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Application of the Favorskiĭ Rearrangement to 2,3-Epoxycyclohexanones[1]

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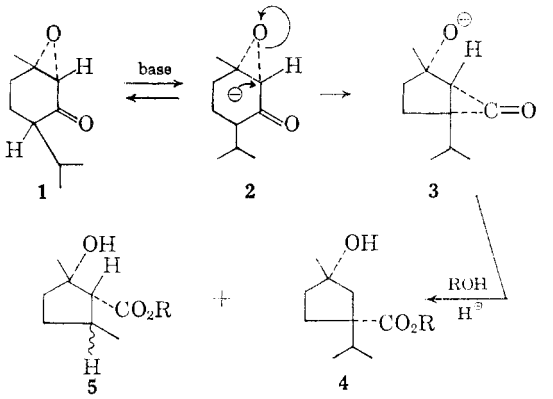
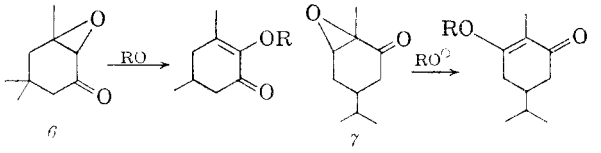
The reactions of isophorone oxide and piperitone oxide with sodium methoxide or potassium hydroxide in methanol or methanol–water mixtures have been studied. Under these conditions each oxide afforded γ-hydroxy acid derivatives corresponding to a non-stereospecific Favorskiĭ rearrangement. Two abnormal displacement products **12** and **13** were obtained from piperitone oxide. The reaction of piperitone oxide with potassium *t*-butoxide in 1,2-dimethoxyethane yielded products corresponding to a stereospecific Favorskiĭ rearrangement.

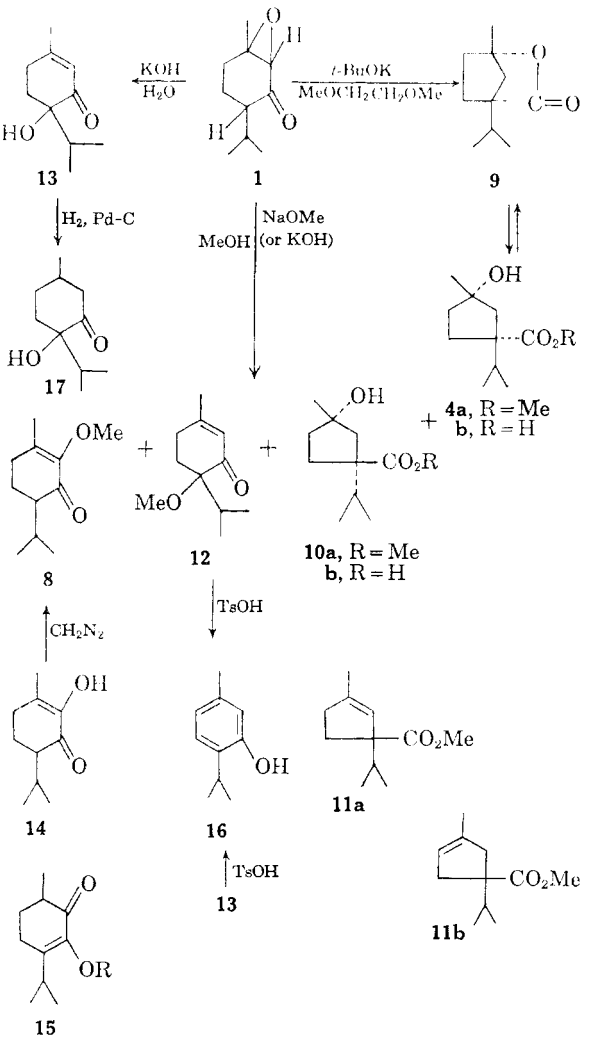
It was apparent that a study of the rearrangement of a 2,3-epoxycyclohexanone such as **1** might provide a unique opportunity to determine the stereochemistry of a Favorskiĭ rearrangement[3] in a cyclic system in which the group being displaced was not bonded to a tertiary carbon atom. For example the direct displacement mechanism **2** leading to a cyclopropanone intermediate **3**[3,4] should produce only the *cis*-hydroxy acid derivatives **4** and **5**.



A previous study[5] included the reactions of piperitone oxide (**1**) isophorone oxide (**6**) and carvone oxide (**7**) with hydroxide and methoxide ions. From the oxides **6** and **7** the reported[5] products are indicated in the accompanying equations. From piperitone oxide (**1**) two major products were described, a crystalline hydroxy acid m.p. 112–113° (now known to be **4b**) as well as the methyl ester and lactone derived from this acid and a liquid (which we believe to have been a mixture) assigned the structure **8**. The structure of the hydroxy acid **4b** was established by further chemical transformations.[5,6]



This paper reports a study of the reactions of piperitone oxide (**1**) and isophorone oxide (**6**) with several bases. For this study a mixture of the epimers of piperitone oxide (**1**) was employed since these epimers, although separable, were readily equilibrated in the presence of bases (triethylamine in acetone) too weak to cause rearrangement. Reaction of piperitone oxide (**1**)



with either methanolic sodium methoxide or methanolic potassium hydroxide under a variety of conditions (Table I) afforded as major products the *cis*-hydroxy acid derivatives **4**, the lactone **9**, the *trans*-hydroxy acid derivatives **10** and the enol ether **8** as well as small amounts of the unsaturated

(1) This work was supported in part by a National Science Foundation Grant, NSF-G5101.

(2) This author is indebted to the Solvay Process Division of Allied Chemical Corporation for a predoctoral fellowship held during the period 1959–1961.

(3) A. S. Kende, *Org. Reactions*, **11**, 261 (1960).

(4) For a discussion and leading references see H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3980 1961).

(5) (a) W. Triebs, *Ber.*, **63**, 2423 (1930); (b) **64**, 2178, 2545 (1931); (c) **65**, 163, 1314 (1932); (d) **66**, 610, 1483 (1933).

(6) (a) R. H. Reitsema and V. J. Varnis, *J. Am. Chem. Soc.*, **78**, 3792 (1956); (b) R. H. Reitsema, *ibid.*, **78**, 5022 (1956).

ester **11** and the methoxy piperitone **12**. The presence of additional water in the reaction mixture favored the formation of the methoxy piperitone **12** and a new component, the hydroxy ketone **13**. When piperitone oxide (**1**) was stirred with aqueous potassium hydroxide, the sole neutral component was the hydroxy ketone **13** formed in 88% yield. Reaction of piperitone oxide (**1**) with potassium *t*-butoxide in 1,2-dimethoxyethane yielded the lactone **9** (70% yield) as the only neutral component. The methyl ester **4a**, prepared by reaction of the *cis*-hydroxy acid **4b** with diazomethane, has an n.m.r. spectrum (60 mc.) fully compatible with the assigned structure **4a**, significant peaks being located at 6.33τ (singlet, $-CO_2CH_3$), 7.72τ (singlet, O–H) and 8.73τ (singlet, $CH_3-\overset{|}{C}-O$), with two doublets (J = 6 c.p.s.) located at 9.27 and 9.17τ and 9.22 and 9.12τ attributable to the two methyl groups of an isopropyl group.[7] The non-equivalence of the two methyl groups is apparently the result of restricted rotation of the isopropyl group in the *cis* isomer **4a**. Assignment of the *cis* stereochemistry to the hydroxy acid **4b** followed the ready conversion of the acid **4b** to the lactone **9** in boiling benzene; hydrolysis of the lactone **9** with dilute, aqueous alkali regenerated the acid **4b**. Treatment of either the lactone **9** or the methyl ester **4a** with a solution of sodium methoxide in boiling methanol afforded an equilibrium mixture of the ester **4a** (25–28%) and the lactone **9** (75–72%). The *trans*-hydroxy acid **10b** was characterized as the methyl ester **10a**, m.p. 73.5–75°. Reaction of the *trans* ester **10a** with 0.2 equivalent of *p*-toluenesulfonic acid in boiling benzene afforded a mixture of the lactone **9** and the unsaturated ester **11** thereby establishing the carbon skeleton of the product. The n.m.r. spectrum (60 mc.) confirmed the location of the hydroxyl function as in **10**, peaks being present at 6.37τ (singlet, $-CO_2CH_3$), 7.92τ (singlet, O–H) and 8.73τ (singlet, $CH_3-\overset{|}{C}-O-$) with a doublet (J = 7 c.p.s.) at 9.07 and 9.18τ attributable to an isopropyl group.[7] The presence of an unsplit C-methyl peak at 8.73τ, the absence of additional peaks in the region 6.75 to 5.15τ attributable to the grouping $\diagdown$CH–O– and the presence of a hydroxyl peak at 7.92τ are all consistent with the formulation of **10a** as a tertiary alcohol.

