The ethereal solution was washed with a 75-ml. and three 25-ml. portions of water and with 25 ml. of brine, and dried over magnesium sulfate. The solvent was evaporated and the crude product was recrystallized from petroleum ether (35 mg., 46% yield). It melted at 65.4–66.2° after two more recrystallizations. The residue from evaporation of the mother liquor (17 mg.) was shown by gas chromatography on base-washed Silicone oil to contain no 9,10-octalin oxide (XXI). The m.p. was that reported by Hückel (65°) for *cis*-9-decalol (XXII) (the *trans* isomer melts at 54°).[27]

Solvolysis of 3-Cycloöcten-1-yl Brosylate with Trifluoroacetic Acid.—To a solution of 1.03 g. (0.0125 mole) of anhydrous sodium acetate in 22.8 g. (0.2 mole) of trifluoroacetic acid was added 3.45 g. (0.01 mole) of 3-cycloöcten-1-yl brosylate[4] over a period of 3 minutes, and the mixture was stirred for 70 minutes at 30–34° with exclusion of atmospheric moisture. A white solid precipitated. A solution of 25 g. of sodium hydroxide in 100 ml. of water was added dropwise to the mixture, which was cooled in an ice-bath. The mixture was shaken for 44 hours at room temperature to saponify esters. The product was extracted continuously with methylene chloride, and the extract was dried over magnesium sulfate. The crude product was distilled in a short path still at 0.3 mm. pressure; 0.765 g. (60.5% yield) of product was obtained and analyzed by gas chromatography on Silicone oil. *trans*-2-Vinylcyclohexanol (XXIII) (6.7%) was found to be present and was collected from the effluent gas of the gas chromatogram. The infrared spectrum of this sample was identical with that of authentic *trans*-2-vinylcyclohexanol (XXIII).[4] The remainder of the product was 3-cyclöcten-1-ol, identified by comparison of the infrared spectrum with that of an authentic sample.

Solvolysis of 4-Cycloöcten-1-yl Brosylate (I) in the Presence of *trans*-2-Vinylcyclohexanol (XXIII).—To a solution of 1.03 g. (0.0125 mole) of anhydrous sodium acetate in 22.8 g. (0.2 mole) of trifluoroacetic acid was added 3.28 g. (0.0095 mole) of 4-cycloöcten-1-yl brosylate (I)[4] and 0.060 g. (0.0005 mole) of *trans*-2-vinylcyclohexanol.[4] The mixture was stirred at room temperature for 2 hours, taken up in ether, washed free of acid, saponified and distilled in a short path still as described previously. Gas chromatography of the product (on Silicone oil at 190°), obtained in 55% yield, showed the presence of 4.0% of *trans*-2-vinylcyclohexanol (5.0% was added initially), which corresponds to an actual recovery of 47%. The other products were those described previously.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY]

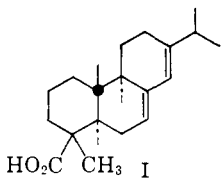
The Synthesis of Substituted 1-Methylcyclohexanecarboxylic Acids and the Stereochemistry of the Favorskii Rearrangement

BY GILBERT STORK AND IRVING J. BOROWITZ

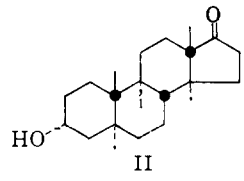
RECEIVED DECEMBER 4, 1959

The stereoelectronic requirements of the Favorskiĭ reaction are examined. It is concluded that the formation of the cyclopropanone intermediate is *concerted*, (at least in the case of 1-chloro-1-acetylcyclohexane), in disagreement with a recent proposal. Some extensions of the reaction are also described.

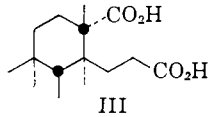
The synthesis of 1-methylcyclohexanecarboxylic acids presents a certain interest because of the presence of this structural unit in, *e.g.*, the terpene acids (*cf.* abietic acid, I) and in precursors (*e.g.* III) of the C/D ring system of the steroid 17-ketones (*cf.* androsterone, II) in which the cyclopentanone ring can be formed by cyclization.



I



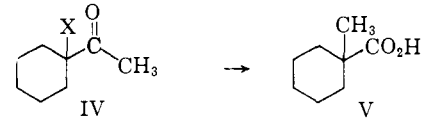
II



III

Various methods are available for the synthesis of 1-methylcyclohexanecarboxylic acid itself, among which may be mentioned Diels–Alder addition with methyl methacrylate and butadiene, followed by reduction[1]; the introduction of a 1-substituent into a suitable methylcyclohexane derivative, followed by its transformation into a carboxyl[2,3]; and the converse method of introducing a 1-methyl into a properly constituted derivative of cyclohexanecarboxylic acid.[4–6] The penultimate method has been used in the resin acid field while the last has been frequently employed in steroid syntheses.

Still another method attracted our interest: The Favorskiĭ rearrangement of 1-halo-1-acetylcyclohexane (IV) which has been shown to give the anticipated tertiary acid V on treatment with base.[7a,b] This result is consonant with the mechanism of the rearrangement



IV V

proposed, and elegantly supported, by Loftfield.[8] According to this scheme, a cyclopropanone is first formed, and this then opens to produce the less unstable carbanion,[9] leading to V in this particular case.

(1) J. D. Roberts, A. K. Jeydel and R. Armstrong, THIS JOURNAL, **71**, 3248 (1949); V. N. Ipatieff, J. E. Germain and H. Pines, *Bull. soc. chim. France*, 259 (1951).

(2) G. Stork and J. W. Schulenberg, THIS JOURNAL, **78**, 250 (1956).

(3) T. Reichstein, H. R. Rosenberg and R. Eberhardt, *Helv. Chim. Acta*, **18**, 721 (1935).

(4) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

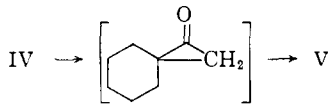
(5) R. Robinson and J. Walker, *ibid.*, 747 (1936).

(6) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

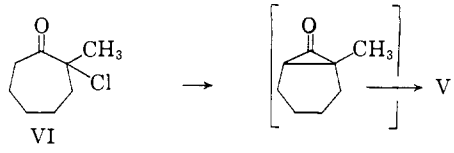
(7) (a) B. Tchoubar and O. Sackur. *Compt. rend.*, **208**, 1020 (1939). (b) B. Tchoubar, *Bull. soc. chim. France*, **10**, 1363 (1955), gives an excellent review of reactions of nucleophilic agents on α-haloketones.

