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THE AMINOLYSIS AND ESTERIFICATION OF UNSYMMETRICAL EPOXIDES

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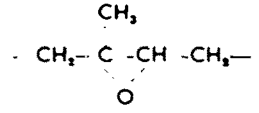
Abstract—The reactions of 1,2-epoxypropane (I) and 2-methyl-2,3-epoxypentane (II) with various primary and secondary amines and with hexahydrophthalic anhydride in the presence of hydroxylic catalysts have been studied. The direction of ring opening of the epoxides on reaction with the amines is unaltered by the presence of phenol as catalyst, and involves attack at the least substituted carbon atom of the epoxide ring. The structures of the piperidino adducts (*viz.* IV and V) derived from the phenol-catalysed reaction of piperidine with I and II, respectively, were proved by unambiguous syntheses of IV and V by the interaction of the corresponding chlorhydrin with piperidine. With hexahydrophthalic anhydride in the presence of water, I gave a low molecular weight polymeric ester whereas II afforded mainly a diadduct derived from the reaction of two molecules of II with one molecule of the anhydride. Reaction mechanisms are discussed briefly.

Little work has been reported on the reaction of highly alkyl-substituted epoxides, particularly those derived from trialkylethylenes, with amines and carboxylic acid anhydrides in the absence of hydroxylic solvents. Results to be reported elsewhere[1] describe the partial or complete epoxidation of natural rubber to give modified rubbers which contain the epoxide structure III, and which can be subsequently crosslinked with bifunctional reagents such as primary diamines or carboxylic acid anhydrides. The present paper is concerned with the reactions of 1,2-epoxypropane (I) and 2-methyl-2,3-epoxypentane (II)—the latter being a model for natural rubber epoxide—with amines and a carboxylic acid anhydride.



$$-CH_2-\overset{CH_3}{C}-CH-CH_2- \quad (\text{C}-\text{O}-\text{CH epoxide bridge})$$

III

Aminolysis of epoxides. The data in Table 1 indicate the comparative reactivities of primary and secondary alkylamines with 2-methyl-2,3-epoxypentane (II) in the presence or absence of phenol as catalyst and in the absence of hydroxylic solvents. Interaction of II occurs with primary alkylamines but not with the more sterically-hindered diethylamine. n-Butylamine reacts only in the presence of phenol, this effect being in keeping with the known catalysis by phenols of the aminolysis of epoxides.[2] Primary alkyldiamines are more reactive than n-butylamine and yield both mono- and diadducts by reaction with either one or two molecules of the epoxide; the relative proportions of the mono- and di-adducts depend on the relative proportions of the reactants and catalyst (phenol). Reaction of piperidine with II under the conditions

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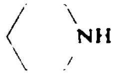
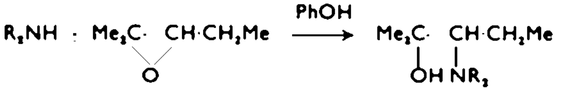
[1] T. Colclough, to be published.

[2] L. Shechter, J. Wynstra and R. P. Kurkjy, *Industr. Engng. Chem.* **48**, 94 (1956).

Table 1. Reaction of 2-methyl-2:3-epoxypentane (II) with amines at 140° (*in vacuo*)

Amine	Mole ratio Epoxide:amine:phenol	Reaction time (hr)	Yield of products Monoadduct (mole % initial amine)	Diadduct
Bu^nNH_2	1:1:0	40	0	.
Bu^nNH_2	1:1:0·1	40	70	.
$NH_2(CH_2)_2NH_2$	1:1:0	14	25	~5
$NH_2(CH_2)_2NH_2$	1:1:0·1	14	50	~45
$NH_2(CH_2)_2NH_2$	2:1:0·2	14	~20	80
$NH_2(CH_2)_6NH_2$	1:1:0·1	16	40	10
Et_2NH	1:1:0	5	0	
Et_2NH	1:1:0·1	17	0	...
	1:1:1·0	40	100	.

specified in Table 1 gave a quantitative yield of 2-methyl-3-piperidinopentan-2-ol (V; Reaction 1), identified and estimated as its hydrochloride. Phenol was recovered in 94 per cent yield.

