The Effect of Solvent Change on the Favorskii Rearrangement of α-Halo Ketones[1]

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Received April 1, 1965

The reactions of 2-bromo-2,4-dimethyl-3-pentanone (**1**), 9-chloro-*trans*-1-decalone (**8**), and 9-chloro-*cis*-1-decalone (**9**) with sodium methoxide in either methanol or 1,2-dimethoxyethane have been studied. The acyclic ketone **1** gave primarily hydroxy and methoxy ketones **3–5** in either reaction solvent, whereas both chloro ketones **8** and **9** gave the products **18–22** of stereospecific Favorskii rearrangements in 1,2-dimethoxyethane. Noteworthy is the rearrangement of the *trans* chloro ketone **8** to ester **18**, a *trans*-fused perhydroindan with a bridgehead substituent. In methanol solution, both chloro ketones **8** and **9** yielded α-methoxy ketones **12–16** with partial retention of configuration. This latter result indicates that these methoxy ketones must originate, at least in part, from some intermediate other than the planar dipolar intermediate **17b**.

Studies[3,4] of the Favorskii rearrangement of α-halo ketones have demonstrated that the reaction conditions used often influence both the stereochemical course of the rearrangement and the nature of the products obtained. To obtain good yields of esters in which a stereospecific rearrangement (inversion of configuration at the carbon atom originally bonded to the halogen atom) has occurred, it appears appropriate to use strong bases[3c] in nonpolar, aprotic solvents[4a,c] and to employ α-halo ketones in which the halogen atom may occupy a position coplanar with the carbonyl function.[4b] In this paper we report an examination of the latter two of these generalities in the reactions of sodium methoxide with the bromo ketone **1** and the *cis*- and *trans*-9-chloro-1-decalones **8** and **9**.

The compositions of the product mixtures obtained from the bromo ketone **1** and sodium methioxide in methanol and in 1,2-dimethoxyethane[5] (DME) are summarized in Scheme I on p. 2949. Although the product composition was altered substantially by the change in reaction solvent, the product of Favorskii rearrangement, **2**, was only a minor product in both cases. The β-methoxy ketone **4** is believed to result from the base-catalyzed addition of methanol to the conjugated ketone **6**, the product initially formed in the reaction mixture, whereas the α-hydroxy ketone **5** is believed to arise by hydrolysis of the initially formed epoxy ether **5a**.[3a,6] Consequently, it would appear that the major product **5** in the sodium methoxide–methanol reaction arises by a process which is unrelated to a cyclopropanone intermediate of the type proposed[3a] in Favorskii rearrangements. It is of interest to compare these results with the recently reported[7] products resulting from photolysis of tetramethylcyclobutane-1,3-dione. When this reaction was conducted in methanol or ethanol, the products isolated included the hemiketal of tetramethylcyclopropanone[7b,c]; thermal decomposition of the methoxy hemiketal in methanol yielded the products **2** and **3**,[8] and analogous products were obtained from the ethoxy hemiketal.[7b] Thus, the products **2** and **3** observed in our study may have their origins in cyclopropane intermediates which decompose predominantly by pathways which do not lead to Favorskii rearrangement (*i.e.*, ester **2**).

To augment a previous study[4b] of the reaction of 9-chloro-*trans*-1-decalone (**8**) with methanolic sodium methoxide we wished to study the reaction of the corresponding *cis* isomer **9**. Whereas the *trans* isomer may be expected to exist very largely in the indicated conformation with an axial chlorine atom (favorable to ionization but not internal nucleophilic displacement),[4b] the *cis* isomer is expected to exist as a mobile equilibrium between conformations **9a** (equatorial chlorine atom) and **9b** (axial chlorine atom). Consequently, if the success of a Favorskii rearrangement can be attributed in part of the availability of an appreciable concentration of a conformation (*e.g.*, **9a**) which is geometrically favorable for an intramolecular nucleophilic displacement (as in **9c**) of the α-halogen atom, then the *cis*-chloro ketone **9** would be expected to undergo Favorskii rearrangement more readily than the *trans*-chloro ketone **8**. Apparent support for this idea was found in the reaction of methanolic sodium methoxide with the *trans* isomer **8** to give a mixture of methoxy ketones **12–15** in which no Favorskii product (*i.e.*, esters **18–22**) was detected.[4b] Under the same reaction conditions chloro ketones such as **7** afforded good yields of esters from a nonstereospecific Favorskii rearrangement.[4a,c]

A variety of methods to synthesize the pure *cis*-chloro ketone **9** were examined including chlorination

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(1) This research has been supported by Grant No. GM-08761 from the National Institutes of Health.

(2) (a) Sun Oil Co. Fellow, 1962–1963; (b) National Institutes of Health Predoctoral Fellow, 1963–1965.

(3) (a) A. S. Kende, *Org. Reactions*, **11**, 261 (1960); (b) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960); (c) A. W. Fort, *ibid.*, **84**, 2620, 2625, 4989 (1962); (d) R. C. Cookson and M. J. Nye, *Proc. Chem. Soc.*, 129 (1963); (e) J. M. Conia and J. L. Ripoll, *Bull. soc. chim. France*, 755, 763 (1963); (f) J. M. Conia and J. Salaün, *Tetrahedron Letters*, **No. 18**, 1175 (1963); (g) for the related reactions of α-halo sulfones, see L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4085, 4089, 4383 (1964).

(4) (a) H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972, 3980 (1961); (b) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 164 (1963); (c) A. Gaudemer, J. Parello, A. Skrobek, and B. Tchoubar, *Bull. soc. chim. France*, 2405 (1963).

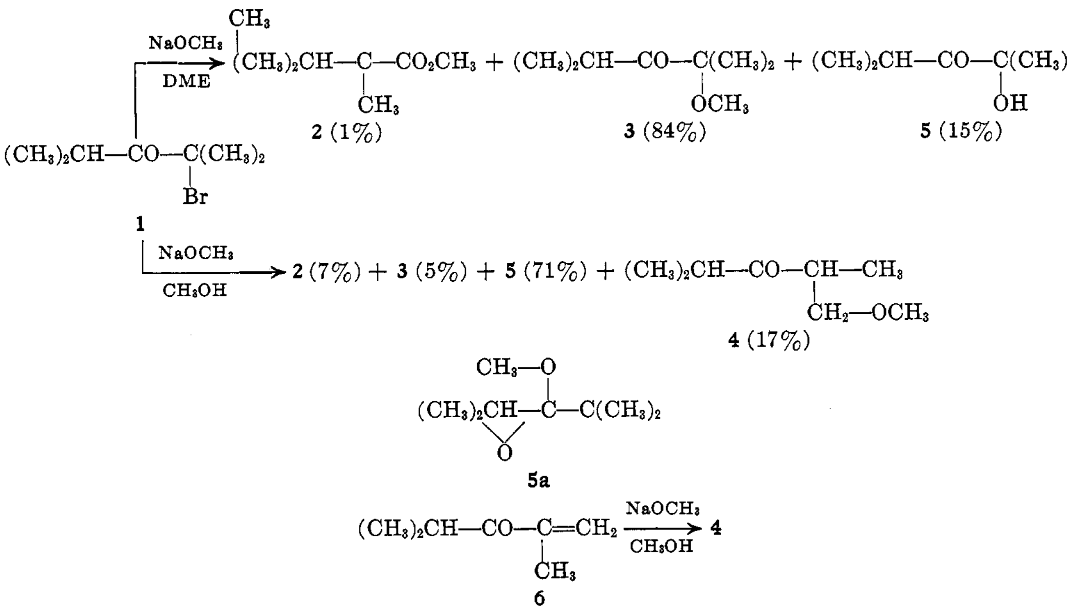
(5) A. A. Sacks and J. G. Aston [*J. Am. Chem. Soc.*, **73**, 3902 (1951)] reported the formation of only the α-methoxy ketone **3** from the bromo ketone **1** and sodium methoxide in ether. These authors obtained poor yields of Favorskii rearrangement products when the bromo ketone **1** was heated with sodium isopropoxide or sodium benzyloxide.

(6) For example, see C. L. Stevens and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1958).

(7) (a) N. J. Turro, G. W. Byers, and P. A. Leermakers, *J. Am. Chem. Soc.*, **86**, 955 (1964); (b) H. G. Richey, J. M. Richey, and D. C. Clagett, *ibid.*, **86**, 3906 (1964); (c) P. A. Leermakers, G. F. Vesley, N. J. Turro, and D. C. Neckers, *ibid.*, **86**, 4213 (1964); (d) I. Haller and R. Srinivasan, *ibid.*, **87**, 1144 (1965); (e) R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *Proc. Chem. Soc.*, 144 (1964); (f) for a related study, see R. C. Cookson and M. J. Nye, *J. Chem. Soc.*, 2009 (1965).

(8) (a) Private communication from Professors P. A. Leermakers and N. J. Turro. These authors found that the methoxy hemiketal reacted with methanolic sodium methoxide to yield a mixture containing the methoxy ketone **3**, the ester **2**, and other products; the ester **2** was the major constituent in this mixture. (b) The attack of a nucleophile at a cyclopropane ring leading to ring opening has been suggested recently by J. Meinwald, J. W. Wheeler, A. A. Nimetz, and J. S. Liu [*J. Org. Chem.*, **30**, 1038 (1965)].

