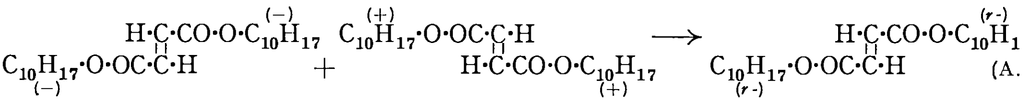
153. *Optically Inactive Bornyl Fumarates.*

By Alex. McKenzie and Edward B. Abbot.

The present research was rendered possible by the fact that (+)borneol, (—)borneol, and *dl*-borneol are readily accessible, and it was initiated to solve the following problem. Would the optically inactive ester resulting from mixing equal amounts of (—) and (+)bornyl fumarates be identical with, or would it differ from, the optically inactive ester which might be expected to be produced by esterifying either (+)bornyl hydrogen fumarate with (—)borneol, or (—)bornyl hydrogen fumarate with (+)borneol?

Experiment showed that two different optically inactive dibornyl fumarates were produced.

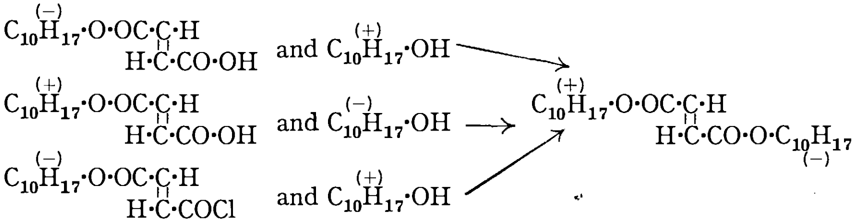
A mixture of equal amounts of (—)bornyl fumarate and (+)bornyl fumarate was dissolved in acetone. The resulting *ester* (A), which crystallised from alcohol in plates, m. p. 116—117°, was not a *dl*-conglomerate, as was shown by the application of Roozeboom's criterion. The fact that its m. p. is about 10° higher than that of the (—) or (+) esters is an argument that we are dealing here with a racemic compound:



$$\begin{matrix} \mathrm{H\cdot C\cdot CO\cdot O\cdot}\overset{(-)}{\mathrm{C_{10}H_{17}}} & \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & \longrightarrow & \mathrm{H\cdot C\cdot CO\cdot O\cdot}\overset{(r\text{-})}{\mathrm{C_{10}H_{17}}} \\ \underset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} \quad + & \mathrm{H\cdot C\cdot CO\cdot O\cdot}\underset{(+)}{\mathrm{C_{10}H_{17}}} & & \underset{(r\text{-})}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} \end{matrix}$$

(A.)

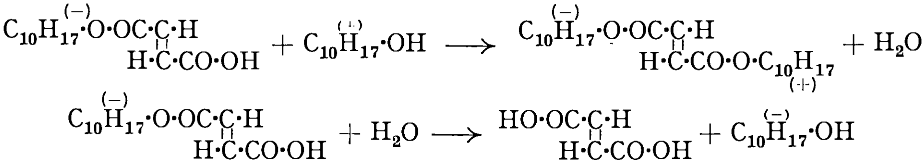
The isomeric dibornyl ester (B) was prepared in three ways as outlined thus:



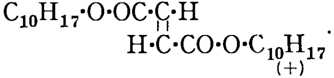
$$\begin{matrix} \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & & \\ \mathrm{H\cdot C\cdot CO\cdot OH} & \text{and } \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot OH} \searrow & \\ \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & & \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} \\ \mathrm{H\cdot C\cdot CO\cdot OH} & \text{and } \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot OH} \longrightarrow & \mathrm{H\cdot C\cdot CO\cdot O\cdot}\underset{(-)}{\mathrm{C_{10}H_{17}}} \\ \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & & \\ \mathrm{H\cdot C\cdot COCl} & \text{and } \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot OH} \nearrow & \end{matrix}$$

(B.)