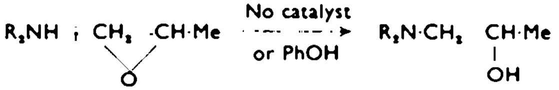


(1)

II V

(where R_2NH piperidine)

The adduct V was synthesized unambiguously by interaction of 2-methyl-3-chloropentan-2-ol with piperidine under conditions leading to direct displacement of the chlorine atom by the piperidino group, i.e. without the intermediary formation of the epoxide.[3] Consistently, the interaction of 1,2-epoxypropane (I) with piperidine either in the absence or presence of phenol yields 1-piperidinopropan-2-ol (IV) as the sole product (Reaction 2), indicating that opening of the epoxide ring in these systems, as in others reported in the literature,[4] occurs by exclusive or predominant attack of the amine at the least substituted carbon atom. Reaction of I to give IV exclusively is also observed when water plus phenol is used to catalyse Reaction 2 and when piperidine is replaced by piperidine hydrochloride. The aminoalcohol IV and the isomeric 2-piperidinopropan-1-ol (VI) were synthesized by reaction of piperidine with the appropriate α-chloroalcohol; under the reaction conditions used (see Experimental) both IV and VI were obtained free from their isomers, thus confirming that the aminoalcohols are



(2)

I IV

(where R_2NH = piperidine)

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[3] L. R. Hawkins and R. A. B. Bannard, *Canad. J. Chem.* 36, 220 (1958).

[4a] R. E. Parker and N. S. Isaacs, *Chem. Rev.* 59, 737 (1959); [b] N. B. Chapman, N. S. Isaacs and R. E. Parker, *J. Chem. Soc.* 1925 (1959); 3497 (1960).

formed by direct displacement of the chlorine atom by the amine and not *via* the epoxide which then subsequently reacts with the amine.

The phenol catalysed reaction of 2-methyl-2,3-epoxypentane (II) with piperidine is much slower than the comparable reaction of the less alkyl-substituted 1,2-epoxypropane (Fig. 1). This feature, together with the orientation of addition of piperidine to II in the presence of phenol (Reaction 1) and the lack of reactivity of II towards more sterically hindered secondary alkylamines (Table 1), suggests that Reaction 1 proceeds, as in the case of uncatalysed epoxide-amine interactions,[4a] by an S_N2 mechanism involving attack by the amine at the least substituted carbon atom of the epoxide ring. It is suggested that the function of the phenol or other hydroxylic material is to transfer a proton to the oxy-anion in the transition state:

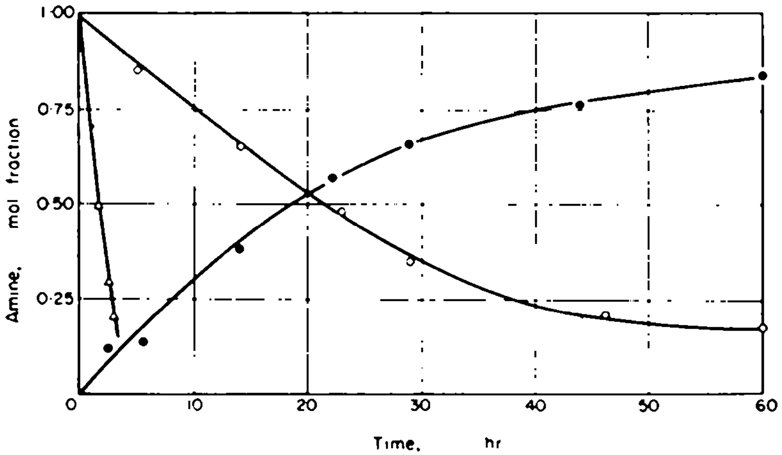
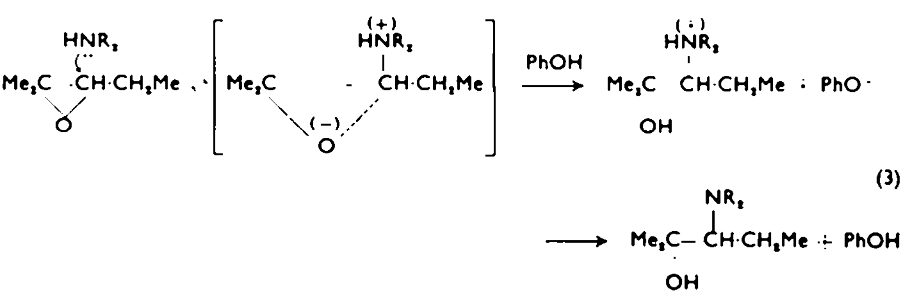


