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%.

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[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%.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.

The Stereochemistry of the Favorskiĭ Rearrangement

BY HERBERT O. HOUSE AND W. FRANKLIN GILMORE[1]

RECEIVED APRIL 14, 1961

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

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[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).

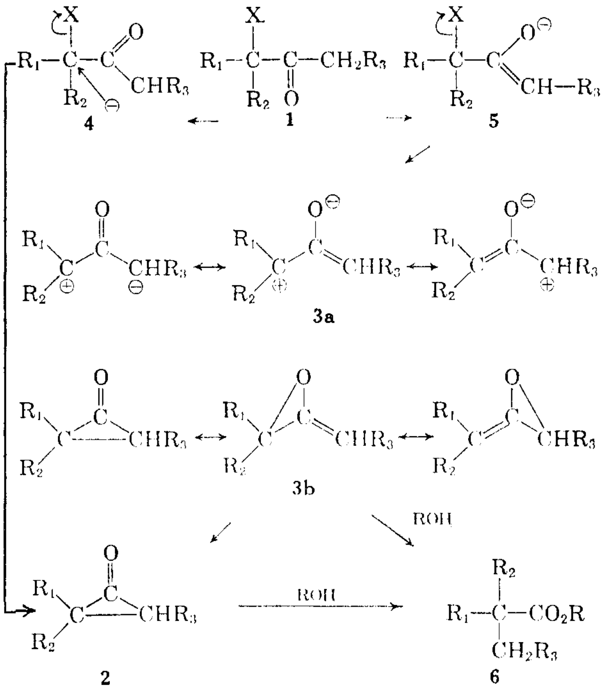
[3] W. D. McPhee and E. Klingsberg, *J. Am. Chem. Soc.*, **66**, 1132 (1944).

[4] (a) J. G. Aston and J. D. Newkirk, *ibid.*, **73**, 3900 (1951); (b) A. A. Sacks and J. G. Aston, *ibid.*, **73**, 3902 (1951).

[5] (a) R. B. Loftfield, *ibid.*, **72**, 632 (1950); (b) **73**, 4707 (1951); (c) R. B. Loftfield and L. Schaad, *ibid.*, **76**, 35 (1954).

resonance hybrid including the structures **3**.[4,6] The difference between the two formulations **2** and **3** for the intermediate may be more precisely defined by considering the manner in which the halide ion X^- is lost. The direct displacement of the halide ion by the enolate anion as in structure **4** leads to the cyclopropanone **2** whereas the rate-determining ionization of the enolate as in structure **5** or a concerted proton abstraction and ionization produces the intermediate **3** which may then either enjoy an appreciable lifetime or be converted immediately to the cyclopropanone **2**. Burr and Dewar[6a] have noted that the geometry of the enolate anion is especially unfavorable for the displacement represented in structure **4** and therefore favored the ionization process **5** leading to the zwitterion **3** for which these authors predicted substantial resonance stabilization. It should be noted that a rate-determining ionization comparable to **5** has been suggested[7] for the reaction of salts of α-halocarboxylic acids with nucleophiles. The ionization process **5** may be facilitated by overlap of the developing p-orbital with the π-orbital of the enolate anion without requiring the localization of negative charge or distortion of the geometry of the enolate anion implied in the direct displacement **4**.[8]

A differentiation between these mechanistic possibilities becomes important to organic chemists if the intermediate **3** should have a sufficient lifetime to permit further reaction[9] to occur from either side of the planar intermediate **3**.[10] In this event



the configuration of the final product **6** need bear no predictable relationship to the configuration of the starting material **1**. On the other hand, the direct displacement process **4** clearly demands inversion of the configuration of the α-carbon atom in the α-halo ketone **1**. Two previous investigations are pertinent to this question. From the reaction of the 17α-bromo-3α-acetoxypregnane-11,20-dione (partial formula **7**) with sodium methoxide in methanol both stereoisomeric esters **8** and **9** were isolated.[11] However, the reaction of the chloro ketone **10** with sodium benzyloxide in ether was reported to yield only the ester **11**.[12] Similar inversion of configuration was noted in the comparable conversion of the chloro ketone **12** to the ester **13**.[12] The lack of stereospecificity in the rearrangement of the bromo ketone **7** was attributed to the formation of the isomeric bromo ketone **14** prior to rearrangement.[11] However, no compelling evidence was offered to support this suggestion. Another possible explanation[12] for the differing stereochemical outcome of these two investigations involves the assumption that a zwitterionic intermediate comparable to **3** was involved in the rearrangement of the bromo ketone **7** but not the chloro ketones **10** and **12**. Whether this change in mechanism should be attributed to a greater facility for ionization of a carbon–bromine bond as compared to a carbon–chlorine bond or to the change from a polar (methanol), homogeneous reaction medium to a non-polar (ether), heterogeneous reaction medium could not be determined from the published data. Our subsequent finding that application of the Favorskiĭ rearrangement to

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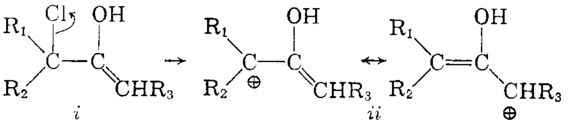
(6) (a) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); (b) A. W. Fort, 138th Meeting of the American Chemical Society, New York, N. Y., September 11–16, 1960, Abstracts of Papers, p. 45-P; (c) A. W. Fort, 140th Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961; Abstracts of Papers, p. 19-Q. The intermediate **3b**, termed a dehydroketone by this author, was preferred to the closely related polarized structures **3a** on the grounds that no charge separation was required. If the author intends the structures **3b** to be planar, then structures **3a** and **3b** may all be considered as contributors to the same resonance hybrid.