An authentic sample of the enol ether **8** was obtained by reaction of the known enolic diketone **14** with diazomethane. The formulation of the enol ether as **8** rather than as **15** (R = Me) is indicated by the n.m.r. spectrum (40 mc.) of the material which has peaks at 6.45τ (singlet, $=\overset{|}{C}-OCH_3$) and at 8.18τ (singlet, $-CO-\overset{|}{C}=\overset{|}{C}-CH_3$) with two doublets ($J$ = 6 c.p.s.) at 9.00 and 9.15τ and at 9.10 and 9.25τ attributable to the methyl groups of an isopropyl group.[7] The enolization of the α-diketone in the direction represented by structure **14** rather than **15** (R = H) would be expected since the steric interaction of an eclipsed methyl group and a hydroxyl group (as in **14**) would be appreciably less than the corresponding interaction of an isopropyl group and a hydroxyl group (as in **15**, R = H).

An authentic sample of the unsaturated ester **11** was prepared as previously described.[5b] Previous degradative experiments[5b,6b] established that this ester was at least in part the β,γ-unsaturated ester **11a**. Although our product exhibited only a singlet peak on gas chromatography with two different columns, we have no evidence which rigorously excludes the possibility that our product **11a** was contaminated with the double bond isomer **11b**.

The carbon skeletons and locations of the carbonyl functions in the two abnormal products **12** and **13** were established by the conversion of each substance to thymol (**16**) on treatment with a catalytic amount of *p*-toluenesulfonic acid in an inert solvent. The infrared (**12**, 1670 cm.$^{-1}$; **13**, 1677 cm.$^{-1}$) and ultraviolet (λ_{max} 239 mμ for **12**, 236 mμ for **13**) absorption of the products established the presence of a disubstituted α,β-unsaturated ketone chromophore. The n.m.r. spectrum (40 mc.) of the methoxy ketone **12** has bands at 4.40τ (singlet, $C=CH-CO-$), 7.00τ (singlet, $C-O-CH_3$) and 8.08τ (singlet, $\diagdown C=$ $C-CH_3$) with two doublets (J = 7 c.p.s.) at 9.08 and 9.25τ and 9.15 and 9.33τ attributable to the methyl groups of an isopropyl group.[7] Similarly, the n.m.r. spectrum (60 mc.) of the hydroxy ketone **13** has peaks at 4.23τ (singlet, $\diagdown C=CH-CO-\diagup$), 6.67$\tau$ (singlet, O—H) and 8.07τ (singlet, $\diagdown C=$ $\overset{|}{C}-CH_3$) with two doublets (J = 7 c.p.s.) at 8.98 and 9.08τ and at 9.28 and 9.40τ attributable to the methyl groups of an isopropyl group.[7] Additional evidence for the location of the hydroxyl group in the hydroxy ketone **13** was obtained by the catalytic reduction of **13** to form a mixture of diastereoisomers **17**. Each of the two diastereoisomeric ketones **17** consumed one equivalent of periodic acid.

The reaction of isophorone oxide (**6**) with either sodium methoxide or potassium hydroxide in methanol (Table II) produced the enol ether **18a** as the major product (81–85%) accompanied by smaller amounts of the enolic α-diketone **18b**. In the reactions employing potassium hydroxide, small amounts of the hydroxy acids **19b** and **20b** were also detected. Addition of water to the reaction mixture increased the yields of the hydroxy acids **19b** and **20b** as well as the enolic α-diketone **18b**. However, no abnormal products, analogous to the compounds **12** and **13** obtained from piperitone oxide, were isolated.

An authentic sample of the enolic α-diketone **18b** was prepared by the procedure previously

(7) S. Goodwin, J. N. Shoolery and L. F. Johnson, *J. Am. Chem. Soc.*, 81, 3065 (1959).

described.[5d,8] Reaction of the enol ether **18a** with 2,4-dinitrophenylhydrazine yielded, in addition to the two geometrical isomers of the mono-2,4-dinitrophenylhydrazone of **18a**, the same bis-2,4-dinitrophenylhydrazone as was obtained from the α-diketone **18b**. The n.m.r. spectrum (40 mc.) of the enol ether **18a** has peaks at 6.43τ (singlet, $-C=C(-)-OCH_3$), 7.80τ (broad singlet, $-CH_2-C=C-$ and $-CH_2-CO-$), 8.18τ (singlet, $CH_3-C=C-CO-$) and 8.93τ (singlet, geminal methyl groups). The enol ether **18a** also exhibits an ultraviolet absorption maximum at 251 mμ (*cf.* **8**, λ_{max} 250 mμ) consistent with its formulation as a trisubstituted α,β-unsaturated ketone.

The mixture of hydroxy acids **19b** and **20b** was converted by reaction with diazomethane to a mixture of the methyl esters **19a** and **20a** for separation and characterization. A solution of the mixed hydroxy acids in boiling toluene was converted in part to the lactone **21** from which the pure *cis*-acid **19b**, m.p. 116–118°, could be obtained by saponification. Esterification of this *cis*-acid **19b** with diazomethane afforded a sample of the pure *cis*-ester **19a**. Reaction of either the *cis*-ester **19a** or the *trans*-ester **20a** with methanolic sodium methoxide produced a partially equilibrated mixture of the two esters **19a** and **20a** and the lactone **21** thereby establishing the epimeric relationship of the two esters. The n.m.r. spectrum (60 mc.) of the *cis*-ester **19a** has single peaks at 6.35 (a), 6.45 (b), 8.68 (c), 8.87 (d) and 8.97 (e) τ with incompletely resolved multiplets in the regions 7.5 (f), 7.8 to 8.0 (g) and 8.2 to 8.3 (h) τ. The assignments of these peaks are shown in structure **24**.

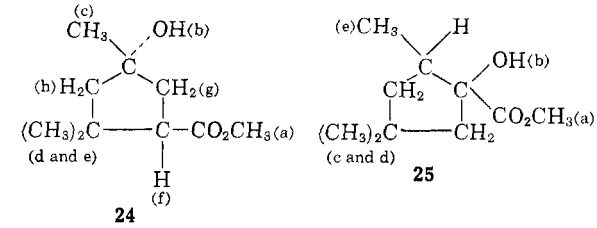
To ensure that the hydroxy acids produced from isophorone oxide (**6**) were not the α-hydroxy acids **22b** and **23b** resulting from the benzilic acid rearrangement of the α-diketone **18b**, this benzilic acid rearrangement was conducted as previously described.[9] The crystalline hydroxy acid obtained proved to be a mixture of diastereoisomers **22b** and **23b** which was converted by reaction with diazomethane to the esters **22a** and **23b** for separation and characterization. Both diastereoisomers **22a** and **23a** were different from the hydroxy esters obtained from isophorone oxide (**6**). The n.m.r. spectra (60 mc.) of the two diastereoisomers are very similar; isomer A has peaks at 6.28(a), 7.22(b), 9.00(c) and 9.05(d) τ with a doublet (J = 6 c.p.s.) at 9.23 and 9.33τ (e) and isomer B has peaks at 6.23(a), 6.69(b), 8.82(c) and 8.92(d) τ with a doublet (J = 8 c.p.s.) at 9.08 and 9.22τ (e). The assignments of these peaks are indicated in structure **25**. We consider the evidence available insufficient to permit assignments of stereochemistry to these isomers.