SCHEME I



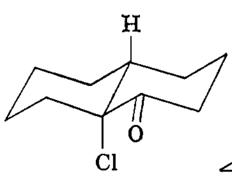
$$\underset{\mathbf{1}}{(CH_3)_2CH{-}CO{-}C(CH_3)_2Br} \xrightarrow[\text{DME}]{\text{NaOCH}_3} \underset{\mathbf{2}\ (1\%)}{(CH_3)_2CH{-}C(CH_3)_2{-}CO_2CH_3} + \underset{\mathbf{3}\ (84\%)}{(CH_3)_2CH{-}CO{-}C(CH_3)_2OCH_3} + \underset{\mathbf{5}\ (15\%)}{(CH_3)_2CH{-}CO{-}C(CH_3)_2OH}$$

$$\mathbf{1} \xrightarrow[\text{CH}_3\text{OH}]{\text{NaOCH}_3} \mathbf{2}\ (7\%) + \mathbf{3}\ (5\%) + \mathbf{5}\ (71\%) + \underset{\mathbf{4}\ (17\%)}{(CH_3)_2CH{-}CO{-}CH(CH_3){-}CH_2{-}OCH_3}$$

5a

$$\underset{\mathbf{6}}{(CH_3)_2CH{-}CO{-}C(CH_3){=}CH_2} \xrightarrow[\text{CH}_3\text{OH}]{\text{NaOCH}_3} \mathbf{4}$$

of 1-decalone with sulfuryl chloride[9] and reaction of 1-acetoxy-$\Delta^{1,9}$-octalin[9c] with chlorine. In these cases mixtures of the 9-chloro ketones **8** and **9** were obtained; the absence of the isomeric 2-chloro-1-decalones in these mixtures could be demonstrated by examining the n.m.r. spectra of the mixtures. Although a portion of the previously described[9a,c] pure *trans* isomer **8** could be separated from the mixture by fractional crystallization at low temperatures, we were unsuccessful in isolating the pure *cis* ketone **9** and were forced to study the pure *trans* isomer **8** and mixtures of the stereoisomers **8** and **9**. The composition of the mixture of chloro ketones used was estimated in two ways. On gas chromatography, the *trans* isomer **8** was dehydrochlorinated to yield almost entirely the unsaturated ketone **10**, whereas mixtures of the chloro ketones gave both unsaturated isomers **10** and **11**. Consequently, it was apparent that this dehydrochlorination of the *cis*-chloro ketone **9** was yielding the unsaturated ketone **11** and also, possibly, the isomer **10**. In the subsequently discussed stereospecific Favorskii rearrangements of chloro ketones **8** and **9**, it was found that the pure *trans* ketone gave predominantly the *trans*-fused esters **18** and **20** while the *cis* isomer **9** present in mixtures of chloro ketones gave the *cis*-fused esters **19**, **21**, and **22**. The combined results of these dehydrohalogenation and Favorskii rearrangement experiments allowed us to conclude that the mixture of chloro ketones being studied contained *ca.* 45% of the *cis* isomer **9** and *ca.* 55% of the *trans* isomer **8**.



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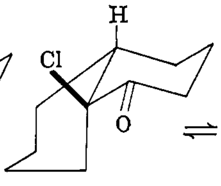
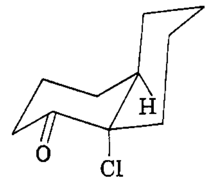
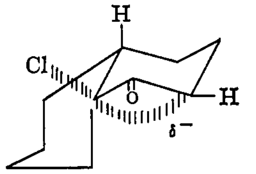


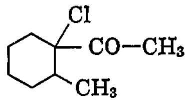
9a



9b



9c



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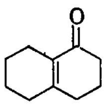

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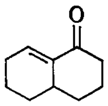

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Reaction of either the pure *trans*-chloro ketone **8** or mixtures of the *cis* and *trans* isomers **9** and **8** with solutions of sodium methoxide in methanol yielded mixtures of the four previously[4b] characterized methoxy ketones **12**–**15**. From reactions run for short periods of time, a fifth methoxy ketone, believed to be one of the stereoisomers of structure **16**, was detected; this product was rapidly epimerized to a mixture of ketones **15** (84.5% at equilibrium) and **14** (15.5% at equilibrium) by the basic reaction mixture. In none of these reactions did we detect the esters **18**–**22** which would result from Favorskii rearrangement. From a knowledge of the composition of the methoxy ketone mixture produced from the *trans*-chloro ketone **8**,[10] the composition of the mixture of chloro ketones **8** and **9** employed, and the composition of the methoxy ketone mixture produced from the chloro ketone mixture **8** and **9**, the composition of the methoxy ketone product from the *cis*-chloro ketone **9** could be estimated. The results of this estimate and the data for the *trans*-chloro ketone **8** are summarized in Scheme II (average values from two different reactions). The estimates for the product mixture from the *cis*-chloro ketone **9** are obviously only approximate especially for the relative proportions of the 2-methoxy ketones **14** and **15** where epimerization is incomplete under the reaction conditions used. However, one clear difference which

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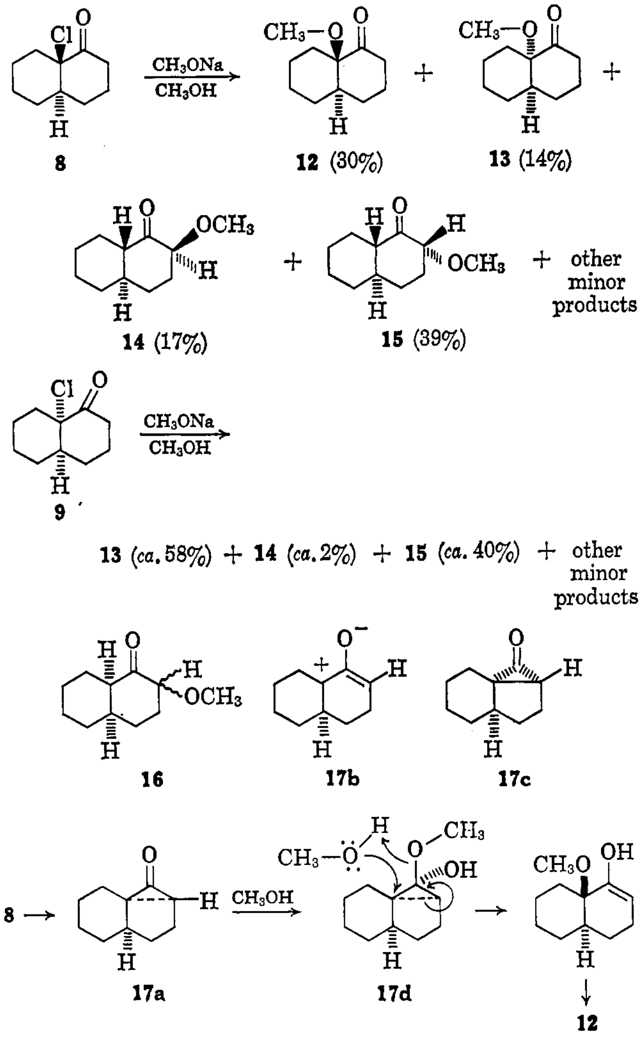
[9] (a) E. W. Warnhoff, Ph.D. Dissertation, University of Wisconsin, 1953; (b) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953); (c) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).

[10] The product compositions reported here, which differ in certain respects from our earlier estimates (ref. 4b), reflect an improvement in our gas chromatographic separations which permit the separation of methoxy ketone **14** from the *cis*-9-methoxy ketone **13**. These two components were not resolved in the earlier product analysis and were obtained in pure form by an indirect procedure.

SCHEME II



emerges is the fact that the *trans*-chloro ketone **8** yields predominantly the 9-methoxy *trans* ketone **12** while the *cis*-chloro ketone **9** yields predominantly (if not exclusively) the 9-methoxy *cis* ketone **13**. This observation clearly is not compatible with earlier suggestions[3c,4] that the α-alkoxy ketone products which often accompany a Favorskii rearrangement are the result of reaction of an intermediate planar, dipolar ion (such as **17b**), or the equivalent diradical, with solvent. If this idea were applicable to the 9-chloro-1-decalones, each of the chloro ketones **8** and **9** should yield the same dipolar ion **17b**, and consequently, the same mixture of methoxy ketones. It will also be noted that the transformations **8** → **12** and **9** → **13**, representing over-all retention of configuration, are not compatible with the formation of the methoxy ketones **12** and **13** by direct bimolecular nucleophilic displacement, a possibility which we had discounted earlier[4b] on other grounds.

One of two general reaction paths would appear appropriate to account for the stereochemical results observed. One general path involves the participation of the ketone oxygen atom in displacement of the chloride ion (with inversion at C-9) to form either an epoxy ether or an alkylidene epoxide. Subsequent rearrangement of the epoxy ether or reaction of the alkylidene epoxide with methanol could result in a second inversion at C-9 and explain the observed stereochemistry.[11] Alternatively, the various α-methoxy ketones could arise by attack of methanol on a cyclopropane intermediate by a process such as the one illustrated in structure **17d**. This displacement by a nucleophile at a cyclopropane ring finds precedent in the previously cited[7b,c,8a] reaction of cyclopropanone hemiketals with alcohols to form α-alkoxy ketones (*e.g.*, the methoxy ketone **3**) and has also been suggested elsewhere.[8b] This sequence, involving two inversions (*i.e.*, net retention) of configuration at C-9, can account both for the observed stereochemical results and the concurrent formation of the 2-methoxy ketones **14** and **15** *via* an analogous displacement at C-2. If this latter hypothesis is correct, it is also necessary to assume that the interconversion of the cyclopropane intermediates (*e.g.*, **17a** $\rightleftharpoons$ **17c**) *via* a dipolar intermediate such as **17b** is significantly slower in the decalone series than for the corresponding intermediates derived from 1-acetyl-1-chlorocyclohexane derivatives. In this latter case, complete loss of stereospecificity was observed[4] when methanol was employed as the reaction solvent. One of the referees has noted that the general scheme suggested by structure **17d** could yield both the indicated enol and the methyl enol ether of methoxy ketone **12**; it is entirely possible that one or more of the minor products formed in this reaction is such an enol ether.