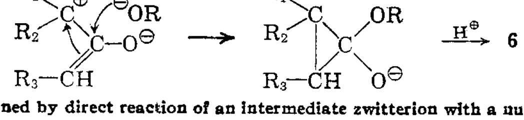
(7) (a) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 841 (1948); (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 270.

(8) A related possibility, the rate-determining ionization i of the enol form of the ketone to the conjugate acid ii of the intermediate **3a**, is difficult to reconcile with the fact (ref. 6b and 6c) that ionization of α-halo ketones occurs readily in the presence of bases but not acids.



However, this possibility cannot be excluded by the data presently available.

(9) Although Burr and Dewar (ref. 6) envisioned the immediate collapse of the zwitterion **3** to the cyclopropanone **2** followed by subsequent reaction with other species in the reaction mixture, we do not believe the evidence at hand excludes the possibility that the zwitterion **3** reacts directly with a nucleophile (as in the accompanying equation) to form Favorskiĭ products (*e.g.*, **6**). As noted in the accompanying paper (ref. 13), certain abnormal displacement products isolated from α-halo ketones and from piperitone oxide are easily explained by direct reaction of an intermediate zwitterion with a nucleophile.

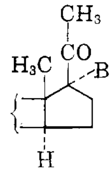


(10) In the case of salts of α-halocarboxylic acids, the claimed [W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1208 (1937)] high degree of retention of configuration suggests that a zwitterionic intermediate, if involved at all, must be converted to an α-lactone very rapidly.

(11) N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(12) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960).

piperitone oxide (**15**) in a non-polar medium was stereospecific (forming derivatives of **16**) but became non-stereospecific in a polar medium (forming derivatives of both **16** and **17**)[13] suggested that the stereochemical outcome of Favorskiĭ rearrangements is dependent on the polarity of the reaction medium. In this paper we report a reinvestigation of the rearrangement of the chloro ketone **10** which establishes the validity of this suggestion.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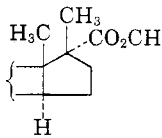
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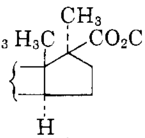
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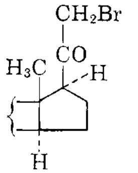
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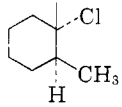
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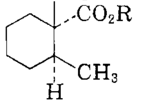
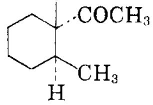

11, R = $C_6H_5CH_2$
21, R = H
23, R = CH_3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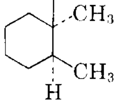
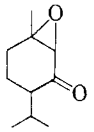

13, R = $C_6H_5CH_2$
24, R = H
26, R = CH_3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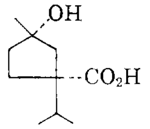
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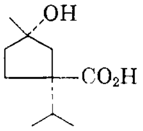
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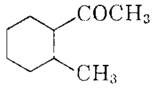
Of the two preparative routes reported[12,14] to yield the pure chloro ketone **10**, we first investigated the direct chlorination of 1-acetyl-2-methylcyclohexane **18** with sulfuryl chloride.[12] In our hands the monochlorinated product from this reaction not only was not the pure chloro ketone **10** but was a gross mixture containing the chloro ketones **10**, **12** and **19**. From this reaction the only product which could be isolated in useful quantity was one of the stereoisomers (presumably the more stable *trans* isomer) of the chloromethyl ketone **19**. The second preparative route *via* the glycidonitrile **20** was much more satisfactory. Although the chloro ketone **10** obtained was not free from the stereoisomer **12**, it was the predominant component and further purification readily could be achieved. The acid **21** was obtained by hydrogenation of the Diels–Alder adduct **22** as previously described.[12] Both acids **21** and **22**, previously handled as crude intermediates, were purified in this study. The acid **21** was further characterized as its previously described[12] anilide and as its methyl ester **23**. The second required acid **24** was obtained by reaction of a mixture of the stereoisomeric 1,2-dimethylcyclohexanols **25** with a mixture of formic acid and concentrated sulfuric acid.[15] Under these conditions, the predominant acidic product was **24** accompanied by smaller amounts of the acid **21** and minor components which were not further investigated. That the predominant formation of the acid **24** rather than **21** was the result of kinetically controlled[16] carbonylation could be demonstrated by treating a mixture rich in the acid **24** with a mixture of formic acid and fuming sulfuric acid.[16a] Under these conditions, an appreciable fraction of the acid **24** was isomerized to the acid **21**.[17] The acid **24** was further characterized as its methyl ester **26** and as its previously described[12] anilide.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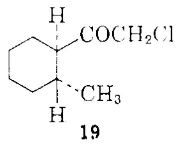
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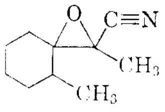
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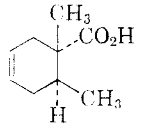
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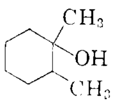
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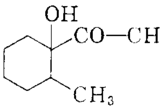
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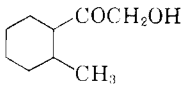
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Reaction of the chloro ketone **10** with a solution of sodium methoxide in methanol yielded a mixture of methyl esters containing the product **23** formed with inversion at C_1 (40.5%) and the product **26** formed with retention at C_1 (51.5%). Reaction of the chloro ketone **10** with a suspension of sodium methoxide in 1,2-dimethoxyethane produced a mixture of esters **23** and **26** in which the product **23** formed with inversion at C_1 was the major constituent (94.6%). To ensure that the change in stereochemical outcome was the result of the change from the relatively non-polar solvent 1,2-dimethoxyethane (dielectric constant at 20°, 5.50[18a]) to the relatively polar solvent methanol (dielectric constant at 25°, 32.6[18b]) rather than to a change to a homogeneous reaction, the reaction was also run with sodium methoxide in 1,2-dimethoxyethane containing a small amount of methanol to effect homogeneity. Under these conditions the ester **23** formed with inversion at C_1 was still the predominant product (84% of the ester mixture).