(8) R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951).

(9) That tertiary carbanions are less stable than secondary, and these in turn less than primary, is well illustrated, *e.g.*, by the order of stability of the metal alkyls (methyllithium is stable in ether while *t*-butyllithium decomposes it to ethylene; methyllithium does not add to ethylene while *t*-butyllithium does (*cf.* P. D. Bartlett, S. Friedman and M. Stiles, THIS JOURNAL, **75**, 1771 (1953)). For another illustration, see base-opening of cyclic ketones such as camphor or estrone in which a primary carbanion is involved rather than the alternative tertiary.



The rearrangement illustrated above has been used repeatedly in the 20-ketosteroid series to produce 17-methyl, 17-carboxy compounds which served as sources of modified hormones,[10] but in the cyclohexane series the example IV → V has remained unique and no synthetic use has been made of this interesting transformation.[11] The attractive possibility of using the reaction in complex cases such as were mentioned at the outset clearly requires a knowledge of the stereochemical course of the reaction and it is this topic which will be the main concern of this paper. Before turning to a consideration of this subject, however, we would like to mention some experiments we carried out on the development of an alternate path, also using the Favorskii rearrangement, to the synthesis of tertiary acids such as V.

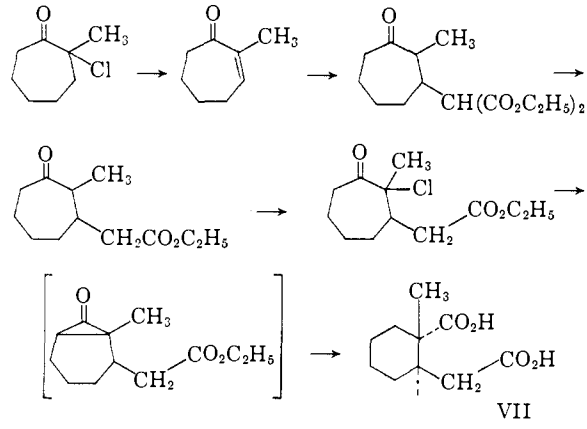


VI

It is well known that the Favorskii reaction on an α-halocyclohexanone leads to derivatives of cyclopentane-carboxylic acid, at least when the formation of a cyclopropanone intermediate is not precluded. In the case of 2-chlorocyclohexanone the chlorine is secondary and it seemed possible that the reaction could be extended to compounds such as 2-methyl-2-chlorocycloheptanone (VI) in which the halogen is tertiary, as it is in IV. Rearrangement of VI would be expected to provide another route to V, assuming again that the intermediate cyclopropanone would open to form the less unstable carbanion.

As a test of the feasibility of this type of reaction, we investigated first the lower homolog of VI, the readily available 2-chloro-2-methylcyclohexanone. Using the best conditions which we had developed for 2-chlorocyclohexanone,[12] we were, however, unable to obtain any 1-methylcyclopentane-carboxylic acid: the haloketone was completely destroyed with the formation of much tarry matter.[13] This result did not appear to augur well for the proposed VI → V rearrangement. It may be recalled, however, that 2-chlorocycloheptanone rearranges to cyclohexanecarboxylic acid[14] under much milder conditions than are necessary with its lower homolog. Possibly, this is a reflection of the smaller strain involved in fusing the three-membered cyclopropanone ring to a six rather than to a five-membered ring. These considerations led us to attempt the reaction with VI itself: Ring enlargement of cyclohexanone with diazoethane readily gave 2-methylcycloheptanone, and this was chlorinated with sulfuryl chloride to 2-chloro-2-methylcycloheptanone. Treatment with sodium benzyloxide in dry benzyl alcohol, followed by hydrogenolysis of the resulting benzyl ester indeed gave, in 40% yield, 1-methylcyclohexanecarboxylic acid (V).

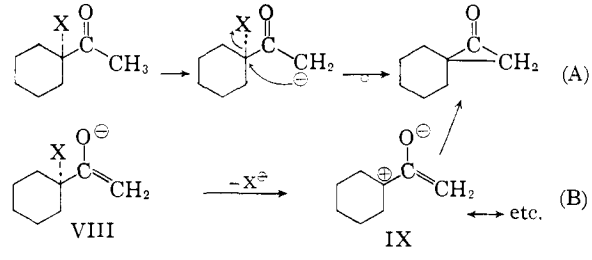
The base-catalyzed rearrangement of 2-alkyl-2-halocycloheptanones thus constitutes an alternative synthesis of the 1-methylcyclohexanecarboxylic acid system (V). It is, however, not a generally suitable method at present because of the difficulty of preparing more complex 2-methylcycloheptanones. We have, nevertheless, utilized it to prepare 2-carboxycyclohexaneacetic acid as



VII

The final product of rearrangement which we isolated turned out to be the *trans*-diacid VII, but no special significance can be attributed to this result as regards the steric course of the rearrangement because VII was obtained pure in only 15% yield.

We now consider the problem of the stereochemistry of the Favorskii rearrangement. At least two possibilities appear worth considering: The reaction by which the intermediate cyclopropanone is formed may be concerted as shown in A or, alternatively, the initially formed anion may lose chloride ion as shown in B, thus giving a dipolar ion IX for which several structures may be written. This then collapses to a cyclopropanone.



VIII IX

The first mechanism is formally analogous to the formation of an epoxide from a chlorohydrin and would result in inversion at the halogen-bearing

(10) Ch. R. Engel, THIS JOURNAL, **77**, 1064 (1955), and earlier papers.

(11) An extensive historical review of the Favorskii reaction is given by R. Jacquier, *Bull. soc. chim. France*, D 35 (1950). An up to date discussion is presented by A. S. Kende, "The Favorskii Rearrangement of Haloketones," Org. Reactions, Vol. XI, John Wiley and Sons, Inc., New York, N. Y., 1960, Chapt. 4.

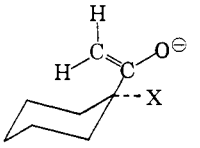
(12) A discussion of the best conditions for carrying out the Favorskii rearrangement is given in the Experimental part.

