasorb 60-80 (1:9); 140°; N$_2$ 3ℓ h^{-1}] and the solid product sublimed (40°/20 mm) to give 1,2-dimethylnonafluorocyclohexanol (5) m.p. 62° (Found: C, 32.9; H, 2.7. F, 58.1 C$_8$H$_7$F$_9$O requires C, 33.1; H, 2.4; F, 58.9%) : ν (OH) 3100-3700 b : τ 1.51, 3, bm; 1.67, 3, dcm, Jd=23; 2.43, 1, s (collapses on shaking with D$_2$O) : δF 124.9, 2, cAB, J=288, Δν=1041; 128.0, 2, cAB, J=288, Δν = 911; 128.3, 2, cAB, J=276, Δν = 1274; 131.4, 2, cAB, J=282, Δν = 1033; 170.7, 1, c. Analysis of the nmr spectra indicated the presence of 2 very closely related species.

(d) With sodium azide followed by dimethyl sulphate. Epoxide (1) (5.0 g) was added to a stirred suspension of sodium azide (3.0 g) in dry acetonitrile (30 cm^3) containing 18-crown-6 ether (0.1 g). After being stirred and refluxed for 4 h, dimethyl sulphate (3.0 g) was added and the mixture stirred for 2 h further at 15°. Water (100 cm^3) was added, and the organic layer and a chloroform extract (20 cm^3) of the aqueous phase combined and extracted continuously with water for 16 h. The chloroform layer was dried (Mg SO$_4$) and evaporated in vacuo. The residue was distilled at 0.5 mm pressure to give 1,2-diazido-nonafluorocyclohexyl methyl ether (6) (2.9 g), b.p. 48°/0.5 mm (Found: C, 23.8; H, 0.8; F, 47.7; N, 23.0. C$_7$H$_3$F$_9$N$_6$O requires C, 23.5; H, 0.8; F, 47.7; N, 23.5%) : ν (CH) 2960, (CN$_3$) 2130 : τ 3.76, cs : δ F 120.7-134.1, 8, complex series of peaks; 140.7, 1, cm : 2 stereoisomers were present.

(e) With potassium cyanide followed by dimethyl sulphate. Epoxide (1) (5.0 g) was added to a stirred suspension of dry potassium cyanide (1.5 g) in dry acetonitrile (30 cm^3), and the mixture was stirred at 80° for 1 h. Dimethyl sulphate (5.0 g) was added and stirring continued for 4 h further. Water (100 cm^3) was then added, the lower layer separated off, washed with water and dried (Mg SO$_4$). The residual brown oil was transferred in vacuo, and the distillate was separated by glc (tube as in (c); 130°; N$_2$ 1.3 ℓh^{-1}) to give (i) unreacted epoxide (1) (0.3 g); (ii) 1-cyano-2-methoxydecafluorocyclohexane (7) (0.8 g), b.p. 90° (Found: C, 29.7; H, 0.7; N, 5.3. C$_8$H$_3$F$_{10}$NO requires C, 30.1; H, 0.9; N, 4.4%) : ν (C≡N) 2255 : τ 3.88, bs : δF 120.6, 4, cAB, J=288, Δν = 970; 122.7, 1, cm; 130.3, 4, cd J=288; 137.0, 1, cm : the nmr spectra could be analysed as for 1 compound only.

The still residue from the vacuum distillation was distilled to give (iii) the heterocycle (8) (0.7 g), b.p. 223° (Found: C, 29.7; H, 0.5; N, 4.4. $C_{15}H_3F_{19}N_2O_2$ requires C, 29.8; H, 0.5; N, 4.6%) : ν (C=O) 1735; (C≡N) 2260 : τ 3.92, bs : δ F 111.2-142.1, complex series of peaks.

(f) With cobalt (III) fluoride. The epoxide (1) (5.0 g) was passed over cobaltic fluoride in a standard small stirred reactor [5] at 250°. The product (4.2 g) trapped at -193° was shown by analytical glc to consist of starting material (74%) and a product (26%). Five further passes through the reactor increased the proportion of product to 95%, and ir and nmr spectroscopy showed it to be perfluoro-n-pentane [6]. At reactor temperatures between 150 and 330° the same product was given.