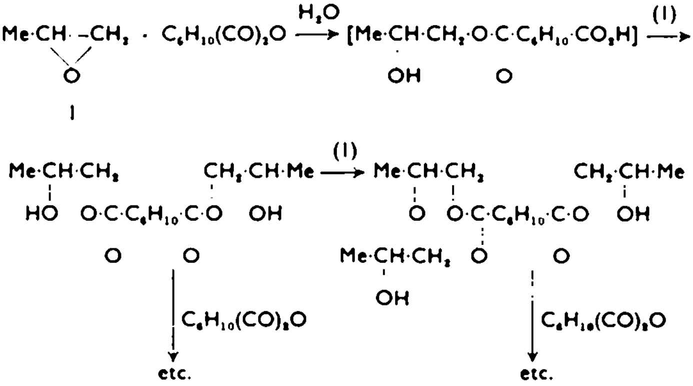
FIG. 1. The phenol-catalysed reactions of equimolar proportions of piperidine with: (a) 1,2-epoxy-propane at 60° (0·03 mole phenol per mole epoxide); and with (b) 2-methyl-2,3-epoxypentane at 140° (0·1 mole phenol per mole epoxide).
System (a) △, unreacted piperidine
System (b) ○, unreacted piperidine
●, 2-methyl-3-piperidinopentan-2-ol.



$$\underset{\diagdown\text{O}\diagup}{\mathrm{Me_2C\text{-}CH\cdot CH_2Me}} + \mathrm{HNR_2} \rightarrow \left[\mathrm{Me_2C\ \text{-}\ \overset{(+)\,HNR_2}{CH}\cdot CH_2Me}\ \ \underset{\mathrm{O^{(-)}}}{}\right] \xrightarrow{\mathrm{PhOH}} \mathrm{\underset{OH}{Me_2C}\ \overset{(+)\,HNR_2}{CH}\cdot CH_2Me : PhO^-} \longrightarrow \mathrm{\underset{OH}{Me_2C}\text{-}\overset{NR_2}{CH}\cdot CH_2Me + PhOH} \qquad (3)$$

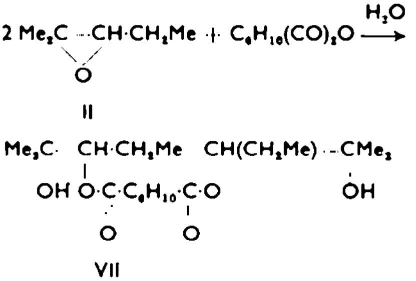
This mechanism implies that weakly acidic phenols should be more effective catalysts than alcohols or water, whereas stronger acids would be less effective than phenols since such acids would be effectively removed by salt formation with the amine. In keeping with this, no reaction occurs between piperidine *p*-toluene sulphonate and II under the conditions used for Reaction 1.

Reactions of epoxides with carboxylic acids and anhydrides. The complex nature of the products resulting from epoxide-carboxylic acid interaction has been described by Hickinbottom and Hogg.[5] The several processes involved *viz*: esterification, etherification, dehydration and isomerization, and their relative proportions are dependent on the structure of the epoxide, the strength of the acid, and experimental conditions. For example, although trichloracetic acid is known to cause isomerization of 2,3-dimethyl-2,3-epoxybutane to a ketone[5] it does not isomerize II with which it reacts exothermically at 25°. Similarly, we have found quite different reactivities displayed by I and II when they are caused to react with hexahydrophthalic anhydride and water at 140°. Thus, the former epoxide gave a 90 per cent yield of a low molecular weight polymer containing both ester and ether groups,[6] suggesting the occurrence of the following sequence of reactions:



(4)