(13) It has been claimed by Mousseron, *et al.* (*Bull. soc. chim. France*, **14**, 83 (1947)) that whereas 2-chloro-2-methylcyclohexanone gives almost no acid on rearrangement, the isomeric 6-chloro compound rearranges to 2-methylcyclopentanecarboxylic acid rather than to the expected 1-methyl compound. These results, if confirmed, would be quite remarkable.

(14) C. D. Gutsche, THIS JOURNAL, **71**, 3513 (1949).

carbon atom while the second possibility would lead to a cyclopropanone intermediate, the stereochemistry of which need bear no relationship to that of the original carbon–halogen bond and would presumably be determined by steric considerations.

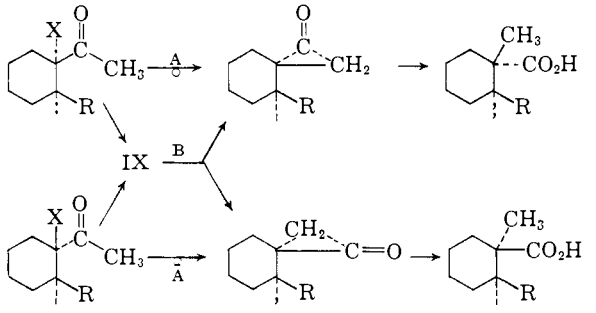
The possible intervention of path B was initially suggested by Aston and Newkirk,[15] and their proposal was rescued from comparative obscurity by Burr and Dewar[16] who pointed out that the similarity of path A to epoxide formation may be more apparent than real: In the enolate ion VIII we have a situation in which the negatively charged carbon atom must be essentially trigonal and coplanar with the carbonyl group, thus preventing the p-orbital of the negatively charged carbon atom from overlapping with orbitals of the halogen-bearing carbon atom (see VIIIa), unless there is some torsion of the carbon–carbon double bond



VIIIa

in the enolate ion, "and so it is very difficult to see how any interaction between these carbon atoms could stabilize the SN2 transition state for expulsion of the halogen with simultaneous formation of a three-membered ring."[16]

Burr and Dewar have further calculated that the change of VIII into IX should be attended by



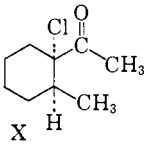
an increase in conjugation energy of about 14 kcal., and that, therefore, "the reaction proceeds by loss of halogen from the initial carbanion to give the zwitterion suggested by Aston and Newkirk." The further transformation of IX into the cyclopropanone was calculated to be exothermic by *ca.* 11 kcal.

Another way to look at the problem, however, is that following path B does not really remove the difficulty: torsion around the double bond has to be achieved *in any event* either to attain some overlap with the electrons of the halogenated carbon or with the vacant p-orbital (*cf.* IX) left after loss of the chloride ion.

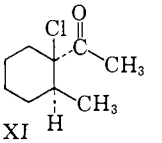
It appeared to us at this point that the problem should be attacked experimentally.

One of the operational differences between mechanisms A and B is that two haloketones epimeric at the halogen-bearing carbon should give two different acids, with inversion in each case, if path A should be correct. Either of the two epimeric haloketones would, however, give the same mixture of acids by mechanism B. This is illustrated by the IX reactions shown.

We decided to make use of a substituent in the cyclohexane ring to differentiate between the products. For this purpose it was felt that the simplest substances on which to test the mechanism of the reaction would be the *cis* and *trans* forms of 1-acetyl-1-chloro-2-methylcyclohexane (X and XI, respectively).

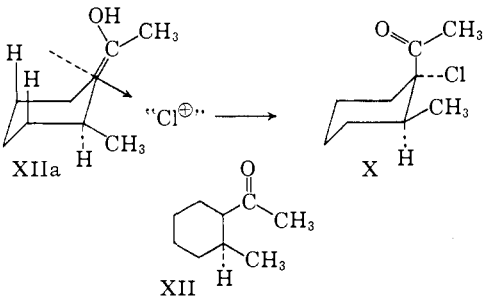


X



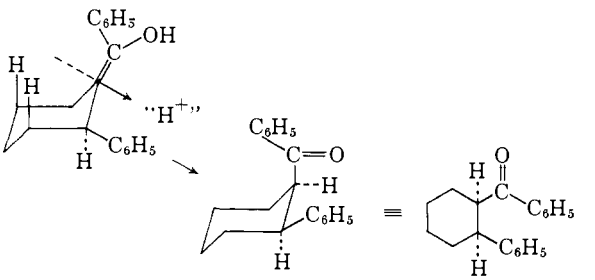
XI

Preparation and Rearrangement of the Epimeric Chloroketones X and XI.—The stereochemical arrangement shown in X was produced by the direct halogenation of 1-acetyl-2-methylcyclohexane (XII): Approach of a chlorinating agent should be easier from the side opposite the two axial hydrogen atoms of the enol (*cf.* XIIa), thus resulting in a



XIIa X XII

compound with the chlorine *cis* to the hydrogen atom on the methyl-bearing carbon. This argument is similar to that which has been proposed by Zimmerman[17] to explain the initial formation of the less stable *cis*-ketone in the ketonization of the enol of 1-benzoyl-2-phenylcyclohexane.



The correctness of the stereochemistry shown in X will be apparent in the sequel. It should be added at this point that this synthesis suffers from low yields, due presumably to polyhalogenation.[18,19]

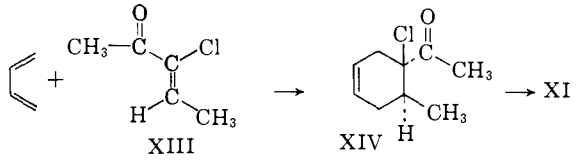
(15) J. G. Aston and J. D. Newkirk, THIS JOURNAL, **73**, 3900 (1951).

(16) J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).

(17) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

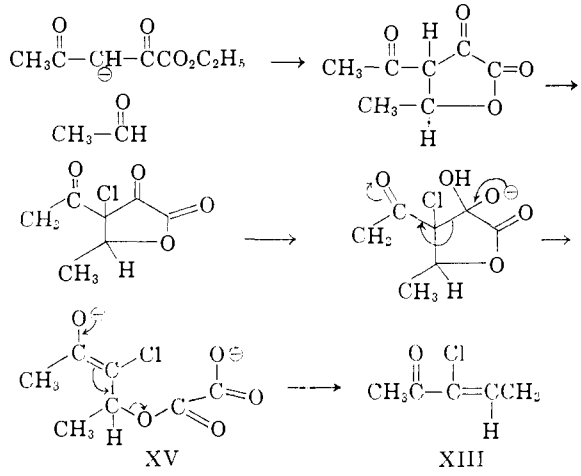
(18) The stereochemistry of the ketone being halogenated is undoubtedly important: The *trans*-ketone being the more stable isomer should go to the common enol less readily than the *cis* compound. The latter should therefore be best for angular halogenation: *cf.* H. E. Zimmerman, THIS JOURNAL, **78**, 1158 (1956). In agreement with these views, we have found that the *trans* isomer (from the reac-

The synthesis of the epimeric chloroketone XI proved more difficult. It appeared that a rational synthesis might be achieved by the reaction of *trans*-3-chloro-3-pentene-2-one (XIII) with butadiene followed by catalytic hydrogenation.