1H,2H/-Nonafluorocyclohex-1-yl methoxymethyl ether (9)

(a) Preparation. Sodium hydride (50% suspension in oil; 0.7 g) was added to stirred solution of 1H,2H-nonafluorocyclohexanol (2) (2.3 g) in dry benzene(30) cm^3). The mixture was stirred for 30 min. at 15°. Chloromethyl methyl ether (3 g) was added slowly. A vigorous exothermic reaction was observed and after the addition was complete, the mixture was stirred for 1 h. Water (50 cm^3) was added, the benzene layer and an ether extract (30 cm^3) of the aqueous layer were combined, dried (Mg SO$_4$) and the solvents removed by distillation (15 cm Dixon gauze column). The residue was distilled in vacuo to yield 1H,2H/-nonafluorocyclohex-1-yl methoxymethyl ether (9) (1.6 g), m.p. 31° (Found: C, 31.2; H, 2.1; F, 55.4. $C_8H_7F_9O_2$ requires C, 31.4; H, 2.3; F, 55.9%) : ν (C-H) 2900-2950 : τ 3.47, 3, s; 4.82, 2, s; 4.28, 1, bm; 5.10, 1, dbm, Jd=42 : δ F 125.0, 2, cd, J=71; 127.3, 2, cAB, J=296, Δν = 577; 131.3, 2, cAB, J=301, Δν = 673; 134.2, 2, cAB, J=282, Δν = 580; 219.5, 1, bm; the nmr spectra could be analysed as arising from 1 stereoisomer only.

(b) Dehydrofluorination. Crude 1H,2H/-nonafluorocyclohex-1-yl methoxymethyl ether (9) (7 g), potassium hydroxide (100 cm^3; 6 M) and silicone antifoaming agent (0.5 cm^3) were refluxed and vibro-stirred [7] for 2 h. The brown mixture was allowed to cool, water (500 cm^3) added, the lower layer was separated, and then dried (Mg SO$_4$). Distillation gave 2H-octafluorocyclohex-1-ene-1-yl methoxymethyl ether (10) (4.1 g), b.p. 159° (Found: C, 33.9; H, 2.1; F, 53.2. $C_8H_6F_8O_2$ requires C, 33.6; H, 2.1; F.53.1%) : ν (C=C) 1670 : τ 3.43, 3, s; 5.09, 2, s; 5.60, 1, bm : δ F 103.1, 1, cm; 119.2, 1, cm; 134.9, 2, cm.

Reaction of Decafluorocyclohexanone with Methyl Lithium.   To a stirred
solution of the ketone (5.5 g) in dry diethyl ether (25 cm^3) at 0°, in a
flask flushed with dry nitrogen, methyl lithium in ether (1 $\underline{M}$; 20 cm^3)
was added during 15 min. After being stirred at 0° for 4 h, the mixture
was treated with sulphuric acid (50 cm^3; 2 $\underline{M}$), the ether layer and an
ether extract of the aqueous phase were dried (Mg SO$_4$) and the ether
distilled off through a 15 cm column packed with Dixon gauzes. Preparative
glc [Pye 104; polyethylene glycol adipate/Chromosorb P30 - 60 (1:6);
170°; N$_2$ 3ℓ h^{-1}] gave (i) ether: (ii) 1 methyldecafluorocyclohexan-1-ol
(11) (2.6 g), m.p. 68° (Found: C, 28.3; H, 1.1; F, 64.2. C$_7$H$_4$F$_{10}$O
requires C, 28.6; H, 1.4; F, 64.6%); ν (OH) 3400 b; τ 1.62, 3, bs; 2.90,
1, bs; δ F 117.4-137.4 complex series of peaks: (iii) the hemi-ketal of
1-methyldecafluorocyclohexanol and decafluorocyclohexanone (12) (0.8 g),
b.p. 223° (Found: C, 26.6; H, 0.6; F, 66.2. C$_{13}$H$_4$F$_{20}$O$_2$ requires C, 27.3;
H, 0.7; F, 66.2. C$_{13}$H$_4$F$_{20}$O$_2$ requires C, 27.3; H, 0.7; F, 66.4%); ν (OH)
3500, b, (CH) 2920; τ 1.56, 3, bs; 2.78, 1, bs: δ F 116.1-143.6, complex
series of peaks.

All compounds made with names underlined are new.

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