In contrast, the comparable reaction of the trialkylethylene epoxide (II) yielded small amounts of a saturated ketone, formed by isomerization of II, and a dimer of the epoxide together with the major product which analysed for the dihydroxyester (VII):



VII

(5)

The direction of ring opening of the epoxides as given in Reactions 4 and 5 has not been unequivocally established, although it conforms with the results of Graham *et al.*[7] on the interaction of 1,2-epoxy-2,4,4-trimethylpentane with acetic acid. Indirect evidence for the attack of carboxylate groups at the least substituted carbon atom of unsymmetrical epoxide rings is that II, unlike I, did not form a polymer on reaction with the anhydride and water, this being attributed to the formation of *tertiary* hydroxyl groups as in VII which cannot react further with carboxylic acid or epoxide

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[5] W. J. Hickinbottom and D. R. Hogg, *J. Chem. Soc.* 4200 (1954).
[6] R. F. Fischer, *J. Polymer Sci.* **44**, 155 (1960), and references therein.
[7] A. R. Graham, A. F. Millidge and D. P. Young, *J. Chem. Soc.* 2180 (1954).

functions. Consistent with this, the *tertiary* alcohol, 2-methylpentan-2-ol does not undergo esterification on reaction with hexahydrophthalic anhydride or succinic acid at 140°, but affords a mixture of Δ^1- and Δ^2-2-methylpentenes.

EXPERIMENTAL

Materials. 1,2-Epoxypropane, b.p. 37°/756 mm, was 100 % pure when analysed by the method of Jungnickel *et al.*[8] using pyridine hydrochloride in chloroform as reagent. 2-*Methyl*-2,3-*epoxypentane*, b.p. 97·2 97·8°/768 mm, n_D^{20} 1·3954 (Found: C, 71·8; H, 12·1; O, 16·4. $C_6H_{12}O$ requires: C, 71·9; H, 12·1; O, 16·0%) was obtained in 80% yield from the interaction of 2-methylpent-2-ene and perbenzoic acid in methylene dichloride at 0 5°, followed by fractionation of the crude epoxide through a 40-plate column, and was found by infra-red analysis to be free from phenyl, hydroxyl and carbonyl groups. 1-Chloropropan-2-ol, b.p. 76·4 77·4°/111 mm, n_D^{20} 1·4401 (Found: C, 37·7; H, 7·3; Cl, 38·3. Calc. for C_3H_7OCl: C, 38·1; H, 7·4; Cl, 37·6%) was prepared by the lithium aluminium hydride reduction of monochloroacetone[9] and 2-chloropropan-1-ol, b.p. 69·2–69·8°/70 mm, n_D^{20} 1·4394 (Found: C, 37·9; H, 7·7; Cl, 37·3%) was prepared by the comparable reduction of α-chloropropionyl chloride;[10] the infra-red spectra of the two chloroalcohols showed them to be free from carbonyl groups. 2-*Methyl*-3-*chloropentan*-2-ol, b.p. 92 94°/84 mm, n_D^{20} 1·4445 (Found: C, 52·6; H, 9·6; Cl, 26·6. $C_6H_{13}OCl$ requires: C, 52·8; H, 9·6; Cl, 26·0%) was prepared from the reaction of 2-methylpent-2-ene with hypochlorous acid by the method of Wilson and Lucas[11]. Amines were dried and fractionated before use. Piperidine hydrochloride, m.p. 242° (Lit, 242°), was purified by recrystallization from ethanol and drying at 70°/0·1 mm; other amine hydrochlorides were recrystallized from methanol–ether mixtures. Hexahydrophthalic anhydride had b.p. 146°/15 mm, m.p. 36–37° (Found: C, 62·1; H, 6·5. Calc. for $C_8H_{10}O_3$: C, 62·4; H, 6·5%).