From the results of reaction of the *trans*-chloro ketone **8** and the mixture of chloro ketones **8** and **9** with a suspension of sodium methoxide in 1,2-dimethoxyethane (DME), the composition of the product derived from the *cis*-chloro ketone **9** was estimated. Compositions of the ester mixtures are summarized in Scheme III. It will be noted that rearrangement to esters has occurred in both cases with practically complete stereospecificity at C-9; none of the methoxy ketones **12–16** was detected among the products of these reactions. From the reaction of a mixture of the chloro ketones **8** and **9** with a solution of sodium methoxide in 1,2-dimethoxyethane which was 4.4 *M* in methanol (*ca.* 20% methanol by volume), the product contained a mixture of the esters **18–22** (*ca.* 75% of the product) and the methoxy ketones **12–15** (*ca.* 25% of the product).

The *trans* ester **18** was cleaved with lithium iodide in collidine[12] to the acid **24** which was identified with an

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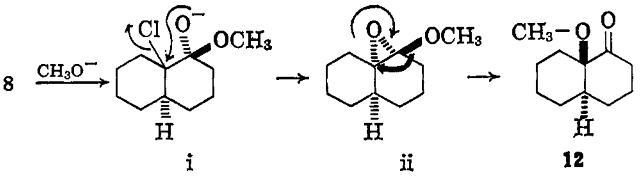
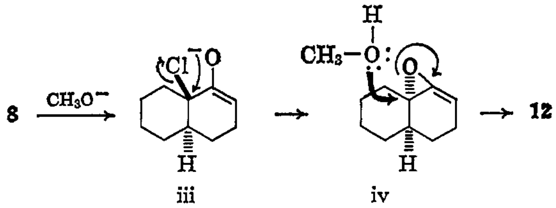
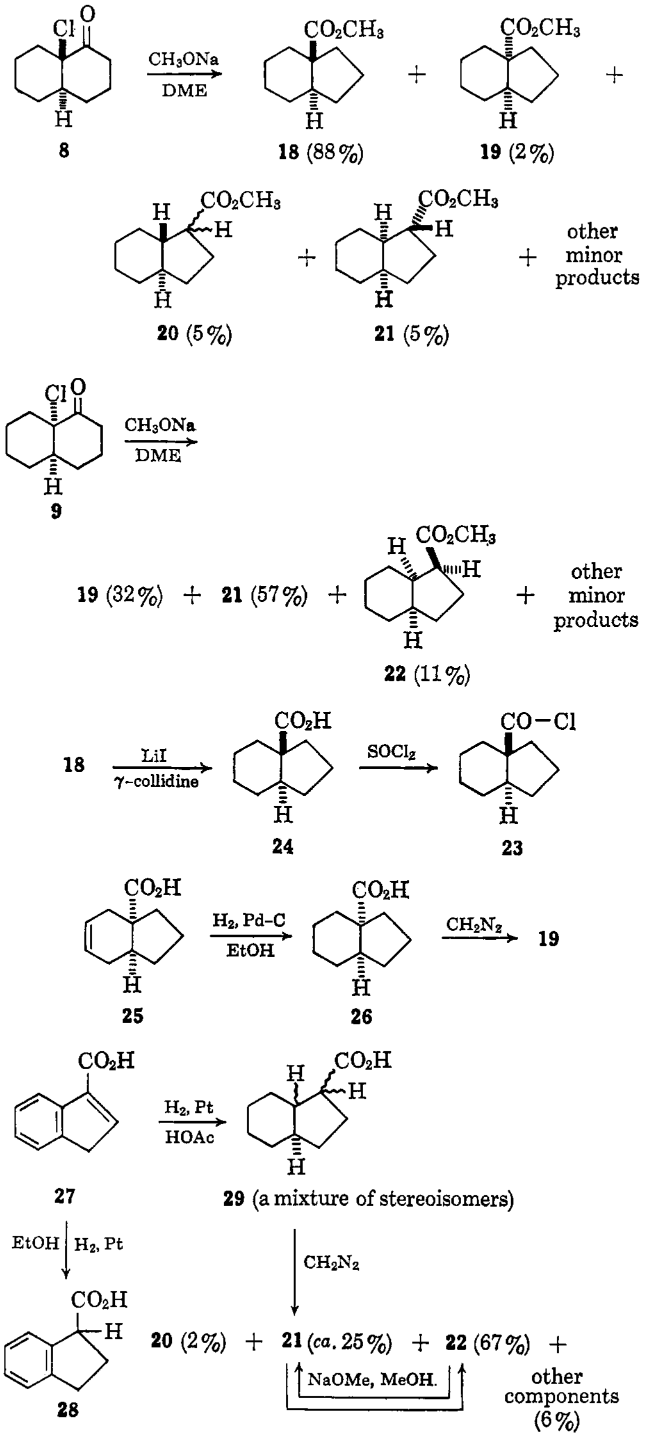
[11] The formation (i) and rearrangement (ii) of an epoxy ether is illustrated in the following equation. However, this rearrangement (as in ii) is not in keeping with the behavior previously observed (ref. 3a and 6) for epoxy ethers and, also, fails to account for the concurrent formation of the 2-methoxy-1-decalones **14** and **15**. At least certain of these objections are overcome by the formation (*e.g.*, iii) of an intermediate alkylidene epoxide (*e.g.*, iv, *cf.* ref. 7f) followed by reaction with methanol as illustrated.





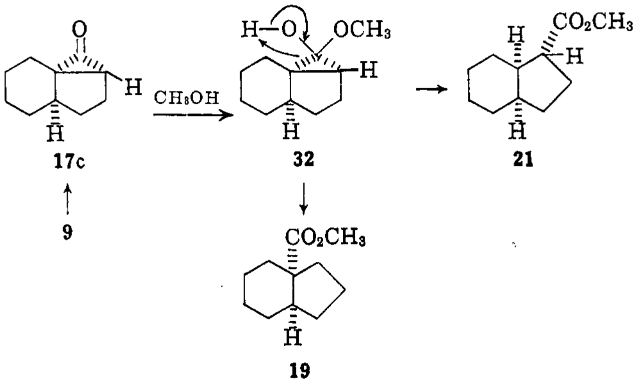
[12] The procedure of F. Elsinger, J. Schreiber, and A. Eschenmoser [*Helv. Chim. Acta*, **43**, 113 (1960)] for the cleavage of hindered esters.

SCHEME III



authentic sample[13]; the acid **24** was also converted to the acid chloride **23**. An authentic sample of the *cis* acid **26**[14] was obtained by hydrogenation of the unsaturated acid **25**[14a] and converted to the ester **19**. Hydrogenation of the indene acid **27** yielded either the indan acid **28** or a mixture of perhydroindan acids **29**. After esterification of acid **29** with diazomethane, the major product was the ester **22** accompanied by lesser amounts of the ester **21** and a small amount of the ester **20**. Since hydrogenation of the indan acid **28**, the initial reduction product of **27**, would be expected to yield predominantly the product resulting from the *cis* addition of hydrogen from the less hindered side, the major product, ester **22**, has been assigned the indicated stereochemistry. The epimeric relationship of ester **21** and **22** was demonstrated by equilibration of **22** with methanolic sodium methoxide to yield a mixture containing the ester **21** (88%) and the ester **22** (12%).[15] The stereochemical relationship of the 2-carbomethoxy group in the single *trans*-fused ester **20** obtained is unknown.

From the above data, it can be concluded that each chloro ketone **8** or **9** will undergo a stereospecific Favorskii rearrangement with sodium methoxide in a nonpolar and aprotic solvent and, furthermore, that the initial conformation of the α-halogen atom (*i.e.*, axial or equatorial) is not a dominant factor in determining whether α-alkoxy ketone or ester products will be obtained. Stereochemical results obtained in these rearrangements are in complete agreement with the idea that cyclopropanone intermediates, such as **17a** and **17c** formed with inversion at C-9, are involved, the reaction paths being **8** → **17a** → **18** + **20** + **21** and **9** → **17c** → **19** + **21** + **22**. It is not clear whether the dominance of the *cis*-fused 2-carbomethoxy derivative **21** and **22** rather than *trans*-fused isomers in this latter case is better attributed to the indicated (structure **32**) intramolecular proton transfer or to a kinetically favored protonation of a relatively free carbanion from the less hindered side.



Finally, it is appropriate to call attention to the synthetic utility of the rearrangement of the *trans*-chloro ketone **8** to the ester **18**, a *trans*-fused perhydroindan derivative with a bridgehead substituent. This process is obviously more direct than other procedures which have been devised to prepare this *trans*-fused ring system as found, for example in the C and D rings of steroids. For the preparation of the simple *trans*-fused

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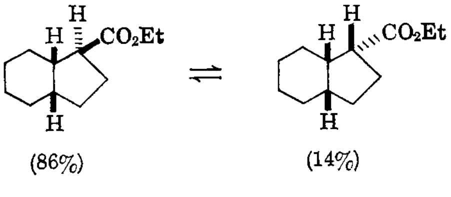
(13) In unpublished work, Professor W. G. Dauben and his associates have prepared and characterized the acid **24**. We are grateful to Professor Dauben for providing us with a sample of this material. The corresponding carboxamide has also been prepared by Professor Dauben and his associates and by W. L. Meyer and J. F. Wolfe [*J. Org. Chem.*, **29**, 170 (1964)].