The formation of both diastereoisomeric hydroxy acid derivatives **19** and **20** from isophorone oxide (**6**) might be explained by partial epimerization of the *cis*-ester **19a** after rearrangement. However, this explanation may be excluded for the formation of both acid derivatives **4** and **10** from piperitone oxide (**1**) since the *cis*-ester **4a** is not converted to the *trans*-ester **10a** under the conditions of the reaction. Consequently, although the formation of the lactone **9** from reaction of piperitone oxide (**1**) with potassium *t*-butoxide in 1,2-dimethoxyethane is stereospecific, the rearrangement of this oxide **1** in methanolic sodium methoxide to form both esters **4** and **10** is not a stereospecific process. Although the over-all transformations **1** to **4** and **10** and **6** to **19** and **20** are analogous to the Favorskiĭ rearrangement of α-halo ketones,[3] it is necessary to consider the possibility that the rearrangements of oxides such as **1** and **6** proceed by an entirely different mechanism before the stereochemical results of this study may be applied to the Favorskiĭ rearrangement. Mechanisms involving initial nucleophilic attack at the carbonyl function of **1** (*i.e.*, **26**) appear most improbable since the expected products **27** are formed in very small amounts if at all. The oxides **1** and **6** could be shown to form readily enolate ions **28** and **29** by demonstrating that the oxide **1** would incorporate one atom of deuterium and the oxide **6** two atoms of deuterium upon treatment with a mixture of triethylamine and acetone-d_6. As noted previously these conditions were sufficient to epimerize piperitone oxide (**1**) but were not sufficient to bring about the rearrangement of either oxide.[10] From a reaction of a solu-

(8) G. B. Payne, *J. Org. Chem.*, **24**, 719 (1959).

(9) O. Wallach, *Ann.*, **414**, 329 (1918).

(10) Both these and subsequently described data indicate that the formation of enolate ions of the type i occurs with extreme difficulty if at all. Since analogous enolate ions can be formed in acyclic systems [H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958)], these results are apparently attributable to the excessive strain which would be required to form this planar system permitting delocalization of the negative charge.



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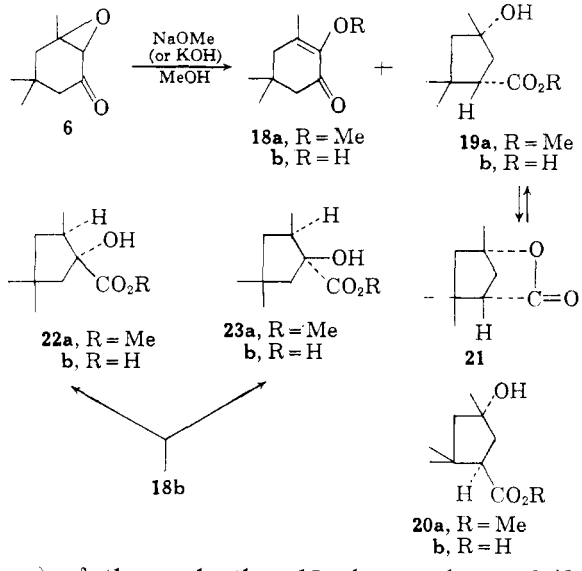

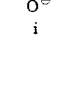

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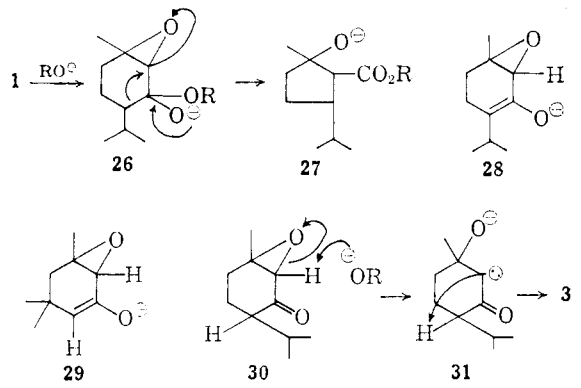
tion of piperitone oxide (**1**) with sodium methoxide in methanol-d_1, which had been stopped prior to completion, the recovered oxide **1** was composed of approximately equal amounts of non-deuterated and monodeuterated material with little, if any, dideuterated oxide **1** present. Each of the hydroxy esters **4a** and **10a** produced contained essentially one deuterium atom bound to carbon. These results are clearly compatible with the proposed mechanism of the Favorskiĭ rearrangement (*i.e.*, **1** → **2** → **3** → **4**) if the stereochemical implications of this scheme are, for the moment, ignored. However, the data are not consistent with an α-elimination process (*i.e.*, **30** and **31**) or with other schemes which would require the intervention of other intermediates capable of incorporating additional deuterium.



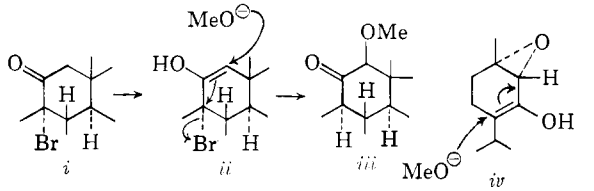
Our data concerned with the non-stereospecific rearrangement of piperitone oxide (**1**) in methanolic sodium methoxide are consistent with the mechanism of the Favorskiĭ rearrangement if the initially formed enolate anion **28** undergoes an ionic dissociation (as in **32**) to form a planar intermediate such as **33**[3,4] rather than undergoing the direct displacement **2** leading to the cyclopropanone **3**. Alternatively, an equilibrium between the two diastereoisomeric forms of the cyclopropanone **3** involving a species such as **33** or its conjugate acid **34** can be envisioned.

The observation that the oxide **1** recovered from the sodium methoxide–methanol-d_1 reaction was only partially deuterated whereas essentially complete deuterium exchange without rearrangement was realized in the triethylamine–acetone-d_6 reaction is consistent with the idea that the enolate anion **28** (or the free enol) undergoes ionization (*i.e.*, **32**) much more rapidly in the polar solvent, methanol, than in the non-polar solvent, acetone.

Such a scheme not only accounts for the lack of stereospecificity in the rearrangement but also accounts for the formation of the displacement products **8**, **12** and **13**. For example, the formation of the methoxy ketone **12** may be pictured as in structure **35**.[11,12] In the reaction of piperitone oxide (**1**) with potassium *t*-butoxide in the non-polar solvent 1,2-dimethoxyethane, a medium which would favor neither the ionic dissociation **32** nor the existence of an intermediate such as **33** or **34**, a direct displacement of the epoxide ring (as in **2**) may be involved. The subsequent intramolecular rearrangement **36** could then lead to the lactone **9**. The formation of appreciable amounts of the unsaturated acid corresponding to the ester **11a** only in this experiment suggests the partial destruction of the lactone by the base-catalyzed elimination **37**. It should be noted that this interpretation of the behavior of piperitone oxide (**1**) in solvents of varying polarity is consistent with the results obtained in our subsequent investigation[4] of the Favorskiĭ rearrangement of α-halo ketones. However, other interpretations obviously are possible.[13]

One possibility which deserves serious consideration is an alternative pathway leading to the enol ether **8** and probably the major route to the enol ether **18a** involving the direct displacement of the epoxide ring (*i.e.*, **38**) by methoxide ion to form the intermediate **39**. Base-catalyzed dehydration of this intermediate **39** would then yield the enol ether **8**. It will be noted that use of the intermediate **39** in the intramolecular displacement **40** provides a conceivable route to the *trans*-hydroxy ester **10a** *via* the cyclopropanone **41**. Although this process may be criticized on the grounds that methoxide ion is normally a poor leaving group and that the deuterium studies require this process to be more rapid than incorporation of deuterium into the molecule, the product studies (Table I) are not inconsistent with this possibility. Thus, the increased yields of the enol ether **8** at higher reaction temperatures are accompanied by decreased yields of the *trans*-acid

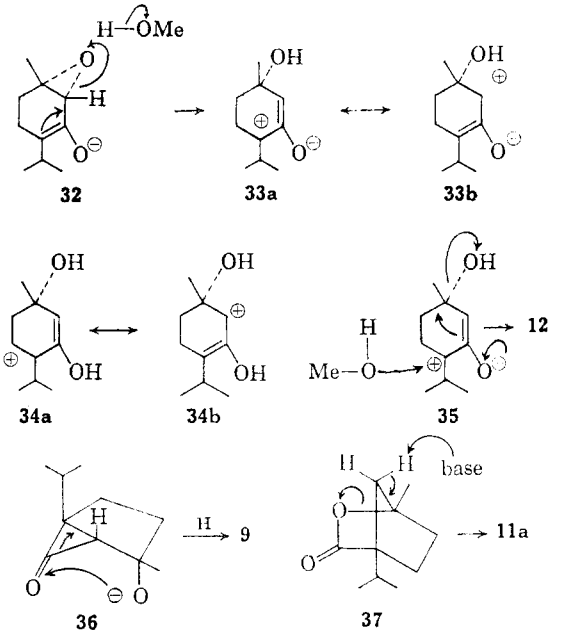
(11) J. S. G. Cox [*J. Chem. Soc.*, 4508 (1960)] recently has described the reaction of a 9α-bromo-11-keto pregnane derivative *i* with sodium methoxide to form the corresponding 12α-methoxy ketone *ii*. The author suggested the operation of an SN2, displacement involving the free enol *iii* as illustrated in the accompanying equation. A similar sequence *iv* can obviously be envisioned for the charge **1** to **12**. However, we believe the alternative scheme involving reaction of an intermediate such as **33** or **34** with the solvent provides an equally satisfactory explanation for both our observations and those of Cox. Furthermore, this scheme appears to be in better agreement with the