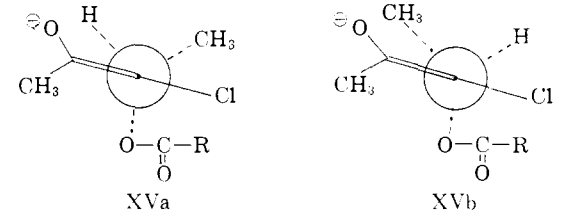
XIII XIV

The synthesis from 1-methyl-2-chloro-1,3-butadiene of a 3-chloro-3-pentene-2-one of undetermined stereochemistry has been described in the literature,[20] but we preferred to apply the general synthesis described by Nield[21]: Reaction of acetaldehyde with the sodium salt of acetopyruvic ester gave 1-oxo-2-acetyl-3-methylbutyrolactone which was chlorinated and treated with aqueous sodium bicarbonate to produce XIII.



XV XIII

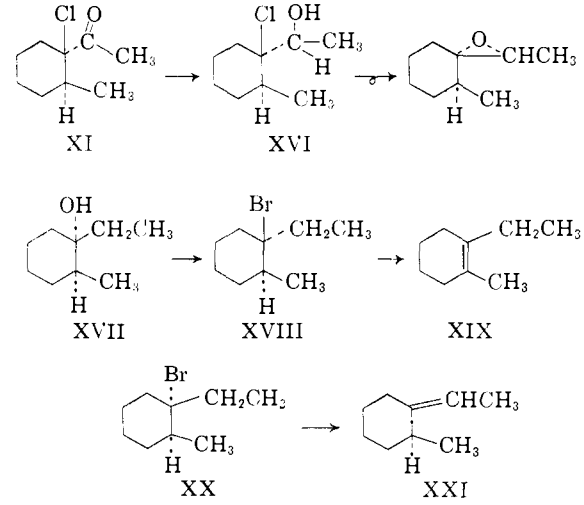
Consideration of the geometry of the intermediate XV leads to the conclusion that XVa is preferred over XVb, thus leading to the *trans* isomer of XIII.



XVa XVb

The presence of some *cis* isomer of XIII was not, in any event, of serious concern as it was felt that equilibration of the *cis* and *trans* forms of XIII might well take place under the conditions of this particular Diels–Alder addition. Such an equilibrium is known to obtain with the related α-chlorocrotonic acid and its position in that case lies, not unexpectedly, on the side of the *trans* isomer.[22,23,24] Addition of XIII to butadiene was successfully carried out by heating the reactants two hours at 160°, followed by twenty-four hours at 130°. The product XIV was hydrogenated over palladium to the desired chloroketone XI.

Evidence for the correctness of the stereochemistry indicated in XI was obtained in two different ways. In the first sequence, the chloroketone was reduced with sodium borohydride to the chlorohydrin XVI which was then transformed into the corresponding epoxide. Lithium aluminum hydride reduction gave the tertiary alcohol[25] XVII which led to the bromide XVIII with phosphorus tribromide. Treatment of XVIII with sodium ethoxide gave, in an over-all yield of 36%, an olefin which would have to be XIX if the initial stereochemistry is properly represented by XI. Had the initial haloketone in reality been the epimeric X, the derived bromide would have been XX and the final olefin XXI.[26] Nuclear magnetic resonance served to distinguish between these two possibilities: The final olefin had no vinyl proton and is therefore XIX, as required.



XI XVI XVII XVIII XIX XX XXI

A more direct proof of the stereochemistry of XI was obtained by adding a derivative of authentic *trans*-α-chlorocrotonic acid to 2,3-dimethylbutadiene, followed by transformation of the carboxyl into a methyl ketone. This proved identical with the product of addition of 2,3-dimethylbutadiene and our 3-chloro-3-pentene-2-one (XIII) thus establishing that the stereochemistry of the Diels–Alder adducts of XIII had been correctly inferred. The benzyl ester of *trans*-α-chlorocrotonic acid was selected for the Diels–Alder addition after it was found that the free acid gave very poor results. Catalytic hydrogenolysis of the adduct gave the crystalline acid XXII, m.p. 102.4–103.1°. This

tion of butadiene with *trans*-3-pentene-2-one, followed by hydrogenation) gave considerably poorer results in halogenation experiments than its *cis* congener.

(19) A much better synthesis of angularly halogenated ketones of this type has been designed. This will be discussed in a separate communication: G. Stork, W. S. Worrall and J. J. Pappas, THIS JOURNAL, **82**, 4315 (1960).

(20) A. A. Petrov and E. A. Leporskaya, *J. Gen. Chem.* (*USSR*), **23**, 1038 (1953).

(21) C. H. Nield, THIS JOURNAL, **67**, 1145 (1945).

(22) J. Wislicenus, *Ann.*, **248**, 283 (1888).

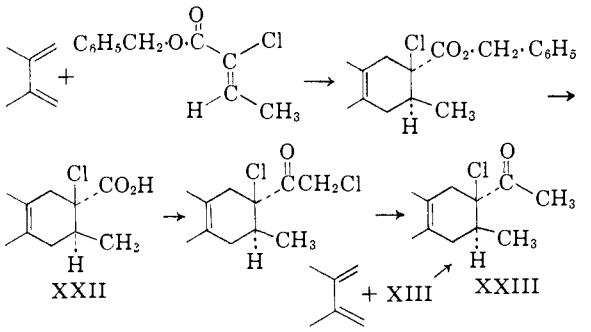
(23) P. Pfeiffer, *Ber.*, **43**, 3041 (1910).

(24) T. C. James, *J. Chem. Soc.*, **97**, 1570 (1910).