(14) (a) R. K. Kronenthal and E. I. Becker, *J. Am. Chem. Soc.*, **79**, 1095 (1957); (b) W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961); (c) H. Koch and W. Haaf, *Chem. Ber.*, **94**, 1252 (1961).

(15) G. J. Fonken and W. Moran [*Chem. Ind.* (London), 1841 (1963)] reported the equilibrium values indicated in the accompanying equation fo the ethyl esters corresponding to **21** and **22**. These authors used essentially the same argument we offer for the assignment of a *cis*-ring juncture.



ester **18**, it was found practical to rearrange a mixture of chloro ketones **8** and **9** since the esters **20–22** were readily separable from the bridgehead esters **18** and **19** by selective saponification and subsequent fractional distillation separated esters **18** and **19**.

Experimental[16]

2-Bromo-2,4-dimethyl-3-pentanone (**1**).—This bromo ketone, obtained by the bromination of diisopropyl ketone in chloroform solution, was isolated as a colorless liquid, b.p. 85° (16 mm.), $n^{25}\mathrm{D}$ 1.4526 [lit.[17] b.p. 50–51° (10 mm.), 59–61° (18–20 mm.), 166–168° (760 mm.)]. The bromo ketone has infrared absorption[18] at 1715 cm.$^{-1}$ (C=O) with n.m.r. peaks[18] at δ 3.51 (1H, seven lines with J = 6.5 c.p.s., >CH–CO), 1.89 (6H singlet, $CH_3\text{–}\underset{|}{\overset{|}{C}}\text{–}Br$), and 1.18 (6H doublet with J = 6.5 c.p.s., CH_3). The mass spectrum of the compound has weak molecular ion peaks at m/e 192 and 194 with abundant fragment peaks at m/e 121 and 123 ($CH_3\text{–}C^{+}\!<^{Br}_{CH_3}$), 71 [$(CH_3)_2CH\text{–}C{\equiv}O^+$], and 43 [$(CH_3)_2CH^+$].

Reaction of the Bromo Ketone 1 with Methanolic Sodium Methoxide.—A solution of 2.895 g. (15 mmoles) of the bromo ketone **1** in 20 ml. of methanol was added to a solution of sodium methoxide prepared from 2.327 g. (100 mg.-atoms) of sodium and 30 ml. of methanol. After the resulting mixture had been stirred for 10 hr. at room temperature, it was diluted with saturated aqueous sodium chloride and extracted with ether. The ethereal extract was dried and concentrated; distillation of the residue (1.647 g. of light yellow liquid) in a short-path still (100–120° at 0.1 mm.) afforded 1.1216 g. of colorless liquid. This liquid contained,[19] in order of increasing retention time, the **ester 2** (*ca.* 8%), the **α-methoxy ketone 3** (*ca.* 8%), the **β-methoxy ketone 4** (*ca.* 14%), and the **hydroxy ketone 5** (*ca.* 70%). In a comparable reaction (employing 2.890 g. or 15 mmoles of the bromo ketone **1**, 73.3 mg. of 1-methylcyclohexene was added as an internal standard and the crude, undistilled product (1.2644 g.) was analyzed.[19] The product contained the **ester 2** (7%), the **α-methoxy ketone 3** (5%), the **β-methoxy ketone 4** (17%), and the **hydroxy ketone 5** (71%), the calculated yields being 4% of **2**, 3% of **3**, 10% of **4**, and 43% of **5**. No higher boiling or acidic products were found. To determine these composition and yield values, a calibration curve was prepared with mixtures containing known weights of the products and the internal standard.

Samples of each of the products from the reaction were collected[19,20] and the ester **2** and α-methoxy ketone **3** were identified with subsequently described samples by comparison of retention times and infrared spectra. A collected sample of the hydroxy ketone **5**, $n^{25}\mathrm{D}$ 1.4182 (lit.[21] $n^{25}\mathrm{D}$ 1.4190), has infrared absorption[18] at 3600, 3480 (unassociated and associated O–H), and 1710 cm.$^{-1}$ (C=O) with n.m.r. absorption[18] at δ 3.43 (1H, broad, OH), 3.03 (1H, five lines of expected seven-line pattern discernible, J = 6.5 c.p.s., >CH–CO), 1.32 [6H singlet, $(CH_3)_2C(OH)<$], and 1.08 [6H doublet with J = 6.5 c.p.s., methyl groups of $(CH_3)_2CH\text{–}CO$]. The mass spectrum has a molecular ion peak at m/e 130 with abundant fragment peaks at m/e 87 [$(CH_3)_2C(OH)\text{–}C{\equiv}O^+$], 71 [$(CH_3)_2CH\text{–}C{\equiv}O^+$], 59 [$(CH_3)_2C{=}O^+H$], and 43 [$(CH_3)_2CH^+$]. To obtain an authentic sample of hydroxy ketone **5**, a mixture of 9.65 g. (50 mmoles) of the bromo ketone **1** and 100 ml. of 2 M aqueous potassium carbonate was refluxed for 14 hr.[22] The ether extract of the reaction mixture was dried and concentrated; distillation of the residual yellow liquid (8.174 g.) separated 7.633 g. of a colorless liquid, b.p. 53–55° (7 mm.), which contained[20] approximately equal amounts of the starting bromo ketone **1** and the hydroxy ketone **5**. A collected sample of the hydroxy ketone, $n^{25}\mathrm{D}$ 1.4196 [lit.[21,22] b.p. 59° (17 mm.), $n^{25}\mathrm{D}$ 1.4190], was identified with the previous sample by comparison of retention times and infrared spectra.

A collected sample of the **β-methoxy ketone 4** has infrared absorption[18] at 1715 cm.$^{-1}$ (C=O) with n.m.r. absorption[18] at δ 3.34 (2H, doublet with J = 7.5 c.p.s., $\text{–}CH_2\text{–}O$) and 3.22 (3H singlet, $O\text{–}CH_3$) with complex absorption in the region δ 2.4–3.2 (2H, >CH–CO–) and three overlapping doublets (J = 7 c.p.s. in each case) at δ 1.03, 1.01, and 0.97 (9H, CH_3–). The mass spectrum of the product has a molecular ion peak at m/e 144 with abundant fragment peaks at m/e 101 [$CH_3OCH_2(CH_3)CH\text{–}C{\equiv}O^+$], 73 [$CH_3OCH_2(CH_3)CH^+$], 71 [$(CH_3)_2CH\text{–}C{\equiv}O^+$], 45 ($CH_3\text{–}O^+{=}CH_2$), and 43 [$(CH_3)_2CH^+$].

To obtain an authentic sample of the β-methoxy ketone **4**, a solution of 4.83 g. (25 mmoles) of the bromo ketone **1** in 25 ml. of γ-collidine was refluxed overnight under a nitrogen atmosphere. The reaction mixture was poured into aqueous acid and extracted with ether. After the ether solution had been washed with aqueous sodium chloride, dried, and concentrated, distillation of the residue in a short-path still (70° at 10 mm.) separated 1.1637 g. (42%) of **2,4-dimethyl-1-penten-3-one** (**6**) as a colorless liquid, $n^{25}\mathrm{D}$ 1.4251 [lit.[22] b.p. 50° (60 mm.), $n^{25}\mathrm{D}$ 1.4260], which exhibits a single peak in gas chromatography.[20] The product has infrared absorption[18] at 1680 (conjugated C=O), 1625 (conjugated C=C), and 860 and 927 cm.$^{-1}$ ($C{=}CH_2$) with n.m.r. peaks[18] at δ 5.88 (1H, broad but coupling not resolved) and 5.73 (1H, partially resolved quartet with J = 1.5 c.p.s.) attributable to the vinyl protons of the grouping $\text{–}C(CH_3){=}CH_2$ as well as absorptions at δ 3.26 (1H, seven lines with J = 6.5 c.p.s., >CH—CO—), a partially resolved multiplet at δ 1.86 (3H, $CH_3\text{–}\overset{|}{C}{=}C<$), and a doublet ($J$ = 6.5 c.p.s.) at δ 1.07 (6H, CH_3).

A solution of 1.1637 g. (10 mmoles) of the unsaturated ketone **6** in 3 ml. of methanol was added to a cold (0°) solution of 1.0 mmole of sodium methoxide in 1 ml. of methanol. The resulting mixture was stirred for 3 hr. and then acidified with dilute, aqueous hydrochloric acid and extracted with ether. After the extract had been dried and concentrated, the residual light yellow liquid (1.09 g.) was found to contain[20] 13% of the starting unsaturated ketone **6** and 87% of the β-methoxy ketone **4**. A collected[20] sample of the methoxy ketone **4** was identified with the previously described sample by comparison of retention times and infrared, n.m.r., and mass spectra.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.45; H, 10.94.