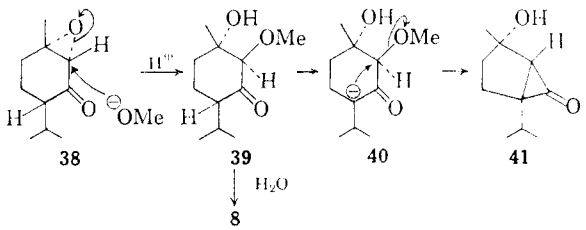
observations of A. W. Fort [140th Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961. Abstracts of Papers, p. 19-Q] that solvolysis products rather than Favorskiĭ rearrangement products predominate in the absence of high concentrations of the highly nucleophilic methoxide ion (ref. 4). In our experiment the preferential SN2′ attack at a tertiary center (as in **iv**) rather than SN2 reaction at a secondary center is not in keeping with the behavior of other allylic systems [see S. Winstein, *Bull. soc. chim. France*, C43 (1951); R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956)]. As noted by the Referee, this latter objection is avoided if the enol pictured in *iv* undergoes solvolysis to form the ion **34** prior to reaction with methanol. This scheme, a variant of the ionization process **32** involving the free enol rather than the enolate anion, is not inconsistent with our data.

(12) Since the hydroxy ketone **13** derived from piperitone oxide **1** is still optically active, any mechanism proposed for the formation of this substance cannot involve a planar or symmetrical intermediate.

(13) The referees have suggested three interpretations of parts of this work which our data do not exclude and doubtless many other possibilities exist. However, we see no reason to seek increasingly obscure interpretations of these data in the absence of experimental evidence indicating that the behavior of α-halo ketones and α,β-epoxy ketones with bases are not analogous.



derivatives **10**. Although we have been unable to isolate the intermediate **39** needed to eliminate rigorously this possibility, the observation that conditions which favor the formation of α-alkoxy ketones lower the yield of Favorskiĭ rearrangement products[3] and the absence of examples of Favorskiĭ rearrangements with α-methoxy ketones lead us to believe that the displacement process **40** does not warrant serious consideration.



Acknowledgment.—The authors are indebted to Professor Klaus Biemann and his associates for the mass spectra described in this paper.

Experimental[14]

Piperitone Oxide (1).—The alkaline epoxidation[15] of 60.9 g. (0.40 mole) of (−)-piperitone, $[\alpha]^{29}D$ −18.3° (*c* 9.747, ethanol), afforded 28.8 g. (42.8%) of a mixture of epimeric piperitone oxides, b.p. 105° (6 mm.), $n^{24}D$ 1.4613, $[\alpha]^{29}D$ + 31.6° (*c* 9.833, ethanol) [lit.[5a] (−)-form, $[\alpha]^{22}D$ −177° (*c* 0.96, ethanol), b.p. 91° (3 mm.), $n^{20}D$ 1.4624, m.p. 14.5–15.5°; (+)-form, αD + 21.0° (prepared from (−)-piperitone, αD −46°)]. The gas chromatogram[16] of this product exhibits two partially resolved peaks corresponding to epimers A and B. A series of fractional crystallizations of the mixture from hexane at Dry Ice temperatures separated pure isomer A, a crystalline solid melting below room temperature, $[\alpha]^{26.5}D$ −0.53° (*c* 1.04, ethanol) and a mixture composed of 41% isomer A and 59% isomer B, $[\alpha]^{26.2}D$ +43.6° (*c* 1.03, ethanol). The infrared spectra[17] of the two fractions exhibit a band at 1705 cm.$^{-1}$ (C=O) with differences in the intensities of several bands in the fingerprint region. The ultraviolet spectra[18] of the fractions have no appreciable absorption above 210 mμ. Since the epimers were readily interconverted by bases, a mixture of the isomers was employed for all studies subsequently described.

Reaction of Piperitone Oxide (1) with Methanolic Potassium Hydroxide.—A solution of 10.0 g. (0.059 mole) of piperitone oxide and 7.8 g. (0.118 mole) of 85% potassium hydroxide in 75 ml. of methanol was refluxed for 80 min. and then diluted with 150 ml. of water. After the mixture had been extracted with five 50-ml. portions of ether, the aqueous phase was acidified and extracted with ether. The ethereal solution of the crude acidic product was dried over magnesium sulfate and concentrated to leave 3.71 g. (33.9%) of crude **1-isopropyl-3-methyl-*cis*-3-hydroxycyclopentanecarboxylic acid (4b), m.p. 108–110°.** Recrystallization first from benzene and then from hexane afforded 3.1 g. (28.2%) of the pure hydroxy acid as white needles, m.p. 112–113° [lit. m.p. 112–113°,[5a] 113–114°[15a]]. The acid exhibits infrared absorption[19] at 1690 cm.$^{-1}$ (carboxyl C=O) with a broad band in the 3 μ region (O–H) and no significant absorption in the ultraviolet[18] (ϵ 115 at 212 mμ).

The ethereal extract containing the neutral products was dried over magnesium sulfate, concentrated and distilled under reduced pressure to separate fractions (4.212 g.) boiling in the range 80–119° (9 min.), $n^{23}D$ 1.4804–1.4814. From the gas chromatogram[20] of the neutral fraction the following components (% yield based on the starting piperitone oxide) were judged to be present: piperitone oxide (2%), 6-isopropyl-2-methoxy-3-methyl-2-cyclohexenone (17%), 6-isopropyl-6-methoxy-3-methyl-2-cyclohexenone (3%), methyl 1-isopropyl-3-methyl-2(and/or 3)-cyclopentenecarboxylate (7%) and a mixture of the methyl ester of 1-isopropyl-3-methyl-*trans*-3-hydroxycyclopentanecarboxylic acid as well as the methyl ester of 1-isopropyl-3-methyl-*cis*-3-hydroxycyclopentanecarboxylic acid (12%). Three pure components were separated from this mixture by a combination of fractional distillation and gas chromatography.[20]

Methyl 1-isopropyl-3-methyl-2-cyclopentenecarboxylate (11a) was shown to be identical with a subsequently described sample by comparison of the retention times and infrared spectra of the two samples. The sample of **6-isopropyl-6-methoxy-3-methyl-2-cyclohexenone (12)** collected was further purified by distillation in a short-path still under reduced pressure. The material, $n^{25}D$ 1.4861, has infrared absorption[17] at 1670 cm.$^{-1}$ (conj. C=O) and 1640 cm.$^{-1}$ (conj. C=C) with an ultraviolet maximum[18] at 239 mμ (ϵ 10,900).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; mol. wt., 182. Found: C, 72.64; H, 10.09; mol. wt., 182 (mass spectrum).

A solution of 0.651 g. (0.00358 mole) of the methoxy ketone 12 and 61 mg. (0.358 mmole) of *p*-toluenesulfonic acid in 6 ml. of *sec*-butylbenzene was refluxed for 15 hr. and then cooled and extracted with aqueous sodium bicarbonate. The organic phase was concentrated and subjected to gas chromatography[20]; the crude thymol collected from the chromatogram separated from petroleum ether as white prisms, m.p. 49–51°, yield 0.143 g. (26.8%), which did not depress the melting point of an authentic sample and the infrared spectra[21] of the two samples are identical. In addition a 0.140-g. (0.933 mmole) sample of the thymol obtained from the methoxy ketone 12 was converted[22] to **2-isopropyl-5-methylphenoxyacetic acid**, m.p. 147–149°, which was identified by a mixed melting point determination and comparison of the infrared spectrum with that of an authentic sample.[22]

(14) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin–Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. The n.m.r. spectra were determined in carbon tetrachloride solution with a Varian Associates high-resolution nuclear magnetic resonance spectrometer, model V 4300B.

(15) R. L. Wasson and H. O. House, *Org. Syntheses*, **37**, 58 (1957).

(16) Obtained with a column packed with No. 1540 Carbowax suspended on 80–100 mesh Chromosorb.

(17) Determined as a solution in carbon tetrachloride.

(18) Determined as a solution in ethanol.

(19) Determined as a solution in chloroform.