(25) The reduction of the epoxide of ethylidenecyclohexane is reported to give, unexpectedly, the *secondary* alcohol methylcyclohexylcarbinol: M. Mousseron, R. Jacquier, M. Mousseron-Canet and R. Zagdoun, *Bull. soc. chim. France*, 1042 (1952). This result, if confirmed, is certainly quite unexpected (see for instance Wendler, *et al.*, ref. 29).

(26) T. D. Nevitt and G. S. Hammond, THIS JOURNAL, **76**, 4124 (1954).

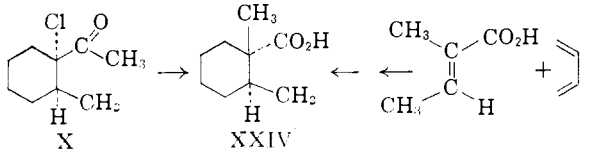
was transformed into the α,α'-dichloroketone *via* the diazoketone and, finally, the primary chlorine was removed by exchange with iodide ion, followed by bisulfite reduction.[27] The methyl ketone XXIII thus obtained was identical with the adduct of our 3-chloro-3-pentene-2-one (XIII) and 2,3-dimethylbutadiene, as demonstrated by the identity of their infrared spectra and, as we will see later, if their respective Favorskiĭ rearrangement products.



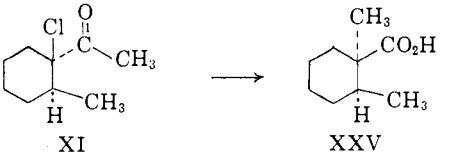
It must be recognized at this point that although the proof of the stereochemistry of XI is quite convincing, the same cannot be said in the case of X: The argument in that case was merely a theoretical one and, unfortunately, the two haloketones X and XI which we have claimed to be epimeric, are liquids which, although obtained in a state of analytical purity, could not be derivatized. Their infrared spectra were also very similar although XI had a medium intensity band at 8.0μ which appeared to be absent in the spectrum of its presumed epimer.

We will now demonstrate that X and XI are indeed epimeric and that each is substantially free from contamination with the other; and that further, the Favorskiĭ rearrangement is stereospecific, thereby ruling out the zwitterion mechanism.

The haloketone X was rearranged with dry sodium benzyloxide in ether and the ester was hydrolyzed or hydrogenolyzed to a liquid acid. This acid was shown to be *cis*-1,2-dimethylcyclohexanecarboxylic acid (XXIV), as it was converted into an anilide, m.p. 113.8–115.8°, in the same yield as authentic XXIV made by Diels–Alder addition of tiglic acid to butadiene. Mixed melting point determination and infrared spectra served to establish identity of the anilides from the two sources.

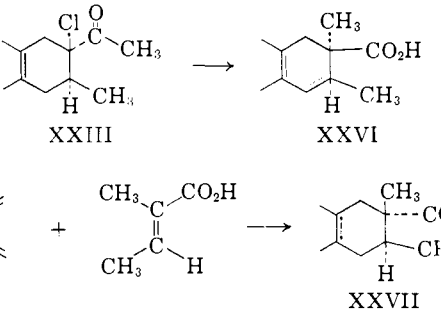


The stereochemistry of tiglic acid is established beyond doubt[28] and hence the stereochemistry of XXIV. The formation of XXIV by the Favorskiĭ rearrangement of X could still be reconciled with either the concerted, inversion mechanism or the dipolar ion suggestion. The stereochemistry of the rearrangement product of the epimeric chloroketone XI thus becomes of paramount interest: Rearrangement of XI, under the conditions used with X, gave a liquid acid which must be correctly represented by XXV since it was converted, in about the same yield as XXIV, into an isomeric anilide, m.p. 81.4–82.6°.



The two anilides derived from XXIV and XXV exhibit a number of differences in their infrared spectra. In particular, the anilide from XXIV has a strong band at 8.7 μ which is absent from the spectrum of its epimer; while the infrared spectrum of the latter has a medium band at 11.5μ which is missing from that of the former. It was thus possible to show by examination of the spectra of the crude anilides before purification, that neither acid could have contained appreciable amounts of its epimer.

The rearrangement of X and XI to different acids proves that these two haloketones are indeed epimeric, as we had concluded on other grounds. Similarly, the formation of the same chloroketone (XXIII) from 2,3-dimethylbutadiene and 3-chloro-3-pentene-2-one on the one hand and *trans*-α-chlorocrotonic acid on the other, which was based in our previous argument merely on comparison of infrared spectra, was confirmed by rearranging samples made by the two different routes to the same acid XXVI, m.p. 80–81.6°, different from the acid XXVII obtained by addition of 2,3-dimethylbutadiene to tiglic acid. The latter melted at 86–87.0° and depressed the melting point of the former to 54–56°. Again, mutually



exclusive bands made it possible to show the substantial absence of the epimeric acid in the total crude acid fraction from the above reactions.

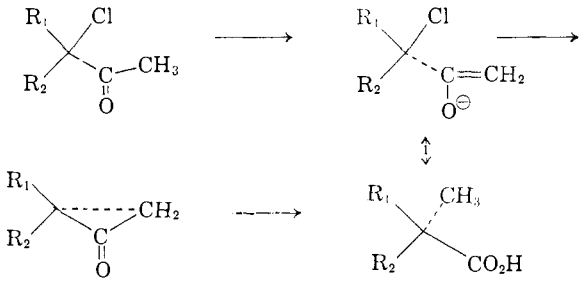
We therefore conclude that the Favorskiĭ rearrangement is stereospecific and the resulting new carbon–carbon bond has the opposite configuration to that of the departing halogen.[29] The reaction

(27) *Cf.* G. Stork and F. H. Clarke, Jr., THIS JOURNAL, **77**, 1072 (1955).

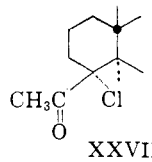
(28) R. E. Buckles, G. V. Mock and L. Locatelli, *Chem. Revs.*, **55**, 659 (1955).

(29) It does not, of course, follow that Favorskiĭ rearrangements *always* take place concertedly rather than by a mechanism such as that involving a dipolar ion intermediate. The latter mechanism could conceivably be involved with 17α-bromo-20-ketosteroids in which rearrangement leads simultaneously to both 17β- *and* 17α-methyl compounds (*cf.*, however, N. L. Wendler, R. P. Graber and C. G. Hazen, *Tetrahedron*, **3**, 144 (1958)). These cases deserve further study.