(1) (—)Bornyl hydrogen fumarate was heated for 24 hours with an excess of (+)borneol at 150—160°. A certain amount of hydrolysis had, however, obviously taken place, thus:



$$\begin{matrix} \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & & & \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & \\ \mathrm{H\cdot C\cdot CO\cdot OH} & + \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot OH} & \longrightarrow & \mathrm{H\cdot C\cdot CO\cdot O\cdot}\underset{(+)}{\mathrm{C_{10}H_{17}}} & + \mathrm{H_2O} \\ \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} & & & \mathrm{HO\cdot OC\cdot C\cdot H} & \\ \mathrm{H\cdot C\cdot CO\cdot OH} & + \mathrm{H_2O} & \longrightarrow & \mathrm{H\cdot C\cdot CO\cdot OH} & + \overset{(-)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot OH} \end{matrix}$$

Whilst the main product was (B), the reaction became somewhat complicated owing to the formation of (—)borneol as depicted above. In one experiment, the recovered borneol gave $[\alpha]_D$ + 20·8° in toluene as compared with the initial value $[\alpha]_D$ + 37·7° in the same solvent; this proves that some (—)borneol had been liberated from the (—) acid ester. Moreover, the crude normal ester after one crystallisation from alcohol gave a dextrorotatory product with $[\alpha]_D$ + 3·6° in chloroform as compared with $[\alpha]_D$ + 59·2° for the optically pure (+)bornyl fumarate,  $\begin{matrix} \overset{(+)}{\mathrm{C_{10}H_{17}}}\mathrm{\cdot O\cdot OC\cdot C\cdot H} \\ \mathrm{H\cdot C\cdot CO\cdot O\cdot}\underset{(+)}{\mathrm{C_{10}H_{17}}} \end{matrix}$. It seems likely that under the experimental conditions adopted the crude normal ester consisted mainly of (B) together with small amounts of (A) and (+)bornyl fumarate. The separation from this mixture of (B), which crystallises in plates, m. p. 131°, is easy, and the yield is 32% of the theoretical.

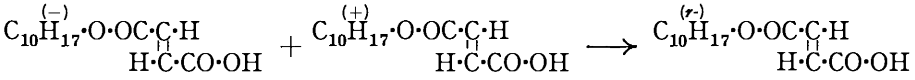
(2) The interaction of (+)bornyl hydrogen fumarate and (—)borneol was conducted

at a lower temperature than in the preceding case, and the proportion of the reactants was different. A better yield (50%) of (B) was obtained than before.

(3) (—)Bornyl hydrogen fumarate was converted into its *chloride*, which gave (B) with (+)borneol in the presence of pyridine. The yield was 80% of the theoretical.

We suggest for (B) the nomenclature (—)*bornyl* (+)*bornyl fumarate.* In a sense this interesting ester is internally compensated, but, of course, it differs from the usual type with which this designation is associated. We are not aware of any other example of a compound of this kind.

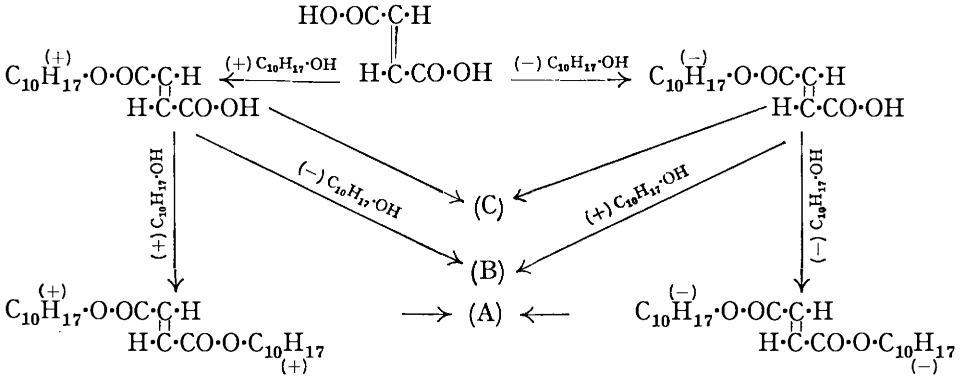
r-*Bornyl hydrogen fumarate* (C) was prepared from a mixture of equal amounts of (—)bornyl hydrogen fumarate and (+)bornyl hydrogen fumarate:



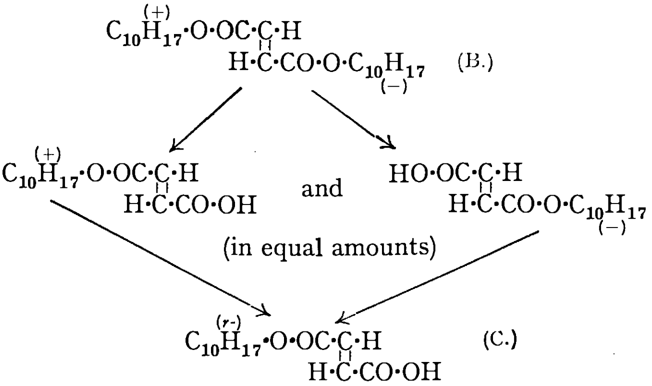
$$\begin{array}{l}\overset{(-)}{C_{10}H_{17}}\cdot O\cdot OC\cdot C\cdot H\\ \qquad\qquad\quad\,\| \\ \qquad\qquad H\cdot C\cdot CO\cdot OH\end{array} + \begin{array}{l}\overset{(+)}{C_{10}H_{17}}\cdot O\cdot OC\cdot C\cdot H\\ \qquad\qquad\quad\,\| \\ \qquad\qquad H\cdot C\cdot CO\cdot OH\end{array} \longrightarrow \begin{array}{l}\overset{(r\text{-})}{C_{10}H_{17}}\cdot O\cdot OC\cdot C\cdot H\\ \qquad\qquad\quad\,\| \\ \qquad\qquad H\cdot C\cdot CO\cdot OH\end{array} \quad (C.)$$

It is dimorphous, the one form, m. p. 118—119°, being readily convertible into the more stable form, m. p. 125—126°.

The esterification of fumaric acid with dl-*borneol* was also investigated. This reaction gave (C) together with a mixture of (A) and (B), from which the latter was readily separated.



(B) was saponified with half the calculated amount of aqueous-alcoholic sodium hydroxide, and *r*-bornyl hydrogen fumarate was isolated:



This work is being extended to other dicarboxylic acids, more particularly with reference to compounds of the type represented by (—)bornyl (+)bornyl fumarate.

EXPERIMENTAL.

The (—)borneol used was obtained from Schimmel and Co., who prepared it from *Blumea balsamifera*. It was optically pure, and gave in toluene $[\alpha]_D^{17°}$ — 38·1° for c = 8·0005 (McKenzie and Mitchell, *Biochem. Z.*, 1929, **208**, 471). This value agrees with the following in toluene: $[\alpha]_D - 37{\cdot}87°$ (Haller, *Compt. rend.*, 1891, **112**, 143); $[\alpha]_D - 37{\cdot}61°$ (Pickard and Littlebury, J., 1907, **91**, 1974); $[\alpha]_D^{14{\cdot}5°} - 37{\cdot}50°$, $[\alpha]_D^{19°} - 37{\cdot}65°$ (Ross and Somerville, J., 1926, 2770).

The dextrorotatory product resulting from the reduction of (+)camphor is far from being homogeneous, consisting as it does of mixed crystals of (+)borneol and (—)*iso*borneol inseparable by crystallisation. One of us was indebted in 1906 to Dr. R. H. Pickard for the suggestion which made the separation of (+)borneol from this mixture possible, but unfortunately several investigators both before and after that date have used the mixed crystals on the erroneous assumption that they were dealing with optically pure (+)borneol.