(20) Obtained with a column packed with either No. 550 or No. 710 Silicone Fluid suspended on 48–100 mesh ground firebrick.

(21) Determined as a suspension in a potassium bromide pellet.

(22) C. F. Koelsch, *J. Am. Chem. Soc.*, **53**, 304 (1931).

A sample of 6-isopropyl-2-methoxy-3-methyl-2-cyclohexenone (8) collected from the neutral fraction was further purified by a shortpath distillation under reduced pressure. The product, $n^{28}D$ 1.4798, which was shown to be identical with the subsequently described authentic sample by comparison of infrared spectra and retention times, has infrared absorption[17] at 1677 (conj. C=O) and 1640 cm.$^{-1}$ (conj. C=C) with a maximum at 250 mμ (ϵ 8,300) in the ultraviolet.[18]

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; mol. wt., 182. Found: C, 72.34; H, 10.00; mol. wt., 182 (mass spectrum).

Complete product analyses of comparable reactions of piperitone oxide with methanolic potassium hydroxide are presented in Table I.

Reaction of Piperitone Oxide (1) with Methanolic Sodium Methoxide.—A solution of 2.7 g. (0.016 mole) of piperitone oxide in methanolic sodium methoxide, prepared from 0.74 g. (0.032 g. atom) of sodium and 30 ml. of methanol, was stirred at 0° for 9 hr. and then diluted with 30 ml. of water and saturated with carbon dioxide. The resulting mixture was extracted with four 30-ml. portions of ether and the combined ethereal extracts were dried over magnesium sulfate and concentrated to leave 2.2 g. of an oil composed of piperitone oxide (13%), 6-isopropyl-6-methoxy-3-methyl-2-cyclohexenone (9%), methyl 1-isopropyl-3-methyl-*trans*-3-hydroxycyclopentanecarboxylate (45%) and a mixture (33%) of the enol ether 8, the *cis*-hydroxy ester 4a and the lactone 9. Fractional distillation of the mixture concentrated the *trans*-hydroxy ester 10a in the higher boiling fractions, b.p. 61–62° (0.1 mm.). A solution of these fractions in petroleum ether deposited the pure **methyl 1-isopropyl-3-methyl-*trans*-3-hydroxycyclopentanecarboxylate (10a)** as white needles, m.p. 73.5–75°, yield 0.271 g. (8.4%), $[\alpha]^{30.7}D$ −10.0° (*c* 1.395, EtOH). The hydroxy ester has infrared absorption[17] at 3660 cm.$^{-1}$ (unassoc. O–H), 3400 (broad, assoc. O–H) and 1725 (ester C=O) with no significant absorption in the ultraviolet[18] (ϵ 186 at 214 mμ).

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.08; H, 10.32.

A solution of 0.20 g. (0.0010 mole) of the *trans*-hydroxy ester 10a and 35.4 mg. (0.2 mmole) of *p*-toluenesulfonic acid in 2 ml. of benzene was refluxed for 14 hr. and then diluted with ether and washed with aqueous sodium bicarbonate. After the organic phase had been dried over magnesium sulfate and concentrated, the residue, 0.175 g. of oil composed of 59% of the unsaturated ester 11a and 41% of the lactone 9, was separated by gas chromatography.[16] Each of the two samples collected was shown to be identical with subsequently described authentic samples by comparisons of the retention times and the infrared spectra of the samples.

From a similar reaction of piperitone oxide with sodium methoxide in which the reaction mixture was refluxed for 80 min., the gas chromatographic[16] peak corresponding to the mixture of *cis*-hydroxy ester 4a and lactone 9 was collected. The infrared spectrum[17] of this fraction exhibits peaks at 1780 (γ-lactone C=O), 1722 (ester C=O) and 3540 cm.$^{-1}$ (O—H) and is consistent with the spectrum expected of a mixture of the lactone 9 and ester 4a. A solution of 0.207 g. (*ca.* 0.001 mole) of this fraction and 2 ml. (0.0025 mole) of 5% aqueous sodium hydroxide in 3 ml. of methanol was stirred at room temperature for 4 hr. After the resulting solution had been saturated with carbon dioxide and extracted with ether, the aqueous phase was acidified and extracted with ether. From this ethereal extract appropriate manipulations separated 0.1112 g. (52.5%) of the *cis*-hydroxy acid 4b, m.p. 112–113°, which was identified by a mixed melting-point determination.

Complete product analyses for comparable reactions of piperitone oxide with methanolic sodium methoxide are presented in Table I.

Reaction of Piperitone Oxide (1) with Aqueous Potassium Hydroxide.—A mixture of 8.0 g. (0.048 mole) of piperitone oxide, 6.24 g. (0.095 mole) of 85% potassium hydroxide and 80 ml. of water was stirred at 0° for 20 hr. and then extracted with ether. The ethereal solution was dried over magnesium sulfate, concentrated and distilled under reduced pressure to separate 7.04 g. (88%) of **6-hydroxy-6-isopropyl-3-methyl-2-cyclohexenone (13)**, b.p. 51° (0.1 mm.), $n^{27}D$ 1.4918, $[\alpha]^{30.7}D$ − 1.23 (*c* 6.094, EtOH), which exhibits a single peak on gas chromatography.[16] The product has infrared absorption[17] at 3530 (O—H), 1677 (conj. C=O) and 1635 cm.$^{-1}$ (conj. C=C) with an ultraviolet maximum[18] at 236 mμ (ϵ 11,000).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 71.39; H, 9.59. Found: C, 71.34; H, 9.57.

Reaction of a 0.150-g. (0.89 mmole) sample of the hydroxy ketone 13 with 15 mg. (0.087 mmole) of *p*-toluenesulfonic acid in 1 ml. of boiling toluene for 12 hr. afforded, after the previously described manipulations, 0.102 g. (76.7%) of thymol, m.p. 49–50°, which was identified by a mixed melting point determination and comparison of infrared spectra.

The aqueous phase from the reaction was acidified and extracted with ether. After the ethereal extract had been dried over magnesium sulfate and concentrated, an ethereal solution of the acidic residue (0.43 g.) was esterified by treatment with excess diazomethane. The mixture of esters obtained was composed[16] of 5% unsaturated ester 11a, 71% *cis*-hydroxy ester 4a and 24% *trans*-hydroxy ester 10a.

Reaction of Piperitone Oxide (1) with Potassium *t*-Butoxide.—To a cold (0°) solution of potassium *t*-butoxide, prepared from 2.75 g. (0.070 g.-atom) of potassium and 5.2 g. (0.070 mole) of *t*-butyl alcohol, in 300 ml. of 1,2-dimethoxyethane was added, dropwise and with stirring over 1 hr., a solution of 10.0 g. (0.0595 mole) of piperitone oxide in 25 ml. of 1,2-dimethoxyethane. The resulting mixture was allowed to warm to room temperature over a 4-hr. period, concentrated under reduced pressure and then poured onto a mixture of ice and water. The ethereal extract of this mixture was dried over magnesium sulfate and distilled to separate 7.01 g. (70.1%) of the **lactone of 1-isopropyl-3-methyl-*cis*-3-hydroxycyclopentanecarboxylic acid (9)**, b.p. 113–114° (8 mm.), $n^{26}D$ 1.4568, which was shown to be identical with a subsequently described sample by comparison of retention times[16] and infrared spectra.[17] After the aqueous phase from the reaction had been acidified, the crude acid product, 2.1 g. isolated in the usual way, was esterified with diazomethane and analyzed by gas chromatography.[16] The ester mixture consisted of the *cis*-hydroxy ester 4a (10%) and the unsaturated ester 11a (90%).

Product Analyses in the Reaction of Piperitone Oxide (1) with Bases.—In order to obtain product analyses for the various reaction conditions outlined in Table I, the reactions were run as previously described and the neutral and acidic fractions were separated and weighed. The acidic fractions were esterified with diazomethane and analyzed by gas chromatography.[16] The neutral fractions were analyzed by a combination of gas chromatograms from two columns.[16,20] Since the *cis*-hydroxy ester 4a and the lactone 9 were not resolved, the amounts of these two components are listed together. In one instance an additional infrared analysis was employed to determine the amounts of these two components present. The percentage yields listed, based on the amount of piperitone oxide introduced into the reaction mixtures, were determined after calibration of the columns with known mixtures.