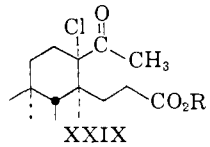
may thus be represented in the cases under discussion as



The Favorskiĭ reaction thus represents a possible route to angularly methylated tertiary acids of definite stereochemistry. It may be noted here that in the case of resin acids such as I and steroid precursors such as III, the requisite chloroketones would have to possess the stereochemistry indicated by XXVIII and XXIX, respectively. In



XXVIII



XXIX

both cases this represents the stereochemistry expected from direct halogenation of the parent ketone. Direct halogenation is, however, not always satisfactory in these and other cases and there is thus need of an alternative method of synthesis of α-haloketones which would produce the same stereochemistry as direct halogenation. Such a synthesis will be described in a separate communication.[19]

Experimental

Effect of Alkoxide Type and Concentration in the Favorskiĭ Rearrangement of 2-Chlorocyclohexanone.—A careful study of various factors affecting the rearrangement of 2-chlorocyclohexanone[30] showed that the best results are obtained by using sodium benzyloxide as the base. Under comparable conditions, the *yields decreased in the order benzyloxide, ethoxide, methoxide and isopropoxide.* The best yields were obtained with a considerable excess of alkoxide in homogeneous benzyl alcohol solution: We used a 3.6 *M* solution of the alkoxide. This is as concentrated as the solubility of sodium benzyloxide in benzyl alcohol allows. For this particular type of haloketone the reaction was better in homogeneous than heterogeneous (ether) medium. This is not the case for 1-chloro-1-acetylcyclohexanes (*vide infra*).

To a 3.6 *M* solution of sodium benzyloxide in benzyl alcohol, containing 3.52 equiv. of sodium, was added 3.3 g. of 2-chlorocyclohexanone over a period of 30 minutes. The initial temperature was 19° and rose to 40° during addition. The mixture was stirred an additional hour and hydrolysis was carried out by removing some of the benzyl alcohol under vacuum and then adding enough water to make a 10% aqueous sodium hydroxide solution. Heating *under nitrogen* on the steam-bath for 2 hours hydrolyzed the ester to the acid which was isolated as usual and distilled at 13 mm. from an oil-jacketed flask at a bath temperature of 110–150°. Cyclopentanecarboxylic acid was thus obtained in 75% yield.

Effect of Alkoxide Type and Concentration on the Rearrangement of 1-Chloro-1-acetylcyclohexane.—Here again we found sodium benzyloxide to be preferable to other alkoxides, especially as the tertiary ester could be hydrogenolyzed rather than hydrolyzed to the corresponding acid. We found, however, that with this type of tertiary haloketone the use of heterogeneous conditions gave a higher yield: To a suspension of sodium benzyloxide (from 1.42 g. of sodium, 3.52 equiv.) in 20 ml. of dry ether was added 2.8 g. of 1-chloro-1-acetylcyclohexane. The initial temperature was 10° and rose to 20° during the addition. The mixture was stirred at room temperature for 17 hours and hydrolysis was carried out by removing the ether, adding 5 ml. of water and refluxing under nitrogen for 48 hours. Usual work up gave 1-methylcyclohexanecarboxylic acid in 72% yield.

Attempted Rearrangement of 2-Chloro-2-methylcyclohexanone.—This ketone was prepared as described by Johnson.[31] Rearrangement was unsuccessful as sodium benzyloxide in benzyl alcohol, sodium ethoxide in ethanol or sodium methoxide in methanol led only to very small amounts of unpurifiable acid fractions, after base hydrolysis.

Rearrangement of 2-Chloro-2-methylcycloheptanone.—The 2-methylcycloheptanone was prepared by ring enlargement of cyclohexanone with diazoethane generated from N-nitroso-N-ethylcarbamate.[32] It had b.p. 178–183°, $n^{29}D$ 1.4528, and was obtained in 63% yield.

The 2,4-dinitrophenylhydrazone had m.p. 111.0–112.5° (reported[32] 121–122°).

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92. Found: C, 54.88; H, 5.40.

2-Methyl-2-chlorocycloheptanone (VI) was prepared essentially by the same procedure as the corresponding cyclohexanone. The yield of product, b.p. 58–60° (2.2 mm.), was 56%. A redistilled sample had b.p. 65–66° (2 mm.), $n^{24}D$ 1.4790 and $\lambda_{max}^{CCl_4}$ 5.87 μ.

Anal. Calcd. for $C_8H_{13}OCl$: C, 59.81; H, 8.16. Found: C, 59.40; H, 7.76.

To a solution of 6.15 g. (0.267 g. atom) of sodium in 76 ml. of dry benzyl alcohol was added, at 6–10°, 12.15 g. (0.0754 mole) of VI over a 28-minute period. The reddish reaction mixture was shaken at room temperature for 1.75 hours and was then worked up by adding 80 ml. of ice-water and extracting with ether. After washing the extract with water and drying, removal of ether and benzyl alcohol was carried out at 18 mm., at a bath temperature of 140°. Distillation of the residue gave 6.88 g. of benzyl ester which came over at a bath temperature of 100–150° (0.05 mm.). The ester (3.0 g.) was dissolved in 24 ml. of ethyl acetate containing one drop of concd. sulfuric acid and reduction was carried out with 0.23 g. of 10% palladium-on-charcoal. Absorption of hydrogen ceased after 5.75 hours. The yield of distilled 1-methylcyclohexanecarboxylic acid (V) was 1.41 g. This boiled at a bath temperature of 135–145° at 0.7 mm.

The anilide, m.p. 110.2–111.4°, after recrystallization from benzene, was obtained in 78% yield and did not depress the m.p. of an authentic sample.

From the original basic aqueous solution from the isolation of the benzyl ester another 2.1 g. of acid could be obtained. This gave the same anilide as above. The total yield of acid V was 5.37 g. (41%).

2-Methylcycloheptenone was prepared from VI by collidine dehydrochlorination by the procedure described for the corresponding cyclohexenone.[31] Reaction occurred here at the higher temperature of 210–220°. After two distillations the yield of enone was 34%, b.p. 87–89°; λ_{max}^{EtOH} 237 mμ, ϵ 5670; $\lambda_{max}^{CHCl_3}$ 6.07μ.

The red **2,4-dinitrophenylhydrazone**, recrystallized from absolute ethanol, had m.p. 121–122°.

Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.30. Found: C, 55.62; H, 5.14.

Methyl 2-Methyl-3-oxocycloheptaneacetate.—To a solution of 0.080 g. (0.035 g. atom) of sodium in 8 ml. of dry ethanol was added, under nitrogen at 0°, 3.67 ml. (3.87 g., 0.0242 mole) of diethyl malonate. After 10 minutes, 3.0 g. (0.0242 mole) of 2-methylcycloheptenone was added and the solution was kept at room temperature for 20 hours under nitrogen. The ethanol was removed under suction and 6.05 ml. of glacial acetic acid, 3.1 ml. of concd. hydrochloric acid and 1.5 ml. of water were added. The

(30) M. S. Newman, M. P. Farbman and H. Hipsher, *Org. Syntheses*, **25**, 22 (1945).

(31) E. W. Warnoff and W. S. Johnson, THIS JOURNAL, **75**, 494 (1953).

(32) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

solution was refluxed for 24 hours. The acetic and hydrochloric acids were removed at 100° bath temperature (20 mm.) and a mixture of 2 ml. of concd. sulfuric acid and 20 ml. of methanol was added. The solution was kept at room temperature for 24 hours. Half of the methanol was boiled off on the steam-bath, the residual solution was added to 50 g. of ice and extracted with ether. The combined ether extracts were washed with water and dried. Distillation at a bath temperature of 105–125° (0.3 mm.) yielded 2.39 g. of methyl 2-methyl-3-oxocycloheptaneacetate, a yield of 52%. The infrared spectrum (chloroform) had carbonyl peaks at 5.82 (ester) and 5.93 μ (ketone).

The orange **2,4-dinitrophenylhydrazone**, recrystallized from methanol–chloroform, had a m.p. of 150.2–152.2°.

Anal. Calcd. for $C_{17}H_{22}O_6N_4$: C, 53.96; H, 5.86. Found: C, 54.03; H, 5.74.

Methyl *trans*-2-methyl-2-chloro-3-oxocycloheptaneacetate was prepared in 80% yield by sulfuryl chloride chlorination in the usual way. The product distilled at a bath temperature of 102–125° (0.1 mm.), $\lambda_{max}^{CHCl_3}$ 5.85μ (broad). Rearrangement was carried out as described below for the case of X, no stirring being used in this case. Hydrolysis, followed by distillation of the acid fraction at a bath temperature of 180° (20 mm.) led to a mixture of oil and solid which was refluxed with dilute sodium hydroxide to open any anhydride which might have been present. The acidic fraction gave only 15% yield of *trans*-2-methyl-2-carboxycyclohexaneacetic acid, m.p. 173.4–176.0° after several acetone–pentane recrystallizations (reported[33] m.p. 175–177.8°). The melting point of a mixture with authentic *cis*-acid[33] (m.p. 161.5–163°) was depressed to 150–165°. The remaining mixture of solid and oil could not be further separated.

***cis*-1-Acetyl-1-chloro-2-methylcyclohexane (X).**—Methylcyclohexene was prepared by the dehydration of 1-methylcyclohexanol with iodine. The olefin boiled at 105–106° (reported[34] 110–111°). This was converted[35] in 40% yield to a mixture of 1-acetyl-2-methyl-1-cyclohexene and 1-acetyl-2-methyl-2-cyclohexene, b.p. 110–115° (16 mm.), and this was hydrogenated: A solution of 23.3 g. (0.169 mole) of the unsaturated ketone mixture in 50 ml. of absolute ethanol containing a pellet of potassium hydroxide was reduced with difficulty on the Parr shaker, using a total of 1.8 g. of 10% palladium-on-charcoal, added in four portions. The reduction had stopped before each new addition. A total 10.5 lb. (*ca.* 0.13 mole) of hydrogen was absorbed. The usual work-up gave the mixture of saturated ketones in 45% yield, b.p. 75–80° (16 mm.); reported[36]: *cis*, b.p. 67–68° (10 mm.); *trans*, b.p. 64–65° (10 mm.). The semicarbazone showed that the ketone was a mixture of *cis* and *trans* isomers, as expected: It had m.p. 162.4–165.2° (reported[37]: *cis*, m.p. 182.0–182.5°; *trans*, m.p. 177–178.5°).

The mixture of *cis*- and *trans*-1-acetyl-2-methylcyclohexane was chlorinated by treating 10.0 g. (0.0713 mole) with 6.9 ml. (0.1085 mole) of sulfuryl chloride under the conditions described for 2-methylcyclohexanone.[31] This gave 2.16–3.83 g. of product, b.p. 88–95° (14 mm.), $n^{24.5}D$ 1.4707, of chloroketone X (17–31% yield). A higher boiling fraction (b.p. 90–100° at 9 mm.) was also obtained. This had $n^{24.5}D$ 1.4794 and was a mixture of mono- and dichloroketones.

Anal. Calcd. for $C_9H_{15}OCl$: C, 61.88; H, 8.66. Found: C, 61.86; H, 8.51.

The chloroketone X did not lose halogen on treatment with NaI in ethanol, in agreement with its tertiary structure.

3-Chloro-3-pentene-2-one (XIII).—2-Keto-3-acetyl-4-methylbutyrolactone was obtained from sodium ethylacetopyruvate and acetaldehyde in 75% yield. It was isolated as its monohydrate, m.p. 89–93° (reported[21] m.p. 94–95°).

To a stirred solution of 26.0 g. (0.15 mole) of the lactone in 57 ml. of methanol and 81 ml. of water was added at 10–15° a total of 11.3 g. (0.161 mole) of chlorine gas over a period of 30 minutes. Potassium bicarbonate (53 g., 0.53 mole) was then added, followed by 105 ml. of water in 10-ml. portions while stirring at 10–15° was continued. Some foaming occurred which could be decreased by adding a little ether. Work up as described by Nield[21] for the corresponding bromo compound gave XIII in 74% yield, b.p. 55–57° (23 mm.), $n^{21}D$ 1.4702; λ_{max}^{EtOH} 237.5 mμ, ϵ 9,120; $\lambda_{max}^{CHCl_3}$ 5.95, 6.20 μ.

The red 2,4-dinitrophenylhydrazone melted at 198.8–199.5° (inserted in bath at 198°) after three recrystallizations from chloroform (reported[20] m.p. 188°).

Anal. Calcd. for $C_{11}H_{14}N_4O_4Cl$: C, 44.22; H, 3.71. Found: C, 44.45; H, 3.68.