While the foregoing data establish that the stereochemical outcome of the Favorskiĭ rearrangement of the chloro ketone **10** is dependent on the polarity of the reaction medium, the possibility exists that this dependence should be attributed to the isom-

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[13] H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972 (1961).

[14] G. Stork, W. S. Worrall and J. J. Pappas, *ibid.*, **82**, 4315 (1960).

[15] Although this reaction has been described previously [H. Koch and W. Haaf, *Ann.*, **618**, 251 (1958)], the characterization of the products was incomplete.

[16] (a) R. E. Pincock, E. Grigat and P. D. Bartlett, *J. Am. Chem. Soc.*, **81**, 6332 (1959); (b) G. Stork and M. Bersohn, *ibid.*, **82**, 1261 (1960).

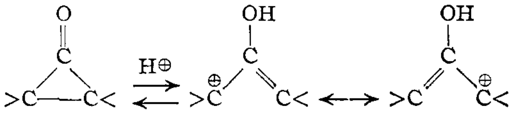
[17] Although our studies were not designed to determine the position of equilibrium between the acids **21** and **24** (or their conjugate acids), it is apparent that either the kinetically favored or thermodyamically favored product may be formed by varying reaction conditions in the 1,2-disubstituted cyclohexane series as was found in the decalin system (ref. 16a). A related reaction (ref. 16b) utilizing more vigorous conditions was reported to yield the thermodynamically favored 1,2-disubstituted cyclohexane.

[18] (a) J. L. Down, J. Lewis, B. Moore and G. Wilkinson, *J. Chem. Soc.*, 3767 (1959); (b) A. A. Maryott and E. R. Smith, "Tables of Dielectric Constants of Pure Liquids," Natl. Bur. Standards Circ. 514, 1951, p. 5.

erization of the chloro ketone **10** to the chloromethyl ketone **19** prior to rearrangement as suggested by Wendler and co-workers.[11] Although a rigorous disproof of this idea would appear to be exceedingly difficult, we believe the following observations render this mode of reaction highly improbable. From a reaction of the chloro ketone **10** with methanolic sodium methoxide carried to only partial completion we were unable to detect the presence of either of the isomeric chloro ketones **12** or **19**. Since qualitative studies of the reaction of mixtures of the chloroketones **10** and **12** with methanolic sodium methoxide indicated that these two chloro ketones react at comparable rates, this observation excludes the possibility that the chloro ketone **10** is isomerizing to **12** prior to rearrangement. However, the failure to detect the chloromethyl ketone **19** after partial reaction of the chloro ketone **10** is of limited value since it was apparent from qualitative observations that methanolic sodium methoxide reacted more rapidly with the chloromethyl ketone **19** than with the chloro ketone **10**. The reaction of the chloro ketone **10** with methanolic sodium methoxide produced, in addition to the esters **23** and **26**, a small amount (5.8%) of a third volatile component **A**. Although we were unable to obtain a sufficient quantity for complete characterization, the infrared spectrum (see Experimental) of the material **A** suggested it was one of the stereoisomers of structure **27**. The corresponding reaction with the chloromethyl ketone **19** produced, besides the two esters **23** (31.6%) and **26** (30.2%), a minor component **B** in 8% yield. Although the quantity of this component available to us also did not permit complete characterization, the infrared spectrum (see Experimental) of the material **B** suggested that it may have the structure **28**. Of special significance was the fact that we were unable to detect any of component **A** in the reaction mixture derived from the chloromethyl ketone **19** or any of the component **B** in the reaction mixture derived from the chloro ketone **10**.