Reaction of the Bromo Ketone 1 with Sodium Methoxide in 1,2-Dimethoxyethane.—A suspension of sodium methoxide was prepared by refluxing a mixture of 3.2 g. (0.1 mole) of methanol and 30 ml. of 1,2-dimethoxyethane with 2.3 g. (0.1 g.-atom) of sodium under a nitrogen atmosphere until all the sodium was consumed. To this suspension was added 2.855 g. (0.015 mole) of the bromo ketone **1**; the resulting mixture was stirred at room temperature for 10 hr. and then poured into aqueous sodium chloride. After the mixture had been extracted with ether, the extract was dried and concentrated to leave 1.282 g. of light yellow liquid which contained[19] the **ester 2** (1%), the **α-methoxy ketone 3** (86%), and the **hydroxy ketone 5** (13%). In a comparable experiment where 274 mg. of 1-methylcyclohexene was added as an internal standard, the compositon of the crude product was **2** (1%), **3** (84%), and **5** (15%), the calculated yields being 1% of **2**, 53% of **3**, and 9% of **5**. No higher boiling or acidic products were found. The ester **2** was identified with an authentic sample by comparison of retention times. A collected[20] sample of the hydroxy ketone **5** was identified with the previously described sample by comparison of retention times and infrared and mass spectra. A collected[20] sample of the previously described[23] α-methoxy ketone **3**, $n^{25}\mathrm{D}$ 1.4101, has infrared absorption[18] at 1715 cm.$^{-1}$ (C=O) with n.m.r. absorption[18] at δ 1.00 (6H doublet with J = 6.5 c.p.s., CH_3) and 1.23 (6H singlet,

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[16] All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

[17] (a) A. J. Oumoff, *Bull. soc. chim. France*, [2] **43**, 568 (1928); (b) A. Unnowa, *J. prakt. Chem.*, [2] **88**, 641 (1913); (c) A. A. Sacks and J. G. Aston, *J. Am. Chem. Soc.*, **73**, 3902 (1951).

[18] Determined as a solution in carbon tetrachloride.

[19] A gas chromatography column packed with Carbowax 20M suspended on ground firebrick was employed.

[20] A gas chromatography column packed with silicone gum, no. SE 30, suspended on ground firebrick was employed.

[21] R. Paul, *Compt. rend.*, **200**, 1481 (1935).

[22] The procedure of J. Colonge and J. C. Dubrin, *Bull. soc. chim. France*, 1180 (1960).

[23] A. A. Sacks and J. G. Aston[17c] reported b.p. 149–151°, $n^{20}\mathrm{D}$ 1.4113–1.4120, for the methoxy ketone **3**.

TABLE I

REACTION OF THE 9-CHLORO-1-DECALONES WITH SODIUM METHOXIDE IN METHANOL

Chloro ketone,[a] mg. (mmoles)	Sodium methoxide, mmoles	Methanol, ml.	Reaction time, min.	Product composition, %[b] 12	13	14	15	16	Yield,[c] %
8, 914.2 (4.9)	30.3	20	600	29	14	15	42	..	74
8, 932.6 (5.0)	30.4	20	600	30	14	20	36	..	80[d]
8, 745.2 (4.0)	26.2	25	10	39	21	22	10	8	74
			1	36	20	7	1	36	77[e]
8 + **9**, 1016.4 (5.4)	29.6	15	600	16	36	11	37	..	79
8 + **9**, 978.1 (5.3)	30.0	15	600	18	32	10	40	..	83[f]
8 + **9**, 986.8 (5.3)	28.4	15	10	16	38	11	34	1	78
8 + **9**, 1007.6 (5.4)	28.2	15	1	24	39	11	4	22	39[e]

[a] As noted in the Experimental section, the mixture of chloro ketones employed contained *ca.* 45% of the *cis* isomer **9** and 55% of the *trans* isomer **8**. [b] The values listed refer to the proportion of each methoxy ketone identified in the mixture of the five methoxy ketones **12–16**. Other unidentified minor by-products were also present. [c] The yield calculated from gas chromatographic data for the five methoxy ketones **12–16**. [d] After a solution of 2.4 mmoles of this product mixture in 10 ml. of methanol containing 16.1 mmoles of sodium methoxide had been refluxed for 10 hr., the recovered product (76% recovery) contained 34% of **12**, 16% of **13**, 11% of **14**, and 39% of **15**. [e] Some starting material was present in this product mixture. [f] After a solution of 2.8 mmoles of this product mixture in 10 ml. of methanol containing 15.0 mmoles of sodium methoxide had been refluxed for 10 hr., the recovered product (79% recovery) contained 18% of **12**, 40% of **13**, 6% of **14**, and 36% of **15**.

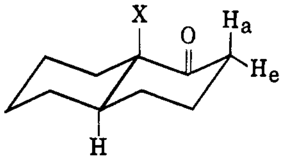
CH_3) as well as a singlet at δ 3.16 (3H, $O–CH_3$) superimposed on a multiplet in the region δ 2.9–3.5 (1H, >CH–CO). The mass spectrum of the product has a very weak molecular ion peak at *m/e* 144 with abundant fragment peaks at *m/e* 73 [$(CH_3)_2C{=}O^+–CH_3$] and 43 [$(CH_3)_2CH^+$].

Methyl 2,2,3-Trimethylbutyrate (2).—2,3-Dimethyl-2-butanol, b.p. 115–118°, $n^{25}D$ 1.4136 [lit.[24] b.p. 118–118.6° (757 mm.)], was prepared in 61% yield by the reaction of 3-methyl-2-butanone with excess methylmagnesium bromide. The product has infrared absorption[18] at 3600 and 3400 cm.$^{-1}$ (unassociated and associated O–H) with n.m.r. peaks[18] at δ 2.26 (1H, O–H), 1.08 (6H singlet, CH_3), and 0.87 (6H, doublet with J = 6.5 c.p.s., CH_3) as well as a multiplet in the region δ 1.1–1.8 (1H, >CH–). The mass spectrum exhibits no molecular ion peak but has abundant fragment peaks at *m/e* 87 [$(CH_3)_2CH–C({=}O^+H)–CH_3$], 59 [$(CH_3)_2C{=}O^+H$], and 43 [$(CH_3)_2CH^+$].

To a solution of 10.2 g. (0.1 mole) of this alcohol in 110 g. of cold (0°), concentrated sulfuric acid was added, dropwise and with stirring over a 20-min. period, 13.8 (0.3 mole) of formic acid.[25] The resulting cold mixture was stirred for 1 hr. and then poured onto 200 g. of ice and extracted with ether. The ethereal solution was extracted with aqueous sodium hydroxide. After the resulting aqueous extract had been acidified with hydrochloric acid and extracted with ether, the ether solution was dried and concentrated to leave 1.0606 g. of crude acidic product. Distillation in a short-path still (110° at 10 mm.) afforded 732.2 mg. of 2,2,3-trimethylbutyric acid [lit.[25b] b.p. 111° (20 mm.)] with infrared absorption[18] at 3000 (broad, associated O–H) and 1710 cm.$^{-1}$ (carboxyl C═O). Esterification of this acid sample with excess ethereal diazomethane followed by filtration and evaporation of the ether afforded 0.81 g. of the crude ester **2** as a colorless liquid. A collected[20] sample of the pure ester **2** has infrared absorption[18] at 1735 cm.$^{-1}$ (ester C═O); the mass spectrum of the sample has a molecular ion peak at *m/e* 144 with abundant fragment peaks at *m/e* 102 [$(CH_3)_2C{=}C(OH^+)–OCH_3$], 85 [$(CH_3)_2CH–C^+(CH_3)_2$], and 43 [$(CH_3)_2CH^+$].

Preparation of the 9-Chloro-1-decalones 8 and 9.—1-Decalone (60.8 g., 0.40 mole) was chlorinated with sulfuryl chloride in carbon tetrachloride as previously described.[9] Repeated crystallization of the crude product from petroleum ether (b.p. 30–60°) at Dry Ice temperature separated 7.494 g. (10%) of the *trans*-chloro ketone **8**, m.p. 39–40° (lit.[9c] m.p. 40–41°). Distillation of the crude product recovered from the mother liquor separated 67 g. of pale yellow liquid, b.p. 80–87° (0.4–0.8 mm.), which was estimated from its spectra and gas chromatogram[19,26] to contain more than 90% of the two chloro ketones **8** and **9**. Repeated fractional distillation of this material separated 9.0509 g. of a mixture containing[19,26] 97% of the chloro ketones **8** and **9**, b.p. 68° (0.35 mm.), $n^{25}D$ 1.5043, as well as other fractions containing predominantly the chloro ketones **8** and **9** accompanied by varying amounts of 1-tetralone and 1-decalone. The gas chromatogram[19,26] of the above-mentioned mixture of chloro ketones **8** and **9** exhibits peaks for the dehydrochlorinated products **10** and **11** in the proportions 38% of **11** and 62% of **10** indicating that 40% or more of the mixture is the *cis*-chloro ketone **9**. The subsequently described ester mixtures from Favorskii rearrangement suggest that the mixture contains 47% of the *cis* isomer **9** and 53% of the *trans* isomer **8**. We therefore conclude that this mixture is approximately 45% *cis*-chloro ketone **9** and 55% *trans*-chloro ketone **8**. Since our efforts to obtain pure samples of the *cis*-chloro ketone **9** have thus far been unsuccessful, this mixture (containing *ca.* 45% of **9**) was used along with the pure *trans*-chloro ketone in subsequent experiments.

The pure *trans*-chloro ketone **8** has the previously noted[9c] infrared[18] and ultraviolet[27] peaks at 1718 cm.$^{-1}$ (C═O) and 300.5 mμ (ε 45) as well as complex n.m.r. absorption[18] in the region δ 1.1–2.5 (14 H) and a complex, partially resolved multiplet in the region δ 2.7–3.5 (1 H). The same pattern, attributable to one proton in the lower field region of the spectrum, is found in the n.m.r. spectrum of the subsequently described 9-methoxy-*trans*-1-decalone (**12**). This low-field absorption is believed to arise from the axial 2-proton (H_a in structure **30**) which is deshielded by the nearby axial, electronegative substituent (X in structure **30**).[28]



30, X = Cl or OCH_3

The previously described mixture of chloro ketones (*ca.* 45% **9** and 55% **8**) has infrared absorption[18] at 1725 cm.$^{-1}$ with ultraviolet maxima[27] at 247 mμ (ε 365, tetralone and/or octalone impurities) and 297 mμ (ε 69). The n.m.r. spectrum[18] of this mixture resembles the spectrum of the *trans* isomer **8** but has an additional broad peak centered at *ca* δ 2.55; however, the spectrum exhibits no absorption at lower field than δ 3.5 indicating the absence of protons in the environment –CO–CHCl– and allowing us to conclude that the mixture is free of the 2-chloro-1-decalones.