Part of the (+)borneol used in the present research was prepared by Dr. J. D. M. Ross (cf. McKenzie and Mitchell, *loc. cit.*), but the bulk was obtained as follows (cf. McKenzie and Wren, J., 1907, **91**, 1215; Pickard and Littlebury, *loc. cit.*). Zinc chloride (63 g.) was added to a solution of the mixed crystals (125 g.) in warm benzene (130 c.c.), and the mixture boiled for 3 hours. The solution was divided into three portions, each of which was washed twice with half its volume of very dilute hydrochloric acid, benzene being added in sufficient quantity to prevent the solid borneol from separating. The combined benzene solutions were dried with sodium sulphate, and the benzene removed. When the residual solid was crystallised from light petroleum (b. p. 40—60°), glistening hexagonal leaflets (43 g.) separated. In toluene for $c = 8{\cdot}0356$: $[\alpha]_D^{21°} + 37{\cdot}7°$, $[\alpha]_{5461}^{20°} + 44{\cdot}4°$. Pickard and Littlebury quote for the same solvent $[\alpha]_D + 37{\cdot}7°$; McKenzie and Mitchell $[\alpha]_D^{15°} + 37{\cdot}5°$; Ross and Somerville $[\alpha]_D^{16°} + 37{\cdot}1°$. For comparison with the value for λ5461, the rotatory power of Schimmel's (—)borneol was determined in toluene; $[\alpha]_{5461}^{21{\cdot}5°} - 44{\cdot}4°$ ($c = 8{\cdot}0365$).

Sometimes, however, the value for the rotatory power of the (+)borneol prepared in the above manner falls slightly short of that demanded for optical purity, and in such cases the product can be purified by means of the hydrogen phthalic ester and its (—)menthylamine salt.

dl-*Borneol*.—A mixture of (—)borneol (20·284 g.) and (+)borneol (20·284 g.) was dissolved in dry chloroform (150 c.c.). The solution examined in a 2 dcm. tube was optically inactive, a criterion of the optical purity of the borneols used. The chloroform was expelled, and the residue crystallised from light petroleum (b. p. 40—60°).

dl-*Borneol* separates in hexagonal plates and resembles the optical antimerides in appearance. It melts at the same temperature as (—) or (+)borneol, *viz.*, about 206—207°. From a study of melting-point curves, Ross and Somerville (*loc. cit.*) prove that it is not a *dl*-conglomerate, but the type of curve depicted by those authors does not in their view give a definite answer as to whether a racemic compound or not is formed when the antimerides are mixed at the temperature of the melting point. The melting-point curve depicted by Ross and Somerville is practically a straight line, and from this the inference might be drawn that *dl*-borneol consists of mixed crystals, and, if any racemic compound is present, it will be largely dissociated.

Optically Active Bornyl Fumarates.—(—)Bornyl fumarate, (+)bornyl fumarate, (—)bornyl hydrogen fumarate, and (+)bornyl hydrogen fumarate were prepared as described by McKenzie and Wren (*loc. cit.*). The melting points and rotatory powers of these esters were in satisfactory agreement with the values quoted previously.

It has now been found that the rotations vary very considerably by alteration of temperature, *e.g.*, (—)bornyl fumarate in chloroform for $c = 5{\cdot}2972$ gave $[\alpha]_D^{40°} - 55{\cdot}6°$ and $[\alpha]_D^{0°} - 65{\cdot}0°$, whilst (—)bornyl hydrogen fumarate in the same solvent gave $[\alpha]_D^{39°} - 44{\cdot}9°$ and $[\alpha]_D^{1°} - 51{\cdot}0°$ for $c = 5{\cdot}574$.

r-*Bornyl Fumarate* (A).—A mixture of (—)bornyl fumarate (0·9896 g.) with $[\alpha]_D^{19°} - 59{\cdot}5°$ ($c = 5{\cdot}2712$) in chloroform and an equal weight of (+)bornyl fumarate with $[\alpha]_D^{18°} + 59{\cdot}2°$ ($c = 4{\cdot}3992$) in the same solvent was dissolved in acetone (85 c.c.). On gradual removal of the solvent at the ordinary temperature, 1·75 g. of crystals separated.

r-*Bornyl fumarate* separates from ethyl alcohol in stellate transparent plates resembling the (—) and (+) esters; m. p. 116—117° [Found: C, 74·2; H, 9·4; *M* (ebullioscopic), 340; *M* (Rast), 382. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%; *M*, 388]. The melting point is some 10° higher than that of the antimerides.