If one accepts these observations as satisfactory evidence that no significant isomerization of chloro ketone **10** to chloro ketone **19** is occurring in the rearrangements studied here, it then follows that the rearrangement itself is non-stereospecific in polar media. Whether the polar medium facilitates the ionization process **5** forming an intermediate such as **3** or effects the interconversion of two stereoisomeric cyclopropanone intermediates **29** by favoring an equilibrium with a planar intermediate such as **3** or its conjugate acid **30**[19] cannot be determined from the data presently available. Other studies[6b,c,13] suggest that in the absence of high concentrations of strong nucleophiles such as metal alkoxides, the reaction of the intermediate **3** or **30** with the solvent to form an α-substituted ketone becomes either an important side reaction or the major reaction.

From this study it can be concluded that the stereospecificity found for certain Favorskiĭ rearrangements by Stork and Borowitz[12] cannot be assumed valid under different reaction conditions. Furthermore, it appears most unwise to assume that a Favorskiĭ rearrangement in an unstudied system will be stereospecific irrespective of what reaction conditions are employed.



29 30

Experimental[20]

Chlorination of 1-Acetyl-2-methylcyclohexane (18).—A 112-g. (1.166 moles) sample of 1-methylcyclohexene, b.p. 110–111°, n^{26}D 1.4480 (lit. b.p. 110–111°,[21] $n^{18.5}$D 1.4503[22]), was acetylated by reaction with 223 g. (0.855 mole) of stannic chloride and 90.4 g. (0.886 mole) of acetic anhydride in 100 ml. of carbon disulfide according to a previously described[23] procedure. The mixture of unsaturated ketones, b.p. 60–78° (7 mm.) [lit. 80–90° (12 mm.),[24] 110–115° (16 mm.)[12]] obtained in 57% yield, was hydrogenated over platinum in an ethanol–acetic acid mixture (2:1 by volume). Fractional distillation of the products separated a mixture of the stereoisomeric acetylmethylcyclohexanes **18**, b.p. 82–84° (15 mm.), yield 53%; gas chromatographic analysis[25] of this material indicated the presence of 75% *trans*-1-acetyl-2-methylcyclohexane (**18**),[26] 24% of the *cis*-methyl ketone **18**[26] and 1% of other components. To a solution of 7.0 g. (0.049 mole) of this mixture of ketones **18** in 60 ml. of carbon disulfide[27] was added, dropwise and with stirring over a 7-hr. period, a solution of 6.60 g. (0.0486 mole) of freshly-distilled sulfuryl chloride in 10 ml. of carbon disulfide. A slow stream of hydrogen chloride was passed through the reaction mixture throughout the reaction. After the solvent had been removed under reduced pressure, fractional distillation separated 5.41 g. of material boiling in the range 60–109° (12 mm.), n^{26}D 1.4561–1.4782. From gas chromatographic analysis[25] of the fractions the following yields could be calculated: 3% **1-chloro-*trans*-1-acetyl-2-methylcyclohexane** (**12**), 13% **1-chloro-*cis*-1-acetyl-2-methylcyclohexane** (**10**), 10% ***trans*-1-chloroacetyl-2-methylcyclohexane** (**19**). The infrared spectra[28] of the tertiary chloro ketones **10** and **12**, collected from the chromatograph, are identical with the spectra of

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[19] The possibility of the interconversion of the cation **30** and a cyclopropanone **29** is supported by the occurrence of a rearrangement resembling a Favorskiĭ rearrangement when an α-amino ketone is treated with nitrous acid [O. E. Edwards and M. Lesage, *Chemistry & Industry*, 1107 (1960)].

[20] 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.

[21] W. A. Mosher, *J. Am. Chem. Soc.*, **62**, 52 (1940).

[22] W. N. Haworth, *J. Chem. Soc.*, 1246 (1913).

[23] E. E. Royals and C. M. Hendry, *J. Org. Chem.*, **15**, 1147 (1950).

[24] L. Ruzicka, D. R. Koolhaas and A. H. Wind, *Helv. Chim. Acta*, **14**, 1161 (1931).

[25] A column packed with Silicone Fluid No. 550 suspended on ground firebrick was employed.

[26] Samples of the two methyl ketones **18** were collected from the chromatograph. The infrared spectrum (CCl_4) of each material has a carbonyl band at 1707 cm.$^{-1}$. The refractive index of the more abundant *trans* isomer was n^{26}D 1.4465. The reported [R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950)] properties of the two stereoisomeric ketones are: *cis* isomer, n^{25}D 1.4532, b.p. 67–68° (10 mm.); *trans* isomer, n^{25}D 1.4464, b.p. 64–65° (10 mm.).