Reaction of the 9-Chloro-1-decalones 8 and 9 with Sodium Methoxide in Methanol. A. General Procedure and Product Analysis.—Samples of either the pure *trans*-chloro ketone **8** or the mixture of chloro ketones (*ca.* 45% of **9** and 55% of **8**) were

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(24) M. Delacre, *Bull. soc. chim. France*, [4] **1**, 456 (1907).

(25) (a) The procedure of W. Haaf and H. Koch, *Ann.*, **618**, 251 (1958); (b) *ibid.*, **638**, 122 (1960).

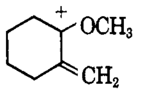
(26) On the column[19] employed for analysis, both chloro ketones **8** and **9** were dehydrohalogenated to form unsaturated ketones **10** and **11**. The major dehydrohalogenated product from the pure *trans* ketone **8** under these conditions was the unsaturated ketone **10** (>95%), whereas mixtures containing the *cis*-chloro ketone **9** also formed the octalone **11**.

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

(28) (a) The deshielding of an axial methyl group by a nearby axial halogen atom has been noted by E. R. Malinowski, M. S. Manhas, G. H. Müller, and A. K. Bose, *Tetrahedron Letters*, **No. 18**, 1161 (1963). (b) For an example of long-range deshielding by a nitro group, see A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).

added to a cold (0°) solution of sodium methoxide in methanol; the quantities used are listed in Table I. After the resulting mixtures (from which sodium chloride began to precipitate within 1–2 min. after mixing) had been stirred at room temperature for the specified times, 10 ml. of water and 10 ml. of petroleum ether were added and the layers were separated. The aqueous phase was washed with petroleum ether and the combined organic layers were washed with saturated, aqueous sodium chloride and dried. After a weighed quantity of benzotrichloride had been added as an internal standard, the solutions were concentrated and the residual liquid was analyzed by gas chromatography to determine the yields and product compositions (Table I). A known mixture of authentic samples was prepared in order to calibrate the gas chromatography columns used for analysis. Two gas chromatography columns were employed for analysis. With the Carbowax 20M column employed,[19] the retention times of the methoxy ketones were *trans*-9-methoxy ketone **12**, 12.4 min.; *cis*-9-methoxy ketone **13**, 15.4 min.; and an unresolved mixture of the thermally equilibrated 2-methoxy ketones **14** and **15** as a broad peak, 24.8 min. With a combination column,[29] the retention times were *trans*-9-methoxy ketone **12**, 33.0 min.; axial 2-methoxy ketone **14**, 36.4 min.; *cis*-9-methoxy ketone **13**, 39.2 min., and equatorial 2-methoxy ketone **15**, 86.0 min. Although resolution of the peaks for ketones **12**, **13**, and **14** on the latter column was not complete, utilizing the combined data from both columns,[19,29] we believe our analysis to be in error by less than ±5% in all cases. From reactions run for short periods of time, an unstable product believed to be the 2-methoxy ketone **16** appeared on our neutral column[29] as a new peak eluted slightly before the equatorial 2-methoxy ketone **15** (relative retention times were **16**, 55.6 min., and **15**, 60.6 min.). As expected, this unstable product (presumably ketone **16**) was epimerized by the ordinary Carbowax column[19] and appeared under the same broad peak as 2-methoxy ketones **14** and **15**.

B. **Identification of Products.**—Samples of each of the four methoxy ketones **12–15** were collected from appropriate gas chromatography columns[19,29] and identified with previously described[4b] samples by comparison of infrared and mass spectra. The equatorial 2-methoxy ketone **15** has an ultraviolet maximum[27] at 279 mμ (ε 79). The mass spectra of the 9-methoxy ketones **12** and **13** differ from the spectra of the 2-methoxy ketones **14** and **15** in that both 9-methoxy compounds give abundant fragment peaks at *m/e* 125 and 111 which are only minor peaks in the spectra of the 2-methoxy compounds. In the mass spectrum of the subsequently described 9-methoxy-2,2-dideuterio-*trans*-1-decalone these peaks are found at *m/e* 125 and at 111, 112, and 113 suggesting that the 125 peak is attributable to the ion



and that the 111 peak arises from several ions. The mass spectra of the 2-methoxy ketones **14** and **15** differ from the 9-methoxy isomers in having very abundant fragment peaks at *m/e* 71 and 58; these peaks are much less intense in the spectra of the 9-methoxy isomers. The corresponding peaks in the previously described[4b] 2,9-dideuterio derivative of the 2-methoxy ketone **15** are found at *m/e* 72 and 59 suggesting that these peaks are attributable to ions $CH_2{=}CH{-}CH{=}O^+CH_3$ and $(CH_2{=}CH{-}O{-}CH_3)^+$, respectively.

After a sample of the *trans*-9-methoxy ketone **12** had been subjected to a series of three exchanges with a refluxing solution of sodium methoxide in a deuterium oxide–methanol-d_1 (1:3 by volume) mixture, the neutral material was recovered and the deuterated ketone was collected.[29] The material, which contained 6% d_0 species, 34% d_1 species, and 60% d_2 species, has infrared absorption[18] at 2110 (shoulder), 2155, 2215 (shoulder), and 2245 cm.$^{-1}$ (C–D stretching). The n.m.r. spectrum[18] of this deuterated sample differs from the previously described[4b] spectrum of the ketone **12** in lacking the complex absorption in the region δ 2.2–2.8 attributable to one proton. As noted earlier, both this absorption and the analogous absorption in 9-chloro-*trans*-1-decalone (**8**) are believed attributable to the axial hydrogen atom at position 2 which is deshielded by the nearby axial electronegative 9-substituent (*cf.* structure **30**).

A 50-μl. sample of the 2-methoxy ketones **14** and **15** was dissolved in 2 ml. of methanol containing 2.0 mmoles of sodium methoxide and the resulting solution was refluxed for 10 hr. After use of the previously described isolation procedure, the recovered methoxy ketone mixture contained[29] 15.5% of **14** and 84.5% of **15** corresponding to an equilibrium constant of 5.5 for the process, axial 2-methoxy ketone $\rightleftharpoons$ equatorial 2-methoxy ketone. This value, corresponding to a free-energy change of *ca.* 1 kcal./mole, is in reasonable agreement with previous estimates[30] of 0.5–0.7 kcal./mole as the energy difference between axial and equatorial methoxyl groups.

A collected sample[29] of the unstable product believed to be the 2-methoxy ketone **16** had infrared absorption[18] at 1730 cm.$^{-1}$ (C=O) with abundant fragment peaks at *m/e* 71, 58, and 55 in its mass spectrum as well as a molecular ion peak at *m/e* 182. As noted earlier, fragment peaks at *m/e* 71 and 58 are characteristic of a 2-methoxy-1-decalone. The n.m.r. spectrum[18] of the material has a singlet at δ 3.31 ($O{-}CH_3$) superimposed on a broad peak in region δ 3.1–3.5 ($>CH{-}O$) and complex absorption in the region δ 1.0–2.5 (aliphatic C–H). However, our efforts to obtain a sample of this material free from other contaminants were unsuccessful.

To ensure that none of the aforementioned methoxy ketones was derived from one of the octalones **10** or **11**, each of these octalones was stirred with methanolic sodium methoxide for 10 hr. at room temperature under a nitrogen atmosphere and the reaction mixture was subjected to the usual isolation procedure. From the $\Delta^{9,10}$-octalone **10** (1.0658 g., 7.12 mmoles) after reaction with 15 ml. of methanol containing 28.5 mmoles of sodium methoxide, only the starting ketone was recovered (83% recovery). From reaction of 960 mg. (6.41 mmoles) of the $\Delta^{8,9}$-octalone **11** with 15 ml. of methanol containing 34.6 mmoles of sodium methoxide, the crude pale yellow oil (685.3 mg.) recovered contained[29] the starting ketone **11** (56% of mixture, retention time 57.2 min.) and two other components, 1-decalone (20%, 30.0 min.) and the octalone **10** (24%, 66.4 min.), neither of which corresponded in retention time to any of the five methoxy ketones **12–16**. A relatively insoluble and nonvolatile yellow solid, m.p. 91–100° dec., also separated during the isolation procedure. A collected[29] sample of the octalone **10** was identified with an authentic sample by comparison of retention times and infrared spectra. A collected[29] sample of 1-decalone had infrared and mass spectra identical with the spectra of an authentic sample.