6-Isopropyl-2-methoxy-3-methyl-2-cyclohexenone (8).—To a solution of 3.9 g. (0.023 mole) of the diosphenol **14**,[5d,6a] m.p. 82–83° [lit. 83–84°,[6a] 82°[23,24]], and 50 ml. of methanol in 100 ml. of ether was added in two portions an ethereal solution containing excess diazomethane. The mixture was allowed to stand approximately a day after each addition. After the ethereal solution had been washed with aqueous sodium hydroxide and then dried over magnesium sulfate, distillation afforded 2.74 g. (65%) of the enol ether 8, b.p. 75° (18 mm.), $n^{27}D$ 1.4782, which was shown to be identical with the previously described sample by comparison of retention times, infrared spectra and ultraviolet spectra.

Hydrogenation of 6-Isopropyl-6-hydroxy-3-methyl-2-cyclohexenone (13).—Hydrogenation of a solution of 100 mg. (0.595 mmole) of the hydroxy ketone in 5 ml. of ethanol in the presence of 10 mg. of a 10% palladium-on-carbon catalyst at 25° and atmospheric pressure resulted in the absorption of 14.9 ml. (1.02 molar equivalents) of hydrogen. After the solution had been filtered, diluted with ether, washed with water and dried over magnesium sulfate, concentration of the ethereal solution left 94 mg. (93%) of a mixture of epimeric dihydro compounds 17 containing

(23) J. Walker and J. Read, *J. Chem. Soc.*, 238 (1934).

(24) R. J. W. LeFevre, F. Mosamba and R. L. Werner, *ibid.*, 2496 (1953).

TABLE I

REACTION OF PIPERITONE OXIDE WITH BASES

Conditions	Percentage yields: Recovd. piperitone oxide (1)	Unsatd. ester 11a	Methoxypiperitone 12	Enol ether 8	Hydroxy piperitone 13	Lactone 9 and *cis*-hydroxy ester 4a	*trans*-Hydroxy ester 10a	Unsatd. acid from ester 11a	*cis*-Hydroxy acid 4b	*trans*-Hydroxy acid 10b	Total
KOH (2 eq.), MeOH, 0°, 5 hr.	1	3	6	9	..	37	29	Trace	7	1	93
KOH (1.2 eq.), MeOH, refl. 80 min.	Trace	4	4	14	..	23[b]	16	Trace	28	Trace	89
NaOMe (2 eq.), MeOH, 0°, 5 hr.	9	2	7	5	..	30[a]	35	Trace	1	Trace	89
NaOMe (2 eq.), MeOH, refl. 80 min.	Trace	4	4	17	..	39	17	Trace	11	Trace	92
KOH (2 eq.), MeOH–H_2O (1:1), 0°, 5 hr.	Trace	Trace	24	6	11	13	8	Trace	20	2	84
KOH (2 eq.), H_2O, 0°, 18 hr.	...	...	..	..	88	..	..	Trace	4	1	93
KO-*t*-Bu, 1,2-dimethoxyethane 25°, 5 hr.	...	...	..	..	..	70[c]	..	17	3	...	90

[a] In a comparable experiment in which the mixture of *cis*-hydroxy ester **4a** and lactone **9** was formed in 20% yield, infrared analysis indicated the presence of 71% of the lactone and 29% of the *cis*-hydroxy ester in the mixture. [b] Ester only. [c] Lactone only.

71% of isomer A and 29% of isomer B. The epimers were separated by gas chromatography[25] and further purified by short-path distillation under reduced pressure.

Isomer A has infrared absorption[17] at 3550 (O–H) and 1710 cm.$^{-1}$ (C=O) with an ultraviolet maximum[18] at 282 mμ (ε 43). Reaction of an acetic acid solution of isomer A with periodic acid resulted in the consumption of 1.04 equivalents of periodic acid.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.51; H, 10.59.

Isomer B exhibits infrared absorption[17] at 3550 (O—H) and 1710 cm.$^{-1}$ (C=O) with an ultraviolet maximum[18] at 276 mμ (ε 160). An acetic acid solution of the compound consumed 1.04 equivalents of periodic acid.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.37; H, 10.41.

Lactone of 1-Isopropyl-3-methyl-*cis*-3-hydroxycyclopentanecarboxylic Acid (9).—A solution of 5.5 g. (0.0295 mole) of the *cis*-hydroxy acid **4b** in 175 ml. of benzene was refluxed for 58 hr. with continuous separation of water. The resulting benzene solution was washed successively with aqueous sodium bicarbonate and water, dried over magnesium sulfate and distilled under reduced pressure. The lactone, collected at 99–110° (10 mm.), $n^{27}D$ 1.4563–1.4564, amounted to 3.818 g. (77.1%) of material which exhibits a single peak on gas chromatography.[20] The product exhibits infrared absorption[17] at 1780 cm.$^{-1}$ (γ-lactone C=O) with an ultraviolet maximum[18] at 216 mμ (ε 110).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.37; H, 9.43.

A solution of 0.376 g. (0.00224 mole) of the lactone and 10 ml. (0.025 mole) of 10% aqueous sodium hydroxide in 10 ml. of methanol was stirred at room temperature for 4 hr. and at reflux for 15 min. The reaction mixture was diluted with water and subjected to the appropriate manipulations to separate 0.31 g. (74%) of the *cis*-hydroxy acid **4b**, m.p. 111.5–113°, identified by a mixed melting point determination.

Methyl 1-Isopropyl-3-methyl-*cis*-3-hydroxycyclopentanecarboxylate (4a).—A solution of 1.81 g. (0.00972 mole) of the *cis*-hydroxy acid **4b** in 100 ml. of ether was treated with excess diazomethane. After the solution had been stirred at 0° for 15 min., it was washed successively with aqueous sodium bicarbonate and water, dried over magnesium sulfate and concentrated under reduced pressure. Distillation of the residue through a short-path still afforded 1.72 g. (88.6%) of the pure ester, b.p. 83–85° (0.4 mm.), $n^{29}D$ 1.4536, which has infrared absorption[17] at 3530 (broad, associated O—H) and 1723 cm.$^{-1}$ (ester C=O) with no significant ultraviolet absorption[18] (ε 144 at 212 mμ).

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.67; H, 9.99.

(25) Obtained with a column packed with 20 M Carbowax suspended on 80–100 mesh Chromosorb.

Equilibration of the *cis*-Hydroxy Ester 10a and the Lactone 9. A.—A solution of 0.5 g. (0.003 mole) of the lactone in methanolic sodium methoxide prepared from 69 mg. (0.003 g.-atom) of sodium and 3 ml. of methanol was refluxed for 80 min. and then poured onto ice and extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate and concentrated to leave 0.43 g. of a residual oil which was distilled under reduced pressure. Analysis of the mixture by infrared spectroscopy indicated the presence of 75% lactone and 25% ester.

B.—The similar equilibration of a 125-mg. (0.625 mmole) sample of the *cis*-hydroxy ester for 80 min. in a refluxing solution of sodium methoxide prepared from 20 mg. (0.00087 g.-atom) of sodium and 3 ml. of methanol afforded 110 mg. of a mixture containing 72% lactone and 28% *cis*-hydroxy ester.

Methyl 1-Isopropyl-3-methyl-2-cyclopentenecarboxylate (11a).—A 3.8-g. sample of a mixture of *cis*-hydroxy ester **4a** (*ca.* 60%) and lactone **9** (*ca.* 40%) was converted to crude methyl 3-chloro-1-isopropyl-3-methylcyclopentanecarboxylate, b.p. 101–125° (17 mm.), yield 1.9 g., as previously described.[5a] Dehydrochlorination of this chloro ester as previously described[5a] afforded 0.85 g. of the unsaturated ester, b.p. 215–216°, $n^{25}D$ 1.4555 [lit. $n^{20}D$ 1.4567,[6a] b.p. 208–209°, 100–101° (22 mm.),[6a] 94–95° (15 mm.)[5a]], which exhibits a single peak on gas chromatography.[20] The product has infrared absorption[17] at 1725 cm.$^{-1}$ (ester C=O) with end absorption (ε 1,800 at 210 mμ) in the ultraviolet.[18]

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.24; H, 9.87.

Reaction of Isophorone Oxide (6) with Potassium Hydroxide in Aqueous Methanol.—To a solution of 36.5 g. (0.554 mole) of 85% potassium hydroxide in a refluxing mixture of 100 ml. of methanol and 200 ml. of water was added, dropwise and with stirring over a period of 1 hr., a solution of 35.0 g. (0.227 mole) of isophorone oxide[15] in 50 ml. of methanol. After the addition was complete, the mixture was refluxed for 30 min. and then extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate and distilled.