Preparation of reference compounds. 1-Piperidinopropan-2-ol, b.p. 105-110°/40 mm, was obtained in 86% yield from the interaction of piperidine (2 moles) and 1-chloropropan-2-ol (1 mole) for 16 hr at 140° *in vacuo*; it gave a hydrochloride, m.p. 159° (Found: N, 7·7; Cl, 19·6. Calc. for $C_8H_{18}NOCl$: N, 7·8; Cl, 19·7%). The comparable reaction of piperidine with 2-chloropropan-1-ol gave 2-piperidinopropan-1-ol (40%), b.p. 118°/80 mm, n_D^{20} 1·4680 (Found: C, 66·8; H, 12·0; N, 9·5. Calc. for $C_8H_{17}NO$: C, 67·1; H, 12·0; N, 9·8%), which gave a hydrochloride having m.p. 117 119° (mixed m.p. with 1-piperidinopropan-2-ol hydrochloride, 116 124°) (Found: C, 53·1; H, 10·1; N, 8·0. Calc. for $C_8H_{18}NOCl$: C, 53·5; H, 10·1; N, 7·8%). There were slight differences between the infra-red spectra of the two isomeric hydrochlorides, but it was not possible to distinguish between the two types of hydroxyl groups present.

2-Methyl-3-piperidinopentan-2-ol (94%) was obtained from the reaction of 2-methyl-3-chloropentan-2-ol (1 mole) with piperidine (2 moles) for 112 hr at 140° *in vacuo*; it was isolated as the *hydrochloride*, m.p. 152°. (Found: C, 59·2; H, 10·8; N, 6·7; Cl, 16·3. $C_{11}H_{24}NOCl$ requires: C, 59·6; H, 10·9; N, 6·3; Cl, 16·0%).

Reaction of epoxides with amines

General procedure. All reactions were conducted in sealed tubes *in vacuo*. Reaction products were analysed for secondary amino groups by use of the dithiocarbamate method[12] and for tertiary amino groups by the potentiometric titration method.[13] The Table 1 records the products resulting from the reaction of 2-methyl-2,3-epoxypentane with various primary and secondary amines at 140° in the presence or absence of phenol as catalyst.

Reaction of 1,2-*epoxypropane with piperidine*

Interaction of equimolar quantities of the two reactants for 16 hr at 140° gave 1-piperidinopropan-2-ol (100%), identified as its hydrochloride, which had m.p. and mixed m.p. with authentic compound,

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[8] J. L. Jungnickel, E. D. Peters, A. Polgár and F. T. Weiss, *Organic Analysis* (Edited by J. Mitchell) Vol. 1, p. 127. Interscience, New York (1953).

[9] J. D. Edwards, W. Gerrard and M. F. Lappert, *J. Chem. Soc.* 348 (1957).

[10] W. Fickett, H. K. Garner and H. J. Lucas, *J. Amer. Chem. Soc.* **73**, 5063 (1951).

[11] C. E. Wilson and H. J. Lucas, *J. Amer. Chem. Soc.* **58**, 2396 (1936).

[12] F. E. Critchfield and J. B. Johnson, *Analyt. Chem.* **28**, 430 (1956).

[13] C. D. Wagner, R. M. Brown and E. D. Peters, *J. Amer. Chem. Soc.* **69**, 2609 (1947).

159° (Found: C, 53·7; H, 10·1; Cl, 19·6. Calc. for $C_8H_{18}NOCl$: C, 53·5; H, 10·1; Cl, 19·7%) and identical infra-red spectrum with that of the authentic compound. The infra-red spectrum differed slightly from that of 2-piperidinopropan-1-ol hydrochloride. Comparable reaction of the epoxide (1 mole) with (i), piperidine hydrochloride (1 mole), (ii) piperidine (1 mole) and phenol (0·1 mole), and (iii) piperidine (1 mole), phenol (0·1 mole) and water (1 mole) all gave the same 1-piperidinopropan-2-ol, (hydrochloride, m.p. and mixed m.p. 159°).

Reaction of 2-methyl 2,3-epoxypentane with piperidine

The reactants (1 mole each) and phenol (1 mole) were heated for 40 hr at 140° and the product was treated with aqueous alkali and then extracted with ether. Treatment of the dried etherial extract with hydrogen chloride gave 2-methyl-3-piperidinopentan-2-ol hydrochloride (100%), m.p. 153° and mixed m.p. with authentic compound 152°, (Found: C, 59·4; H, 10·7; N, 6·3; Cl, 16·3%), having an infra-red spectrum identical with that of the authentic compound. Phenol recovered from the reaction product was identified and estimated as its tribromide, m.p. 91° (94%).