Reaction of the 9-Chloro-1-decalones 8 and 9 with Sodium Methoxide in 1,2-Dimethoxyethane. A. General Procedure and Product Analysis.—Finely divided suspensions of sodium methoxide in 1,2-dimethoxyethane were obtained by refluxing a suspension of sodium in 1,2-dimethoxyethane containing 1 equiv. of methanol for 24 hr. at which time all the sodium had been consumed. Solutions of either the *trans*-chloro ketone **8** or the mixture of chloro ketones (*ca.* 45% of **9** and 55% of **8**) in 1,2-dimethoxyethane were added to these suspensions and the resulting mixtures were stirred, at room temperature and under a nitrogen atmosphere, for 10 hr. The crude product mixtures were isolated by the addition of water and petroleum ether followed by separation of the organic layer as in the previous cases. The combined organic extracts from each run were mixed with a weighed quantity of *m*-methoxytoluene as an internal standard and then dried, concentrated, and analyzed[29] to obtain the data presented in Table II. A known mixture of authentic samples was prepared in order to calibrate the gas chromatography equipment. With the gas chromatography column used,[29] the products are eluted in the following order: *trans* ester **18**, 16.6 min.; *cis* ester **19**, 21.8 min.; ester **20**, 24.0 min.; ester **21**, 29.0 min.; and ester **22**, 35.6 min. All of these materials except ester **22** are eluted more rapidly than the methoxy ketones **12–16**.

In an additional experiment, a *solution* of 34.2 mmoles of sodium methoxide in a mixture of 6.16 g. of methanol and 30 ml. of 1,2-dimethoxyethane (4.4 *M* in methanol) was mixed with 1.0858 g. (5.81 mmoles) of a mixture of approximately equal quantities of the chloro ketones **8** and **9**, and the resulting mixture was stirred

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[29] The first half of the gas chromatography column was packed with silicone fluid, no. 710, suspended on Chromosorb W and the second half of the column was packed with Carbowax 20M suspended on Chromosorb W. The column fluids were washed with aqueous sodium bicarbonate prior to use. The inert support (Chromosorb W) and interior glass surfaces of the column were treated with a solution of dichlorodimethylsilane in toluene and then washed successively with toluene and methanol following a procedure provided by Dr. R. J. Highet of the National Heart Institute. The resulting column did not epimerize the 2-methoxy ketones **14** and **15**.

[30] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 236.

TABLE II

REACTION OF THE 9-CHLORO-1-DECALONES WITH SODIUM METHOXIDE IN 1,2-DIMETHOXYETHANE

Chloro ketone,[a] mg. (mmoles)	Sodium methoxide, mmoles	1,2-Dimethoxyethane, ml.	Product composition, %[b]					Yield,[c] %
			18	19	20	21	22	
8, 666 (3.57)	23.2	35	88	2	5	5	...	88
8, 670.2 (3.59)	22.4	35	88	2	5	5	...	88
8 + **9**, 1050.1 (5.63)	31.7	30	46	16	3	30	5	84
8 + **9**, 916.8 (4.92)	28.5	30	46	16	3	30	5	88

[a] As noted in the Experimental section, the mixture of chloro ketones employed contained *ca.* 45% of the *cis* isomer **9** and 55% of the *trans* isomer **8**. [b] The values listed refer to the proportion of each ester in the mixture of esters **18–22**. Other unidentified minor products were also present in some cases. [c] The yield calculated from gas chromatography data for the five methyl esters **18–22**.

at room temperature for 10 hr. Application of the previously described isolation and analysis procedures afforded 864.5 mg. of a crude product containing[29] the ester **18** (22%), the ester **19** (19%), the ester **20** (*ca.* 2%), the ester **21** (32%), a mixture of the ester **22** and 9-methoxy ketones **12** and **13** (14%), and the methoxy ketone **15** (11%). The calculated yield of these products was 79.5%.

B. **Identification of Products.**—Samples of each of the esters **18–22** were collected[29] from appropriate reaction mixtures. The reaction of 1.9844 g. (10.64 mmoles) of the *trans*-chloro ketone **8** with 60.8 mmoles of sodium methoxide in 70 ml. of 1,2-dimethoxyethane was repeated to yield 1.5828 g. of a crude neutral product as a yellow liquid. Distillation in a short-path still (120° at 10 mm.) afforded 1.2979 g. (67%) of a mixture of esters containing[31] 88% of the *trans* ester **18**. A collected [31] sample of the *trans* **ester 18**, b.p. 218–219°, n^{25}_{D} 1.4723, has infrared absorption[18] at 1735 cm.$^{-1}$ (ester C═O) with a molecular ion peak at *m/e* 182 in the mass spectrum as well as abundant fragment peaks at *m/e* 123 ($M - CO_2CH_3$), 81, 67, and 41. The ester has n.m.r. absorption[18] at δ 3.65 (3H singlet, $-CO_2CH_3$) with broad, complex absorption in the region δ 1.0–2.1 (14*H*, aliphatic C–H) and two broad peaks at δ 2.32 and 2.46, together probably attributable to the bridgehead C–H.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.44; H, 9.91.

A solution of 910.4 mg. (5.0 mmoles) of the *trans* ester **18** and 4.4 g. (33 mmoles) of lithium iodide in 100 ml. of freshly distilled γ-collidine was refluxed for 9 hr.[12] and then poured into a mixture of ether, methylene chloride, and cold dilute aqueous hydrochloric acid. After the organic layer had been separated, the aqueous layer was saturated with sodium chloride and extracted with an ether–methylene chloride mixture. The combined organic layers were washed with saturated aqueous sodium chloride, dried, and concentrated to leave 905 mg. of the crude acid as a white solid. Recrystallization from aqueous acetic acid afforded 510 mg. (60.7%) of the pure **acid 24** as fine white crystals, m.p. 94–94.5° (lit.[13] m.p. 91–93.5°). The product, which was identified with an authentic sample[13] by a mixture melting point determination and by comparison of infrared and mass spectra, has infrared absorption[32] at 2950 (broad, associated O–H) and at 1695 cm.$^{-1}$ (carboxyl C═O) with a molecular ion peak at *m/e* 168 in the mass spectrum as well as abundant fragment peaks at *m/e* 123 ($M - CO_2H$), 113, 81, 67, 55, 41, and 39.

Hydrogenation of a solution of 996 mg. (6.00 mmoles) of the unsaturated acid **25**[14a] in 10 ml. of ethanol over 100 mg. of a 20% palladium-on-carbon catalyst at room temperature and atmospheric pressure resulted in the uptake of 144.0 ml. (0.98 equiv.) of hydrogen. After the resulting solution had been filtered and concentrated, crystallization of the residue from aqueous acetic acid afforded 788 mg. (77%) of the *cis* **acid 26** as a waxy white solid, m.p. 39–40° (lit. m.p. 43.5–44.5°,[14b] 43.5–45.5°, or 49°[14a]).

A solution of this acid (**26**, 788 mg., 4.6 mmoles) was esterified with excess ethereal diazomethane. Distillation of the crude product (640 mg. of colorless liquid) in a short-path still (117° at 11 mm.) separated 468.4 mg. (56%) of the pure[31] **ester 19**, n^{25}_{D} 1.4733 [lit.[14a] n^{25}_{D} 1.4701, b.p. 116° (20 mm.)]. The material has infrared absorption[18] at 1735 cm.$^{-1}$ (ester C═O) with n.m.r. absorption[33] at δ 3.77 (3H singlet, $-CO_2CH_3$) as well as complex absorption in the region δ 1.0–2.1 (14H, aliphatic C–H) and a broad peak centered at δ 2.48 (1H, bridgehead C–H). The mass spectrum of the material has a molecular ion peak at *m/e* 182 with abundant fragment peaks at *m/e* 123 ($M-CO_2CH_3$), 81, 67, and 41. This sample was identified with a collected[29] sample of ester **19** from the chloro ketone rearrangement by comparison of the infrared and mass spectra of the two samples.

A collected[29] sample of the **ester 21** has infrared absorption[18] at 1735 cm.$^{-1}$ (ester C═O) with n.m.r. absorption[18] at δ 3.60 (3H singlet, $-CO_2CH_3$) as well as complex absorption in the region δ 1.0–2.8 (15H, aliphatic C–H). The mass spectrum has a molecular ion peak at *m/e* 182 with abundant fragment peaks at *m/e* 150, 96, 87, 81, 67, 55, and 41.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.32; H, 9.96.

A collected[29] sample of **ester 20** has infrared absorption[18] at 1740 cm.$^{-1}$ (ester C═O) with n.m.r. absorption[18] at δ 3.63 (3H singlet, $-CO_2CH_3$) as well as complex absorption in the region δ 1.0–2.6 (15H, aliphatic C–H). The mass spectrum has a molecular ion peak at *m/e* 182 with abundant fragment peaks at *m/e* 150, 108, 87, 81, 67, 55, and 41.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.16; H, 9.88.

A collected[29] sample of the ester **22** was shown to be identical with a subsequently described sample by comparison of retention times as well as infrared and mass spectra.

In a larger scale reaction, 30.982 g. (0.166 mole) of the mixture of chloro ketones **8** and **9** and 0.7676 mole of sodium methoxide in 500 ml. of 1,2-dimethoxyethane was stirred at room temperature under a nitrogen atmosphere for 10 hr. and then diluted with 200 ml. of water. An aliquot of the neutral organic product separated at this time contained[29] **18**, 45%; **19**, 16%; **20**, 3%; **21**, 32%; and **22**, 4%. The mixture was refluxed for 7.5 hr. with aliquots of the neutral organic product being separated periodically for analysis. After this reaction period when the selective saponification of the unhindered esters **20–22** was essentially complete, the organic layer was separated and the aqueous phase was extracted with petroleum ether. The combined organic layers were dried and concentrated to leave 21.88 g. of pale yellow oil containing[29] the *trans* ester **18** (*ca.* 70%), the *cis* ester **19** (*ca.* 25%), and the ester **21** (*ca.* 5%). Distillation of this material afforded 13.817 g. of fractions, b.p. 87–98° (7 mm.). Fractional distillation of this material through a 30-cm. spinning-band column separated 7.6307 g. of fractions, b.p. 75–83° (6 mm.), containing 92–97% of the *trans* ester **18** [n^{25}_{D} 1.4721 for fraction, b.p. 81–82° (6 mm.), containing 97% of ester **18**], and 3.7012 g. of fractions, b.p. 83–88° (6 mm.), containing esters **18** (55–25%), **19** (38–59%), and **21** (7–16%).