Approximately 1 g. of the *r*-ester was shaken with ethyl alcohol (30 c.c.) for 2½ hours at 20°. The saturated solution separated from the solid phase was examined in a 4 dcm. tube and found to be optically inactive for λ5461. To this saturated solution, the solid phase together with about 0·25 g. of the (—)normal ester was added, and the mixture was shaken for 3½ hours at 20°. The saturated solution when examined in a 4 dcm. tube gave $\alpha_{5461}^{20°} - 1{\cdot}35°$, and a solution of the solid phase in chloroform gave $\alpha_{5461}^{20°} - 0{\cdot}82°$ in a 2 dcm. tube.

(—)*Bornyl* (+)*Bornyl Fumarate* (B).

(1) *Action of* (—)*Borneol on* (+)*Bornyl Hydrogen Fumarate.*—An intimate mixture of 9·8 g. of (+)bornyl hydrogen fumarate (1 mol.) and 12 g. of (—)borneol (2 mols.) was heated in an oil-bath at 130—140° for 24 hours, precautions being taken to prevent sublimed borneol from accumulating unduly in the neck of the flask. The product solidified on cooling, and was distilled in steam for several hours to remove free borneol. The residue was extracted with ether and the extract was washed with potassium bicarbonate solution and then with water and dried with sodium sulphate. After removal of the ether the solid residue crystallised from ethyl alcohol in colourless rhombic plates (10·9 g.). But the melting point, 125—129°, and the rotatory power, $[\alpha]_{5461}^{20^\circ}$ — 5·7° (c = 8·0045), in chloroform showed that the product was not homogeneous. The pure compound was obtained by crystallising several times from ethyl alcohol–light petroleum (b. p. 60—80°). Yield, 7·6 g. (—)*Bornyl* (+)*bornyl fumarate* separated in stellate clusters of rhombic plates, m. p. 131° (Found : C, 74·3; H, 9·2. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%), readily soluble in cold benzene or chloroform and moderately so in ether, acetone, or light petroleum.

(2) *Action of* (+)*Borneol on* (—)*Bornyl Hydrogen Fumarate.*—The action was conducted at 150—160° with 12·5 g. of (+)borneol (1½ mols.) and 13·6 g. of the (—)acid ester (1 mol.). The crude di-ester (18 g.) after one crystallisation from rectified spirit gave 14 g. of a dextrorotatory product with $[\alpha]_{D}^{21^\circ}$ + 3·6° (c = 8·172) in chloroform. (B) was obtained as before; m. p. 130—131°, alone or mixed with the ester from the preceding preparation. Yield, 6·6 g.

The recovered borneol was a mixture of unequal amounts of the antimerides, since it gave $[\alpha]_{5461}^{21\cdot5^\circ}$ + 24·8° (c = 12·4976) in toluene, the value for (+)borneol being $[\alpha]_{5461}^{20^\circ}$ + 44·4°.

(3) *Action of* (+)*Borneol on* (—)*Bornyl Fumaryl Chloride.*—(—)*Bornyl fumaryl chloride,* prepared by the action of thionyl chloride (8 mols.) on (—)bornyl hydrogen fumarate (1 mol.), was a colourless oil, b. p. 136—137°/4 mm. (Found : Cl, 13·4. $C_{14}H_{19}O_3Cl$ requires Cl, 13·1%). In chloroform : $l = 2$, $c = 5{\cdot}5635$, $\alpha_{D}^{20\cdot5^\circ}$ — 4·54°, $[\alpha]_{D}^{20\cdot5^\circ}$ — 40·8°; $\alpha_{5461}^{20^\circ}$ — 5·41°, $[\alpha]_{5461}^{20^\circ}$ — 48·6°.