[27] Although this chlorination procedure [ref. 12 and E. W. Warnoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953)] originally used carbon tetrachloride as a reaction solvent, we found the use of carbon disulfide to be definitely superior in this case. In this chlorination the use of carbon tetrachloride led to a deeply colored crude product which contained even less of the desired chloro ketones **10** and **12** and an even poorer yield of monochlorinated products.

[28] Determined in carbon tetrachloride solution.

subsequently described samples. A sample of the chloromethyl ketone **19**, collected from the chromatograph, was redistilled to afford the pure material, b.p. 99–102° (13 mm.), n^{25}D 1.4758, which has infrared absorption[28] at 1734 and 1713 cm.$^{-1}$ (two conformations of an α-chloro ketone) with no band at 1355 cm.$^{-1}$ (CH_3–CO–) as is present in the methyl ketones **10**, **12** and **18**. The material exhibits an ultraviolet maximum[29] at 281 mμ (ϵ 53) with n.m.r. absorption (60 mc.) at 6.03$^{\tau}$ (Cl–CH_2–CO–, singlet with an area corresponding to two protons) with a doublet (J = 7 c.p.s.) at 9.17 and 9.28$^{\tau}$ (CH_3–CH<, the area corresponds to three protons) and broad, partially resolved absorption in the region 7.3 to 9.1$^{\tau}$ with an area corresponding to ten protons.

Anal. Calcd. for $C_9H_{15}ClO$: C, 61.88; H, 8.66. Found: C, 61.63; H, 8.72.

1-Chloro-*cis*-1-acetyl-2-methylcyclohexane (10).—A 10.3-g. sample of the glycidonitrile **20**, b.p. 85–88° (3.2 mm.), n^{28}D 1.4610 [lit.[14] b.p. 90–92° (4.5 mm.), n^{25}D 1.4621], was prepared from 2-methylcyclohexanone as previously described[14] and then converted to crude chloro ketone (yield 9.9 g.) by the published procedure.[14] Gas chromatographic analysis[30] of this crude product indicated the presence of 82% of the *cis*-chloro ketone **10**, 9% of the *trans*-chloro ketone **12** and 9% of other components. A solution of this crude product in petroleum ether, when cooled in a Dry Ice–acetone-bath, deposited the *cis*-chloro ketone **10** as a low-melting crystalline solid. Distillation of this material afforded 5.16 g. (47.5%) of the *cis*-chloro ketone **10** as fractions boiling at 85–87° (11 mm.), nD^{30} 1.4731–1.4738. All of these fractions contained more than 98% of the desired chloro ketone **10**. The purest fraction (no impurities were detected by gas chromatography, n^{30}D 1.4738) had a melting point of 22–23° and has infrared absorption[28] at 1717 (C=O), at 1385 ($CH_3—\overset{|}{\underset{|}{C}}—$) and at 1355 cm.$^{-1}$ (CH_3—CO—) with an ultraviolet maximum[29] at 294 mμ (ϵ 39). The n.m.r. spectrum (60 mc.) of the material has a peak at 7.80$^{\tau}$ (singlet, CH_3–CO) and a doublet (J = 7 c.p.s.) at 9.05 and 9.17$^{\tau}$ (CH_3–CH<) with broad, partially resolved absorption in the region 7.8 to 8.6$^{\tau}$.

The mother liquor from the above crystallization was concentrated and distilled under reduced pressure to separate 4.5 g. of a mixture of the chloro ketones **10** and **12** and other impurities from which a sample of the *trans*-chloro ketone **12** was isolated by gas chromatography. The material exhibits infrared absorption[28] at 1711 (C=O), at 1380 ($CH_3—\overset{|}{\underset{|}{C}}—$) and at 1355 cm.$^{-1}$ (CH_3—CO—). The spectrum of this product **12** differs from the spectrum of the *cis* isomer **10** in the shapes and relative intensities of bands found in the fingerprint region. The physical constants reported for the two isomeric chloro ketones are: *cis* isomer **10**, b.p. 57–60° (1.2 mm.),[14] 88–95° (14 mm.),[12] $n^{24.5}$D 1.4707,[12] $n^{28.5}$D 1.4731[14]; *trans* isomer **12**, b.p. 85–87° (16 mm.),[12] $n^{24.5}$D 1.4707.[12]

1-Methyl-*trans*-2-methyl-4-cyclohexenecarboxylic Acid (22).—A solution of 4.5 g. (0.045 mole) of tiglic acid, 25 ml. (*ca.* 0.28 mole) of butadiene and a small amount of hydroquinone in 50 ml. of toluene was heated to 200° in an autoclave with stirring for 78 hr. After the reaction mixture had been extracted with 10% aqueous sodium hydroxide, acidification of the aqueous alkaline solution followed by extraction with ether produced a solution of the acid components which was dried over magnesium sulfate, concentrated and fractionally distilled. The recovered tiglic acid, b.p. 88–89° (12 mm.), amounted to 1.10 g. (24%) and the crude adduct, b.p. 133–138° (12 mm.), m.p. 56–59° (which contained 3% of tiglic acid)[25] amounted to 2.94 g. (42%). The acid **22** collected from the gas chromatograph[25] was sublimed (45° at 0.03 mm.) to separate the pure crystalline acid, m.p. 63–65°, which exhibits infrared absorption[31] at 2950 (broad, assoc. O—H), at 1695 (broad, carboxyl C=O) and at 1655 cm.$^{-1}$ (weak, C=C) and end absorption (ϵ 430 at 210 mμ) in the ultraviolet.[29]

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.88; H, 9.31.