The 2-methoxy-3,5,5-trimethyl-2-cyclohexenone (18a), collected at 112–118° (18–19 mm.), $n^{29}D$ 1.4732–1.4736, amounted to 16.99 g. (44.5%). The product, which exhibits a single peak on gas chromatography,[16] has infrared absorption[17] at 1685 (conj. C=O) and 1645 cm.$^{-1}$ (conj. C=C) with an ultraviolet maximum[18] at 251 mμ (ε 9,500).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.31.

The aqueous phase from the reaction mixture was neutralized with hydrochloric acid, saturated with sodium bicarbonate and extracted with ether. After the ethereal extract had been dried over magnesium sulfate and concentrated, crystallization of the residue from petroleum ether afforded **2-hydroxy-3,5,5-trimethyl-2-cyclohexenone (18b)**, m.p. 91–92°, yield 3.5 g. (10%), which was identified

by comparison with an authentic sample,[8] m.p. 91–92° [lit.[8] 91–92°].

The remaining aqueous phase from the reaction mixture was acidified and extracted with ether. The ethereal extract was washed with water and dried over magnesium sulfate and concentrated. Crystallization of the residue from a benzene–hexane mixture afforded 5.65 g. (14.5%) of a mixture of the epimeric hydroxy acids **19b** and **20b**, m.p. 93–103°. Esterification of a portion of this acid mixture with diazomethane followed by gas chromatographic[16] analysis of the ester mixture indicated the presence of 88% of the *cis*-hydroxy ester **19a** and 12% of the *trans*-hydroxy ester **20a**.

A 23.27-g. (0.135 mole) sample of the crude mixture of carboxylic acids from a comparable experiment was esterified by reaction in ether solution with excess diazomethane (0.159 mole). The ethereal solution was washed successively with aqueous sodium bicarbonate and water, dried over magnesium sulfate and distilled to separate 17.77 g. of the mixture of hydroxy esters **19a** and **20a**, b.p. 118–124° (8 mm.), $n^{29}D$ 1.4524–1.4539. From the higher boiling fractions which were richer in the *trans*-isomer, the pure **methyl 3,5,5-trimethyl-*trans*-3-hydroxycyclopentanecarboxylate (20a)** was collected by gas chromatography and further purified by distillation. The *trans*-hydroxy ester, b.p. 123–124° (8 mm.), has infrared absorption[17] at 3630 (unassoc. O—H), 3540 (broad, assoc. O—H) and 1732 cm.$^{-1}$ (ester C=O) with no significant ultraviolet absorption[18] (ϵ 150 at 211 mμ).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.44; H, 9.72.

The *cis*-hydroxy ester **19a** collected from the chromatogram was shown to be identical with the subsequently described sample by comparison of the retention times and infrared spectra of the two samples.

A solution of 4.8 g. (0.028 mole) of the acid mixture in 150 ml. of toluene was refluxed for 59 hr. with continuous removal of water. The resulting solution was washed with aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated to leave 1.75 g. (40.6%] of the crude **lactone of 3,5,5 - trimethyl - *cis* - 3 - hydroxycyclopentanecarboxylic acid (21)**, m.p. 53–57°. Recrystallization from petroleum ether followed by sublimation (40° at 0.2 mm.) afforded the pure lactone, m.p. 57–58°, which has infrared absorption[17] at 1780 cm.$^{-1}$ (γ-lactone C=O, band appears as a doublet at 1774 and 1790 cm.$^{-1}$ in a 3% solution)[26] with an ultraviolet maximum[22] at 215 mμ (ϵ 140).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.85; H, 9.24.

Acidification of the bicarbonate extract obtained in the lactone preparation followed by the appropriate manipulations afforded 1.98 g. (41.3% recovery) of the mixture of hydroxy acids, m.p. 92–97°.

3,5,5 - Trimethyl - *cis* - 3 - hydroxycyclopentanecarboxylic Acid (19b).—A solution of 0.235 g. (0.00152 mole) of the lactone **21** in a mixture of 1 ml. of methanol and 2.5 ml. (0.00304 mole) of 5% aqueous sodium hydroxide was stirred at room temperature for 4 hr. and then extracted with ether and acidified. The usual work-up procedure afforded 0.220 g. (84.0%) of the pure acid as white needles, m.p. 116–118°, from a benzene–hexane mixture. This acid, which was also isolated by a series of fractional crystallizations of the crude acid mixture obtained from isophorone oxide, has infrared absorption[21] at 3400 and 3000 cm.$^{-1}$ (broad, assoc. O—H) and 1700 cm.$^{-1}$ (carboxyl C=O) with no significant ultraviolet absorption[18] (ϵ 159 at 210 mμ).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.76; H, 9.23.

Reaction of a 1.3-g. (0.00755 mole) sample of this acid with excess diazomethane in ether solution followed by the usual workup procedure afforded 0.7686 g. (58.5%) of **methyl 3,5,5-trimethyl-*cis*-3-hydroxycyclopentanecarboxylate (19a)** as a colorless liquid, b.p. 118–119° (8 mm.). The product, which exhibits only one peak on gas chromatography,[16] has infrared[17] bands at 3480 (O—H) and 1715 cm.$^{-1}$ with a shoulder at 1730 cm.$^{-1}$ (ester C=O) and no significant ultraviolet absorption[18] (ϵ 84 at 212 mμ).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.51; H, 9.77.

(26) For an analogous double carbonyl band see L. L. McCoy and A. Zagalo, *J. Org. Chem.*, **25**, 824 (1960).

A solution of 0.221 g. (0.00129 mole) of the *cis*-hydroxy ester **19a** in 12.5 ml. (0.00545 mole) of 0.436 *M* methanolic sodium methoxide was refluxed for 4 hr. and then poured onto ice and extracted with ether. The ethereal extract was dried over magnesium sulfate, concentrated and analyzed by gas chromatography.[16] From the mixture composed of the *cis*-hydroxy ester **19a** (73%), the *trans*-hydroxy ester **20a** (23%) and the lactone **21** (4%), a sample of the *trans*-hydroxy ester **20a** was collected and shown to be identical with the sample described previously, by comparison of retention times and infrared spectra. The similar epimerization of a 51-mg. (0.298 mmole) sample of the *trans*-hydroxy ester **20a** in 3 ml. (1.305 mmoles) of 0.435 *M* sodium methoxide in boiling methanol for 4 hr. yielded a mixture composed of the *trans*-hydroxy ester **20a** (85%), the *cis*-hydroxy ester **19a** (15%) and a trace of the lactone **21**.

Reaction of 2-Methoxy-3,5,5-trimethyl-2-cyclohexenone (18a) with 2,4-Dinitrophenylhydrazine.—A solution of 0.84 g. (0.0050 mole) of the enol ether, 1.39 g. (0.0070 mole) of 2,4-dinitrophenylhydrazine and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 10 min. and allowed to cool. The solid which separated was chromatographed on 80 g. of Merck acid-washed alumina. The first fraction, eluted with petroleum ether–ether mixtures, crystallized from ethanol as orange needles, m.p. 170–173.5°, yield 0.53 g. (30.5%). Recrystallization afforded the pure **mono-2,4-dinitrophenylhydrazone m.p. 173–174°**, which has ultraviolet maxima[19] at 259 mμ (ϵ 16,100) and 387 mμ (ϵ 29,700).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 54.86; H, 5.73; N, 16.03.

The second fraction, eluted from the chromatogram with ether, crystallized from an ethanol–ethyl acetate mixture as red-orange plates, m.p. 190–192.5°, yield 1.03 g. (58.4%). An additional crystallization gave the pure **mono-2,4-dinitrophenylhydrazone, m.p. 191.5–193°**, which exhibits ultraviolet maxima[19] at 261 mμ (ϵ 16,600) and 385 mμ (ϵ 28,200).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.15; H, 5.73; N, 16.27.

The third fraction, eluted with ether–ethyl acetate mixtures, crystallized from an ethanol–ethyl acetate mixture as red-orange prisms of the **bis-2,4-dinitrophenylhydrazone of 3,5,5-trimethyl-1,2-cyclohexanedione, m.p. 223–225° dec.**, yield 14 mg. (0.5%). An authentic sample of this derivative was obtained by reaction of 36 mg. (0.23 mmole) of the enolic α-diketone **18b** with excess 2,4-dinitrophenylhydrazine in an ethanol solution containing 2 drops of concentrated hydrochloric acid. The pure bis-2,4-dinitrophenylhydrazone crystallized from an ethanol–ethyl acetate mixture as red prisms, m.p. 224–226° dec., yield 12 mg. (10%).