A 7.1-g. (40-mmole) sample of the above *trans* ester **18** was cleaved with 36 g. (0.3 mole) of lithium iodide in 400 ml. of refluxing γ-collidine as previously described to give 5.627 g. (89%) of the acid **24**, m.p. 90–93°. An additional recrystallization from aqueous acetic acid narrowed the melting range of the acid **24** to 92–93°.

The aqueous layer from the above selective saponification was acidified, saturated with sodium chloride, and extracted with ether. This ethereal solution of acidic products was dried, concentrated, and esterified with excess diazomethane and then concentrated. Distillation of the residue (7.3 g. of light yellow liquid) afforded 7.1 g. of a mixture of esters, b.p. 137–142°(7 mm.), containing[29] the *cis* ester **19** (2%), the ester **20** (8%), the ester **21** (79%), and the ester **22** (11%). Collected[29] samples of each of the esters **20–22** were identified with previously described samples by comparison of retention times and infrared spectra.

Hydrogenation of Indene-3-carboxylic Acid (27). A. Partial Hydrogenation to 28.—A solution of 1.60 g. (10 mmoles) of indene-3-carboxylic acid (**27**)[34] in 25 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure over the catalyst from 157 mg. of platinum oxide. After the hydrogen

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[31] A gas chromatography column packed with silicone fluid, no. 710, suspended on ground firebrick was employed.

[32] Determined as a solution in chloroform.

[33] Determined as a solution in deuteriochloroform.

[34] This sample, obtained from the Aldrich Chemical Co., melted at 158–159° after recrystallization. The reported melting point for this acid is 159–161°: A. Melera, M. Claesen, and H. Vanderhaeghe, *J. Org. Chem.*, **29**, 3705 (1964).

uptake (240 cc., 1.0 equiv.) ceased, the reaction mixture was filtered and concentrated to leave 1.551 g. of crude acidic product. Crystallization from petroleum ether afforded 860.4 mg. (53%) of the pure acid **28** as white needles, m.p. 58–59° (lit.[35] m.p. 57–58°), with infrared absorption[18] at 3000 (broad, O–H) and at 1710 cm.$^{-1}$ (carboxyl C═O), a molecular ion peak at *m/e* 162 in the mass spectrum, and n.m.r. absorption[18] at δ 12.20 (1H, $-CO_2H$) as well as complex absorption in the regions δ 7.0–7.5 (4H, aryl C–H) and 2.0–4.3 (5H, aliphatic C–H).

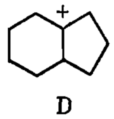
B. Complete Hydrogenation to Acid 29.—A solution of 9.6 g. (0.060 mole) of the unsaturated acid **27** in 120 ml. of acetic acid was hydrogenated at 60° and 2–3-atm. pressure over the catalyst from 1.0 g. of platinum oxide. The hydrogen uptake (0.256 mole, 1.07 equiv.) ceased after 12 hr. and the reaction mixture was filtered and concentrated to leave 9.083 g. of the crude acid **29**[36] as a brown oil. An ethereal solution of this product was esterified with excess diazomethane to give, after washing, drying, and concentration, 6.928 g. (64% based on the starting unsaturated acid **27**) of a mixture of esters as a pale yellow liquid. This material contained[29] the ester **20** (2%, 15.4 min.), the ester **21** (18.6 min.) partially resolved from a small amount of an unknown component A (*ca.* 20 min., total 25%), the ester **22** (67%, 23.4 min.), and two additional compounds B (1%, 29.4 min.) and C (5%, 38.6 min.). Collected[29] samples of esters **20–22** were identified with previously described samples by comparison of retention times and infrared and mass spectra. The collected sample of ester **22** has infrared absorption[18] at 1740 cm.$^{-1}$ (ester C═O) with a molecular ion peak at *m/e* 182 in its mass spectrum as well as abundant fragment peaks at *m/e* 150, 108, 87, 81, 67, 55, and 41. The n.m.r. spectrum[18] of ester **22** has a singlet at δ 3.74 (3H, $-CO_2CH_3$) with a broad multiplet centered at δ 2.85 (1H, $CH-CO_2R$) and complex absorption in the region δ 1.0–2.5 (14H, aliphatic C–H).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.62; H, 10.05.

A collected[29] sample of component B, with infrared absorption at 1710 and 1645 cm.$^{-1}$ and a molecular ion peak at *m/e* 180 in the mass spectrum, appears to be one or more of the tetrahydroindancarboxylic esters. No further characterization of components A, B, and C was attempted.

The above ester mixture (602.2 mg., 3.4 mmoles) from hydrogenation and subsequent esterification was dissolved in 5 ml. of methanol containing 16 mmoles of sodium methoxide. After the resulting mixture had been refluxed for 24 hr., it was diluted with water and petroleum ether. The organic layer was separated, dried, and concentrated at which time the residual yellow liquid contained[29] primarily the ester **21** accompanied by smaller amounts of esters **20** and **22** as well as components B and C. A collected sample of ester **21** from this reaction was identified with the previously described material by comparison of retention times and infrared spectra. A comparable equilibration employing 28.2 mg. (0.16 mmole) of the pure[29] ester **22** in 1 ml. of methanol containing 0.9 mmole of sodium methoxide afforded a mixture composed of[29] 88% of the ester **21** and 12% of the ester **22**.[15] Application of the same equilibration procedure to the ester **20** failed to reveal the formation of a second component. However, it is possible that the two epimers of the *trans*-fused ester (**20** and its C-1 epimer) were not resolved by the gas chromatography column[29] used.

Preparation of the Acid Chloride 23.—A solution of 3.74 g. (22 mmoles) of the *trans* acid **24** in 4.5 ml. of thionyl chloride was refluxed for 2 hr. and then concentrated under reduced pressure. Distillation of the residue afforded 3.783 g. (92%) of the acid chloride **23** as a colorless liquid, b.p. 90–92° (7 mm.), $n^{25}D$ 1.4956. The product has infrared bands[18] of equal intensity at 1790 and 1815 cm.$^{-1}$ ($\mathrm{O{=}\overset{|}{C}{-}Cl}$, doublet presumably caused either by Fermi resonance or by the presence of comparable concentrations of two rotation isomers) with abundant fragment peaks in its mass spectrum at *m/e* 123 (D), 122, 93, 81, 80, 79, 67, 55, and 41.



D

Anal. Calcd. for $C_{10}H_{15}ClO$: C, 64.33; H, 8.10; Cl, 18.99. Found: C, 64.61; H, 8.01; Cl, 18.62.

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[35] R. A. Heacock, R. L. Wain, and F. Wightman, *Ann. Appl. Biol.*, **46**, 352 (1958).

[36] Preparations of the acid **29** have been reported by (a) D. W. Mathieson [*J. Chem. Soc.*, 3251 (1953)], who reported m.p. 94–95° for one isomer believed to have a *cis*-fused ring juncture, and (b) M. J. LeGoffic and F. LeGoffic [*Compt. rend.*, **255**, 539 (1962)], who prepared a *p*-bromophenacyl ester derivative, m.p. 88–89°, of uncertain stereochemistry.

The Synthesis and Attempted Rearrangement of a Blocked Dienone

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Received November 30, 1964

In order to determine whether the dienone–phenol rearrangement would proceed in a manner which would disrupt the aromaticity of a benzene ring, 3,4,4-trimethyl-1-oxo-1(4H)-dihydronaphthalene has been synthesized. The Friedel–Crafts reaction of 3,4,4-trimethylbutyrolactone and benzene gave 3,4,4-trimethyl-1-tetralone, 3,3,4-trimethyl-1-tetralone, and a third isomeric ketone of unknown structure. The structures of the first two ketones were confirmed by alternate syntheses. In an effort to identify the third compound, 3,4-dimethyl benzosuberone, 2,2,3-trimethyl-1-tetralone, 3-methyl-3-isopropyl-1-indanone, 3,3-dimethyl-1-indanone, and 3-isopropyl-1-indanone were synthesized. The desired dienone was prepared by bromination followed by dehydrobromination of 3,4,4-trimethyl-1-tetralone. Attempted rearrangement of this compound gave no phenol, but did afford a disulfonation product.

Although many studies of the dienone–phenol rearrangement have been carried out in recent years in order to more clearly define the course of this rearrangement, all attempts to design a system where the rearrangement would proceed through an aromatic ring have failed. The two reported attempts[3] both proceeded in an anomalous, though logical, manner without disrupting the aromaticity of the systems involved.

In order to have available a system where rearrangement without disrupting the aromatic character of the system is precluded, we have prepared and treated with acid 3,4,4-trimethyl-1-oxo-1(4H)-dihydronaphthalene (I). It will be noted that protonation of I could give rise to a carbonium ion (II), which although it may rearrange to ion III can undergo no further normal rearrangement, and in fact might be expected to revert to I. It was anticipated that, if rearrangement did occur, it would of necessity proceed from I

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[3] (a) E. N. Marvell and A. C. Geiszler, *J. Am. Chem. Soc.*, **74**, 1259 (1952); (b) E. N. Marvell and J. L. Stephenson, *ibid.*, **77**, 5177 (1955).