1-Methyl-*trans*-2-methylcyclohexanecarboxylic Acid (21).—A solution of 2.52 g. (0.0163 mole) of the unsaturated acid **22** in 50 ml. of ethyl acetate was hydrogenated over 0.1 g. of platinum catalyst at 25° and atmospheric pressure. After 1.25 hr. the uptake of hydrogen (415 ml. or 1.02 equiv.) ceased. The reaction mixture[32] was filtered, concentrated and distilled to separate 2.40 g. (94%) of the crude acid, b.p. 130–132° (8 mm.) [lit.[12] 110–120° (8 mm.)], m.p. 44–55°. A sample of the *trans*-acid **21** collected from the gas chromatograph[25] was sublimed (50° at 0.03 mm.) to separate the pure acid, m.p. 63–65°, which has infrared absorption[31] at 2950 (broad, assoc. O—H) and at 1690 cm.$^{-1}$ (broad, carboxyl C=O) with no significant absorption (ϵ 265 at 210 mμ) in the ultraviolet.[29]

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.98; H, 10.35.

An ethereal solution of 0.52 g. (3.3 mmoles) of the *trans*-acid **21** was treated with excess ethereal diazomethane and then concentrated and distilled to separate 0.40 g. (71%) of the crude ester, b.p. 74–76° (12 mm.), which contained[25] 95% of the *trans*-ester **23** and 4% of the *cis*-ester **26**. A pure sample of the *trans*-ester **23** collected from the chromatograph and redistilled, b.p. 75–76° (12 mm.), n^{25}D 1.4500, has infrared absorption[28] at 1727 cm.$^{-1}$ (ester C=O) with no significant ultraviolet absorption[29] (ϵ 118 at 213 mμ).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.72; H, 10.57.

After reaction of a 100-mg. (0.64 mmole) sample of the *trans*-acid **21** with 0.5 ml. of boiling thionyl chloride for 12 hr., reaction of the crude acid chloride with 119 mg. (1.3 mmoles) of aniline followed by appropriate manipulations separated 126 mg. (85%) of the crude anilide, m.p. 108–112°. Recrystallization from aqueous ethanol afforded 63 mg. (43%) of the **pure anilide** as white needles, m.p. 114–116° (lit.[12] 115.4–116.6°), with infrared absorption[33] at 3310 (assoc. N—H) and 1655 cm.$^{-1}$ (amide C=O) and an ultraviolet maximum[28] at 241 mμ (ϵ 12,900) [lit.[12] 243 mμ (ϵ 17,350)].

1-Methyl-*cis*-methylcyclohexanecarboxylic Acid (24).—To 166.5 ml. of cold (10°), concentrated (96%) sulfuric acid was added, dropwise and with stirring over a period of 4 hr., 60.0 g. (0.468 mole) of a mixture of stereoisomeric 1,2-dimethylcyclohexanols **25** and 101.3 g. (2.2 moles) of formic acid, the two reactants being added simultaneously from two dropping funnels. After addition was complete, the mixture was stirred for 15 min. and then poured onto ice and extracted with ether. Since the reaction was incomplete, the organic extract was again subjected to the same reaction conditions. After an ethereal solution of the resulting organic product had been extracted with aqueous sodium bicarbonate,[34] the bicarbonate extract was acidified and extracted with ether. This ethereal solution was dried over magnesium sulfate, concentrated and distilled to separate 7.4 g. (10.1%) of the crude acids, b.p. 125–135° (11 mm.), n^{26}D 1.4673.[35] The gas chromatogram[25] of this material indicated the presence of 78% of the *cis*-acid **24**, 12% of the *trans*-acid **21** and 10% of an unidentified lower-boiling component.

The original ether solution, remaining after extraction with sodium bicarbonate,[34] was concentrated and distilled to separate an 11.26-g. fraction, b.p. 120–143° (12 mm.), which was dissolved in ether and extracted with sodium hydroxide. After the alkaline extract had been acidified and extracted with ether, the resulting ethereal solution was dried over magnesium sulfate, concentrated and distilled to separate 3.01 g. (4.1%) of an acid fraction, b.p. 126–129° (11 mm.), n^{25}D 1.4672, which contained predominantly the *cis*-acid **24** and a small amount (*ca.* 2%) of a lower-boiling, unidentified component. A 0.100-g. sample of this

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(29) Determined as a solution in 95% ethanol.

(30) A column packed with 20 M Carbowax suspended on ground firebrick was employed.

(31) Determined as a solution in chloroform.

(32) Analysis of this mixture (footnote 25) indicated the presence of 96% of the *trans*-acid **21** and 4% of the *cis*-acid **24**.