Anal. Calcd. for $C_{21}H_{22}N_8O_8$: C, 49.03; H, 4.31; N, 21.78. Found: C, 49.22; H, 4.42; N, 21.68.

In order to establish that the two mono-2,4-dinitrophenylhydrazones were geometrical rather than structural isomers a solution of 0.20 g. (0.58 mmole) of the higher-melting mono-2,4-dinitrophenylhydrazone (m.p. 191.5–193°) 0.30 g. (1.51 mmoles) of 2,4-dinitrophenylhydrazine and 5 ml. of concentrated hydrochloric acid in 30 ml. of ethanol was refluxed for 30 min. and then worked-up by chromatography of the crude product as previously described. The two mono-2,4-dinitrophenylhydrazones, m.p. 172.5–174°, yield 38 mg. (19%), and m.p. 191.5–193°, yield 58 mg. (29%), were isolated as well as the bis-2,4-dinitrophenylhydrazone, m.p. 223–225° dec., yield 30 mg. (10%).

Product Analyses in the Reaction of Isophorone Oxide (12) with Bases.—The product analyses under the various reaction conditions outlined in Table II were obtained from reactions run as previously described. The crude reaction mixture was separated into a neutral fraction analyzed by gas chromatography,[16,20] an acidic fraction insoluble in aqueous sodium bicarbonate from which the enolic α-diketone **18b** was isolated and an acidic fraction which was soluble in aqueous sodium bicarbonate. The mixture of dicarboxylic acids from the last fraction was esterified with diazomethane and the ester mixture was analyzed by gas chromatography.[16]

***cis*- and *trans*-Methyl 2,4,4-Trimethyl-1-hydroxycyclopentanecarboxylate (22 and 23).**—A mixture of 25.54 g. (0.166 mole) of the enolic α-diketone **18b**, 87.5 g. (1.32

TABLE II

REACTION OF ISOPHORONE OXIDE WITH BASES

Conditions	Recovd. isophorone oxide (6), %	Enol ether 18a, %	α-Diketone 18b, %	*cis*-Hydroxy acid 19b, %	*trans*-Hydroxy acid 20b, %	Total, %
KOH (2 eq.), MeOH, refl. 80 min.	1	81	9	3	3	97
NaOMe (4 eq.), MeOH, 25°, 72 hr.	..	85	4	..	..	89
KOH (2 eq.), MeOH–H_2O (1:2), refl. 90 min.	..	46	10	12	2	70
KOH (4 eq.), H_2O, 0°, 72 hr.	73	..	15	4	1	93

moles) of 85% potassium hydroxide and 175 ml. of water was heated under reflux in a copper pot for 26 hr. and then poured into 200 ml. of ice-water and neutralized with hydrochloric acid. The mixture was saturated with sodium bicarbonate and extracted with ether. By appropriate manipulations 3.4 g. (13%) of the starting α-diketone, m.p. 90–91°, was recovered from this ethereal extract. The original aqueous phase was acidified with hydrochloric acid and extracted with ether. After this extract had been dried over magnesium sulfate and concentrated, crystallization of the residue from hexane afforded a mixture of the crystalline α-hydroxy acids, m.p. 80–92° (lit.[9] 88–89°), yield 19.4 g. (68.3%).

Esterification of a 19.4-g. (0.113 mole) sample of these α-hydroxy acids with excess diazomethane afforded a 11.35-g. (54%) mixture of α-hydroxy esters, b.p. 45–54° (0.5 mm.), $n^{27}D$ 1.3415–1.3425, which was separated by gas chromatography.[20] Both isomers have infrared absorption[17] at 3550 (O—H) and at 1725 cm.$^{-1}$ (ester C=O) and no significant absorption in the ultraviolet[18] (isomer A, ε 114 at 213 mμ; isomer B, ε 116 at 213 mμ).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found for isomer A: C, 64.53; H, 9.65. Found for isomer B: C, 64.44; H, 9.77.

Deuterium Exchange Experiments. A. Exchange Catalyzed by Triethylamine.—A solution of 0.5331 g. (0.00316 mole) of piperitone oxide, 0.4820 g. (0.00312 mole) of isophorone oxide and 3.7 g. (0.037 mole) of triethylamine in 8.6 g. (0.135 mole) of perdeuterioacetone was heated at 100° in a sealed tube for 48 hr. and then cooled and concentrated. The two oxides were separated from the residue by gas chromatography[20] and purified by distillation through a short-path still under reduced pressure. The recovered isophorone oxide (0.325 g. of 67%) contained the following isotopic species[27,28]: non-deuterated material, 1%; d_1-species, 10%; d_2-species, 89%; d_3-species, <1%. Similarly, the recovered piperitone oxide (0.421 g. or 89%) contained[27,28]: non-deuterated material, 16%; d_1 - species, 84%; d_2-species, <1%. Comparable results were obtained when each of the pure oxides was heated with triethylamine in perdeuterioacetone.

B. Reaction of Piperitone Oxide (1) with Sodium Methoxide in Methanol-d_1.—A solution of 1.0 g. (0.0051 mole) of piperitone oxide in methanolic sodium methoxide prepared from 0.117 g. (0.0051 g.-atom) of sodium and 10 ml. of methanol-d_1 was allowed to stand at 0° for 4 hr. and then poured into 10 ml. of cold water which had been previously saturated with carbon dioxide. The resulting mixture was extracted with ether and the ethereal extract was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The gas chromatogram[16] of the residual neutral oil (0.95 g.) indicated the presence of: (a) the unsaturated ester **11a** (3%), (b) unchanged piperitone oxide (23%), (c) methoxypiperitone **12** (32%), (d) the *trans*-hydroxy ester **10a** (20%) and (e) a peak corresponding in retention time to the components *cis*-hydroxy ester **4a**, lactone **9** and enol ether **8** (22%). Fractions b, d and e were collected from the chromatogram. After the piperitone oxide (fraction b) had been further purified by a short-path distillation under reduced pressure, analysis[27,28] indicated the presence of: non-deuterated material, 52%; d_1-species, 47%; d_2-species, <1%. The *trans*-hydroxy ester **10a** (fraction d), after purification by crystallization, exhibited no infrared absorption attributable to O–D stretching and contained[27,29]: non-deuterated material 11%; d_1-species, 89%. The fraction e was saponified with excess sodium hydroxide in aqueous methanol and the *cis*-hydroxy acid **4b** was isolated and esterified to form the *cis*-hydroxy ester **4a** (0.055 g.) as previously described. The infrared spectrum[17] of the *cis*-hydroxy ester **4a**, purified by collection from a gas chromatography column,[16] indicated the absence of absorption attributable to O–D stretching although the ester was contaminated with some of the lactone **9**. Analysis[27,29] of this *cis*-hydroxy ester fraction indicated the presence of: non-deuterated material, 10%; d_1-species, 89%; d_2-species, 1%.

(27) The deuterium analyses were obtained with a CEC 21-103 C Mass spectrometer equipped with a heated inlet system.

(28) For these deuterium analyses the parent peaks of the partially deuterated products were compared with the parent peaks of the non-deuterated samples.

(29) Since a parent mass peak of sufficient intensity for analysis could not be obtained with these compounds, it was necessary to use a fragment peak resulting from the loss of a unit of mass 28 (ethylene or, possibly, carbon monoxide) from the original molecule. Although the entire mass spectrum in each case is consistent with the analyses cited, the results of the analysis cannot be assumed to be more accurate than ±5%.

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The Stereochemistry of the Favorskiĭ Rearrangement

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A reinvestigation of the Favorskiĭ rearrangement of 1-chloro-*cis*-1-acetyl-2-methylcyclohexane (**10**) in the presence of sodium methoxide has demonstrated that the rearrangement is essentially stereospecific (forming the ester **23**) in the non-polar solvent 1,2-dimethoxyethane, but becomes non-stereospecific (forming both esters **23** and **26**) in the polar solvent methanol.

Studies of the Favorskiĭ rearrangement of α-halo ketones[2] **1** have demonstrated the intervention of a symmetrical intermediate[3–5] which has been formulated as a cyclopropanone **2**[5] or as a

(1) This author is indebted to the Solvay Process Division of the Allied Chemical Corporation for a predoctoral fellowship held during the period 1959–1961.

(2) For a recent comprehensive review see A. S. Kende, *Org. Reactions*, **11**, 261 (1960).

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