A solution of 3 g. of the acid chloride (1 mol.) in 5 c.c. of benzene was added slowly to a solution of 1·75 g. of (+)borneol (1 mol.) and 1·3 g. of pyridine (1·5 mols.) in 25 c.c. of benzene. After boiling for 1 hour, the dark-brown solution containing a granular solid was poured into water, and distilled in steam to remove the borneol. The ethereal solution of the residue was washed with potassium bicarbonate and then with water and dried with sodium sulphate. After removal of the ether, the product was decolorised in alcoholic solution with charcoal, and crystallised from rectified spirit. The crystals had m. p. 130·5—131°, alone or mixed with (B) from the preceding preparation. Yield, 3·4 g.

r-*Bornyl Hydrogen Fumarate* (C).—A mixture of 1·0018 g. of (—)bornyl hydrogen fumarate with $[\alpha]_{5461}^{20^\circ}$ — 56·1° (c = 6·797) in chloroform and 1·0018 g. of (+)bornyl hydrogen fumarate with $[\alpha]_{5461}^{21^\circ}$ + 55·8° (c = 6·7765) in the same solvent was dissolved in chloroform. The solution, which was optically inactive, was evaporated to dryness.

r-*Bornyl hydrogen fumarate* crystallises from light petroleum (b. p. 60—80°) in lustrous leaflets resembling the optically active antimerides [Found : C, 66·5; H, 8·1; *M* (ebullioscopic), 268; *M* (Rast), 250. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%; *M*, 252]. It had m. p. 118—119°, but when the molten mass was cooled and the m. p. taken again, the value rose to 125—126°, the (—) and (+) esters having m. p. 117·5—118·5°. It was then observed that the transformation of the lower-melting into the higher-melting form could also be effected by nucleating the solution of the former in light petroleum with the higher-melting form, which resembles the other in crystalline appearance. In one case the unstable form had changed after preservation for a month in a closed tube, the m. p. now being 125—126° with some preliminary softening. Presumably, this particular specimen had been inoculated with a trace of the higher-melting form, since another specimen preserved its low m. p. on keeping. The behaviour of these two modifications recalls the experience of Wren and Still (J., 1917, **111**, 513) with the two forms of (—)menthyl hydrogen (+)diphenylsuccinate melting at 144—145° and 154—154·5° respectively.

Half Saponification of (—)*Bornyl* (+)*Bornyl Fumarate.*—The ester (8 g.) was half-saponified by the calculated quantity of aqueous-alcoholic sodium hydroxide as described by McKenzie and Wren (*loc. cit.*) for the preparation of (+)bornyl hydrogen fumarate. The crude product was optically inactive in chloroform, and was the metastable form of (C). After two crystallisations from light petroleum (b. p. 60—80°), the stable form separated in lustrous leaflets, m. p. 125—126°, alone or mixed with the authentic specimen. The formation of this stable form was attributed to nucleation from the laboratory dust.

Esterification of Fumaric Acid by dl-*Borneol.*—An intimate mixture of fumaric acid (15 g.)

and of *dl*-borneol (30 g.) was heated at 150—160° for 24 hours, and the product worked up to give the normal esters according to the method outlined for the action of (—)borneol on (+)bornyl hydrogen fumarate. The acid ester was obtained by acidifying the alkaline extract with sulphuric acid and extraction with chloroform. The inactive bornyl hydrogen fumarate so obtained proved to be identical with (C), the two forms of which were again observed. The inactive normal ester product after one crystallisation from rectified spirit melted indefinitely, 105—108° (Found : C, 74·4; H, 9·4. Calc. : C, 74·2; H, 9·3%). After several recrystallisations from ethyl alcohol–light petroleum, (—)bornyl (+)bornyl fumarate (B) was obtained as the more sparingly soluble constituent of the mixture. It melted at 130—131°, alone or mixed with an authentic specimen.

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