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

(34) As the subsequent description will indicate, extraction with sodium bicarbonate does not remove all the *cis*-acid **24** from an ether solution.

(35) From a similar experiment, Koch and Haaf (ref. 15) considered that they obtained three C_9-acids (in 70% yield) with the following physical properties: (1) b.p. 135–136° (20 mm.), m.p. 60–70°, 27% of the mixture, (2) b.p. 140° (20 mm.), n^{20}D 1.4679, 33% of the mixture; and (3) b p. 144° (20 mm.), m.p. 57°, 40% of the mixture. We presume that their mixture contained the same products described here.

acid mixture was esterified with excess diazomethane in the usual way. The resulting crude ester (0.075 g. or 69%) was found to contain the *cis*-ester **26** (93%), the *trans*-ester **23** (4%) and an unidentified component (3%). A sample of the *cis*-ester 26 collected from the chromatograph[30] was shown to be identical with the subsequently described sample by comparison of the infrared spectra of the two samples. The *cis*-acid **24** was collected from the chromatograph[25] of this material and redistilled in a short path still to afford the pure *cis*-acid, $n^{25}\text{D}$ 1.4672. Sublimation (45° at 0.02 mm.) onto a cold surface afforded this acid as a waxy, crystalline solid, m.p. 32–34°, which has infrared absorption[31] at 2950 (broad, assoc. O—H) and 1695 cm.$^{-1}$ (broad, carboxyl C=O) with no significant ultraviolet absorption[29] (ϵ 220 at 211 mμ).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.24; H, 10.47.

A 1.0-g. sample of the mixture of acids obtained by sodium bicarbonate extraction was esterified by reaction with excess diazomethane in ether solution. The crude mixture of esters, 0.81 g. (74%), contained[25] 77% of the *cis*-ester 26, 14% of the *trans*-ester **23** and 9% of an unknown component. Distillation afforded 0.60 g. (55%) of the ester mixture, b.p. 72–73° (13 mm.), $n^{25}\text{D}$ 1.4480–1.4483, from which the *cis*-ester 26 was separated by gas chromatography[25] and redistilled, b.p. 72–73° (13 mm.), $n^{14.5}\text{D}$ 1.4492. The material has infrared absorption[28] at 1727 cm.$^{-1}$ (ester C=O) with no significant ultraviolet absorption[29] (ϵ 115 at 213 mμ).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.62; H, 10.52.

The *trans*-ester **23** also collected from the chromatograph[30] was shown to be identical with the previously described sample by comparison of the infrared spectra of the two samples.

A 0.1825-g. (1.17 mmoles) sample of the *cis*-acid **24** was converted to its anilide as previously described. Two recrystallizations of the crude product, 0.224 g. or 83%, m.p. 83–86°, from aqueous ethanol afforded the pure **anilide**, m.p. 88–89° [lit.[12] 81.4–82.6°], which has infrared absorption[33] at 3320 (assoc. N—H) and 1655 cm.$^{-1}$ (amide C=O) with an ultraviolet maximum[29] at 241 mμ (ϵ 13,100) [lit.[12] 243 mμ (ϵ 17,950)].

A solution of 1.0 g. (6.4 mmoles) of the previously described acid mixture (containing 78% of the *cis*-acid **24**, 12% of the *trans*-acid 21 and 10% of an unidentified component) in 0.5 g. of formic acid was added to a cold (0°) mixture of 2 ml. of concentrated (96%) sulfuric acid and 1 ml. of fuming sulfuric acid (30% sulfur trioxide). After the resulting mixture had been stirred at 0–5° for 1.5 hr., it was poured onto ice and extracted with ether. The ethereal solution was washed with water, dried over magnesium sulfate and concentrated to leave 0.813 g. (81%) of a mixture of acids containing[25] 45% of the *cis*-acid **24**, 45% of the *trans*-acid **21** and 10% of an unidentified component. Esterification of this mixture with excess diazomethane in ether solution produced an ester mixture containing 45% of the *cis*-ester **26**, 46% of the *trans*-ester **23** and 9% of an unidentified component. Samples of the esters **26** and **23** were collected and their infrared spectra were shown to be identical with the spectra of the samples previously described.