Reaction of epoxides with hexahydrophthalic anhydride and water

(1) 1,2-*Epoxypropane*. Interaction of the epoxide (8·32 g, 2 mole), the anhydride (11·01 g, 1 mole and water (0·43 g, 0·33 mole) for 2·5 hr at 140° *in vacuo* gave a viscous product from which unreacted epoxide (11%), but no anhydride, was recovered on distillation at 140°/0·01 mm. Treatment of the residue with aqueous sodium hydroxide followed by ether extraction gave an ether-soluble fraction (12·2 g, 62 wt % of reactants) which was mainly a low polymer in the form of an ester of a 2:1 epoxide: dicarboxylic acid mixture, (Found: C, 60·1; H, 8·3; O, 30·6; M(ebul, benzene), 1160; Sapn. value, 142. Calc. for $(C_{14}H_{22}O_5)_4 . H_2O$: C, 61·2; H, 8·2; O, 30·6%; M, 1099; Sapn. value, 137). Strong absorption in the infra-red spectrum of the polymer at 1730 cm^{-1} and at 1170 cm^{-1} could be attributed to ester and ether groups, respectively; absorption at 3530 cm^{-1} indicated the presence of —OH groups, but anhydride and 1,2-dicarboxylic acid groups appeared to be absent. Acidification of the aqueous alkali extract yielded a lower molecular weight condensation product of the reactants (5·7 g, 29 wt % of reactants), (Found: C, 58·7; H, 8·0; O, 31·2%; M(ebul, benzene), 390; Sapn. value 216; -CO_2H, 15·8 wt.%).

(2) 2-*Methyl*-2,3-*epoxypentane*. Heating a mixture of the epoxide (7·22 g, 2 mole), the anhydride (5·54 g, 1 mole) and water (0·27 g, 0·4 mole) *in vacuo* for 4 hr at 140° gave a product which on distillation afforded the following fractions: (i) a saturated ketone (1·8 g, 25% of epoxide), b.p. ~ 80°/760 mm, which is probably 2-methylpentan-3-one formed by isomerization of the epoxide; (ii) an unidentified product (1·6 g, 22% of epoxide), b.p. 26–37°/0·07 mm, (Found: C, 70·8; H, 11·9; O, 17·2; M(ebul, benzene), 202,190. Calc. for $C_{12}H_{24}O_2$: C, 71·9; H, 12·1; O, 16·0%; M, 200) which contained ether and hydroxyl groups but no carbonyl groups, and (iii) a viscous residue (8·3 g), undistillable at 140°/0·01 mm, which was probably mainly di-(2-methyl-2-hydroxy-3-pentyl) hexahydrophthalate contaminated with some unreacted anhydride (0·8 g) (Found: C, 64·9; H, 9·0; O, 26·0; Sapn. value 220; M(ebul, benzene), 362,357. Calc. for $C_{20}H_{36}O_6$: C, 64·6; H, 9·7; O, 25·8%; Sapn. value, 186; M, 372). The infra-red spectrum of (iii) was consistent with it being an hydroxy-ester or half-ester.

Reaction of 2-methylpentan-2-ol with hexahydrophthalic anhydride and with succinic acid

(1) After 4 hr heating at 140° a mixture of the alcohol (5·4 g, 2 moles) and anhydride (4·02 g, 1 mole) gave a volatile fraction (4·7 g), b.p. 65–67°/760 mm, identified by infra-red spectrometry as a mixture of 2-methylpent-1-ene (0·7 g) and 2-methylpent-2-ene (3·8 g). The residual crystalline solid was hexahydrophthalic acid (4·1 g), m.p. 182–184° (Found: C, 56·0; H, 7·4. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·1%).

(2) Reaction of the alcohol (7·4 g, 2 moles) with succinic acid (4·28 g, 1 mole) for 4 hrs at 140° yielded a volatile material (7·15 g), b.p. 54–76°/760 mm, comprising water and an olefinic mixture (Found: C, 86·0; H 14·0. Calc. for C_6H_{12}: C, 85·6; H, 14·4%) of 2-methylpent-1-ene (0·7 g) and 2-methylpent-2-ene (4·8 g). Succinic acid (96%), m.p. 185°, was recovered.

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