Rearrangement of 1-Chloro-*cis*-1-acetyl-2-methylcyclohexane (10). A. In Methanol.—To a solution of sodium methoxide, prepared from 0.658 g. (0.0286 g.-atom) of sodium and 40 ml. of methanol, was added a solution of 1.00 g. (5.73 mmoles) of the pure chloro ketone **10** in 5 ml. of methanol. The resulting solution was stirred at room temperature for 17.5 hr. and then diluted with 50 ml. of water and extracted with ether. The aqueous layer was concentrated under reduced pressure and again extracted with ether. The combined ethereal extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure to leave 0.735 g. (79.5%) of a neutral residue which was distilled under reduced pressure in a short-path still. The distillate, 0.695 g. (75.1%), b.p. 70–77° (12 mm.), $n^{25}\text{D}$ 1.4516, was shown by gas chromatography[25,30] to contain the *cis*-ester 26 (51.5%), the *trans*-ester **23** (40.5%) and a component believed to be **27** (8%), corresponding to yields of 38.7, 30.4 and 5.8%, respectively. Samples of each of the three components were collected and the esters **23** and **26** (collected sample $n^{25}\text{D}$ 1.4482) were identified by comparison of their spectra with the spectra of previously described samples. After appropriate manipulations to isolate and transform any acids formed in this reaction to their methyl esters, we were unable to detect additional quantities of the esters **23** and **26**. The component, believed to have structure **27**, exhibits infrared absorption[28] at 3480 (assoc. O—H), 1700 (C=O), 1380 (CH_3—$\overset{|}{\underset{|}{\text{C}}}$—) and 1360 cm.$^{-1}$ (CH_3—CO).

From a comparable reaction in which a reaction time of 4.5 hr. was employed, the neutral residue (0.822 g. or 89.9%) was found to contain the *cis*-ester **26** (36.6%), the *trans*-ester **23** (27.9%), the component believed to be **27** (7.3%) and the unchanged chloro ketone **10** (28.2%). However, neither the chloro ketone **12** nor the chloromethyl ketone **19** could be detected in the mixture.

B. In 1,2-Dimethoxyethane.—A suspension of sodium methoxide, prepared by the reaction of 0.658 g. (0.0286 g.-atom) of sodium with 3.17 g. (0.0991 mole) of methanol in 40 ml. of boiling 1,2-dimethoxyethane (distilled from sodium hydride immediately prior to use), was cooled to room temperature and treated with a solution of 1.00 g. (0.00573 mole) of the chloro ketone **10** in 5 ml. of 1,2-dimethoxyethane. The resulting mixture was stirred at room temperature for 14.5 hr. and then worked-up as previously described. Distillation of the neutral residue (0.785 g. of 85%) through a short-path still afforded 0.782 g. (84.5%) of an ester mixture, b.p. 75–77° (14 mm.), $n^{26}\text{D}$ 1.4484, which contained[25,30] 94.6% of the *trans*-ester **23** and 5.4% of the *cis*-ester **26**. The acidic fraction from this reaction was esterified with diazomethane to yield an additional 73 mg. of the *trans*-ester **23**. Thus, the total yields of the *trans*-ester **23** and the *cis*-ester **26** were 87.9 and 4.5%, respectively. A sample of the *trans*-ester **23** ($n^{25}\text{D}$ 1.4495) collected from the chromatograph[30] was identified by comparison of its infrared spectrum with the spectrum of the previously described sample.

In a comparable experiment employing the sodium methoxide prepared from 0.0987 g. (0.00429 g.-atom) of sodium and 4 ml. of methanol, the excess methanol was removed by heating the sodium methoxide to 150° at 60 mm. pressure. The resultant sodium methoxide was suspended in 150 ml. of 1,2-dimethoxyethane and then treated with a solution of 0.50 g. (0.0029 mole) of the chloro ketone **10**. After the reaction mixture had been stirred at room temperature for 43 hr. and worked-up in the usual way, the yields of the *trans*-ester **23** and the *cis*-ester 26 were 86.4 and 6.2%, respectively.

In order to obtain an initially homogeneous reaction mixture, a solution of sodium methoxide was prepared by reaction of 0.329 g. (0.0143 g.-atom) of sodium with 5 ml. of methanol. After the solution had been diluted with 40 ml. of 1,2-dimethoxyethane, a solution of 0.50 g. (0.0029 mole) of the chloro ketone 10 in 3 ml. of methanol was added. The initially clear solution was stirred at room temperature for 15 hr. and then worked-up in the usual way. The *trans*-ester 23, the *cis*-ester 26 and an unidentified component were obtained in yields of 68.6, 12.6 and 6.9%, respectively.

Rearrangement of 1-Chloroacetyl-2-methylcyclohexane (19).—To a solution of sodium methoxide, prepared from 0.066 g. (0.0029 g.-atom) of sodium and 4 ml. of methanol, was added 0.100 g. (0.572 mmole) of the chloromethyl ketone **19**. After the reaction mixture had been stirred at room temperature for 7 hr., the usual isolation procedure afforded 0.068 g. (70%) of a neutral residue containing[25,30] the *cis*-ester 26 (43.2%), the *trans*-ester 23 (45.5%) and a component believed to have structure **28** (11.3%) corresponding to yields of 30.2, 31.6 and 8%, respectively. Samples of the esters **23** and **26** were collected[30] and identified by comparison of their infrared spectra with the spectra of authentic samples. The component believed to be **28** was also collected from the chromatograph[30] and has infrared absorption[28] at 3480 (assoc. O—H), at 1710 with a shoulder at 1725 (two conformations of an α-hydroxy ketone C=O) and at 1380 cm.$^{-1}$ (CH_3—$\overset{|}{\underset{|}{\text{C}}}$—) with no absorption at 1355 cm.$^{-1}$ (CH_3—CO).