***trans*-1-Acetyl-2-chloro-2-methylcyclohexane (XI).**—A mixture of 4.0 g. of XIII (0.0338 mole) and 12 ml. (0.136 mole) of 1,3-butadiene was heated with a few milligrams of hydroquinone for 2 hours at 160° and 24 hours at 130°. Two such runs were combined and distilled to give 6.23 g. (53% yield) of colorless liquid, b.p. 68–69° (2.5 mm.). The 1-acetyl-2-chloro-2-methyl-4-cyclohexene (XIV) thus obtained could not be ketalized with ethylene glycol using *p*-toluenesulfonic acid–benzene and a water separator. The substance was reduced catalytically: A solution of 4.0 g. of XIV in 30 ml. of cyclohexane was reduced at atmospheric pressure in the presence of 0.16 g. of 10% palladium-on-charcoal. The required amount of hydrogen was absorbed in 14.5 hours. The saturated ketone XI, obtained in 72–82% yield, had b.p. 85–87° (16 mm.), $n^{24.5}D$ 1.4707 and $\lambda_{max}^{CCl_4}$ 5.89 μ.

Anal. Calcd. for $C_9H_{15}OCl$: C, 61.88; H, 8.66. Found: C, 62.27; H, 8.54.

Degradation of XI to 1-Ethyl-2-methylcyclohexene (XIX).—Reduction of chloroketone XI to the chlorohydrin XVI was carried out by treating a mixture of 13.87 g. of *trans*-haloketone XI in 300 ml. of methanol previously cooled to 5–10° with 1.7 g. of sodium borohydride. The mixture was kept at room temperature for 14 hours. Addition of 20 ml. of water and removal of most of the methanol at 20 mm. gave a residue which was extracted with ether. The ether extracts were washed with water, dried and distilled to yield 11.18 g. (80%) of liquid chlorohydrin XVI, b.p. 85–91° (4.5 mm.). This was transformed into epoxide in 46–54% yield by treatment of XVI with 3.2 equivalents of potassium hydroxide in refluxing methanol for 42 hours. The epoxide distilled at 66–75° (20 mm.) with much foaming. It was reduced by refluxing 5 hours in tetrahydrofuran solution with 4.9 equivalents of lithium aluminum hydride. Decomposition of the excess reducing agent with ethyl acetate and work up gave 73–81% yield of alcohol XVIII which distilled from an oil-jacketed flask at a bath temperature of 125–130° (28 mm.). Conversion into bromide was carried out by refluxing for 22 hours in benzene, under nitrogen, with 2 equivalents of phosphorus tribromide. The benzene solution was washed with water until free of acid and the benzene was removed on the water-pump giving a residue of bromide XVIII which was used without further purification.

The olefin XIX was obtained by treating the crude bromide with 2 equivalents of sodium hydroxide in refluxing ethanol, under nitrogen, for 17 hours. The yield was 1.49 g. (86% from the alcohol) of an oil which distilled from an oil-jacketed flask at a bath temperature of 130–160° (reported[38] for 1-ethyl-2-methylcyclohexene b.p. 156.7–157°).

Anal. Calcd. for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 86.77; H, 13.07.

The olefin was evidently 1-ethyl-2-methylcyclohexene (XIX) and contained no 2-methylethylidenecyclohexane (XXI) since (a) it had no peak in the infrared around 12.3 μ (ethylidenecyclohexane[39] has a strong peak at 12.28 μ) and (b) the nuclear magnetic resonance spectrum showed no hydrogen on a double bond. For comparison, ethylidenecyclohexane showed chemical shift of 2.27 parts per million (making the hydrogens of benzene equal to zero).

Synthetic Proof of the Configuration of the Chloroketone XI. (a) Formation of the Chloroketone XXIII by Addition of 2,3-Dimethylbutadiene to the Chloropentenone XIII.—A mixture of 2.0 g. (0.169 mole) of the chloropentenone XIII and 2 ml. (0.018 mole) of 2,3-dimethylbutadiene was

(33) W. E. Bachmann and S. Kushner, THIS JOURNAL, **65**, 1963 (1943).

(34) W. A. Mosher, *ibid*, **62**, 52 (1940).

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

(36) E. R. H. Jones, E. A. Braude, H. P. Koch, R. W. Richardson, F. Sondheimer and J. B. Toogood, *J. Chem. Soc.*, 1896 (1940).

(37) R. B. Turner, THIS JOURNAL, **72**, 878 (1950).

(38) G. Egloff, "Physical Constants of Hydrocarbons, Vol. II, Reinhold Publishing Corp., New York, N. Y., 1940, p. 336.

(39) A. J. Birch, *J. Chem. Soc.*, 809 (1945).

heated in a sealed tube with a little hydroquinone at 130° for 19.5 hours. Distillation of the products gave 68–74% of 1-acetyl-1-chloro-2,3,5-trimethyl-4-cyclohexene (XXIII) as a colorless liquid, b.p. 67–69° (0.6 mm.), ϵ_{212}^{EtOH} 1260, λ_{max}^{EtOH} 285 mμ, ε 53; $n^{19.5}D$ 1.4905; $\lambda_{max}^{CCl_4}$ 5.89 μ.

Anal. Calcd. for $C_{11}H_{17}OCl$: C, 65.82; H, 8.54. Found: C, 65.67; H, 8.39.

(b) **Formation of the Ketone XXIII from *trans*-2-Chlorocrotonic Acid.**—*trans*-2-Chlorocrotonic acid was made by chlorination of *trans*-crotonic acid in 88% yield to 2,3-dichlorobutyric acid, m.p. 50–52° (reported[22] m.p. 62°). This was dehydrochlorinated with pyridine[23] to give *trans*-2-chlorocrotonic acid in 65% yield.

The latter had m.p. 99–100° (reported[23] m.p. 99.5°) after purification through the potassium salt.[22] It had $\lambda_{max}^{CCl_4}$ 5.90 and 6.15 μ. **The benzyl ester** was prepared in 60% yield by refluxing under nitrogen for 24 hours a mixture of 25 g. of acid and 67.5 ml. of benzyl alcohol in 300 ml. of dry benzene containing 0.15 g. of *p*-toluenesulfonic acid. The water formed was removed with a water separator. Washing with water, 2% sodium bicarbonate and then drying and distillation gave 2 g. of liquid ester, b.p. 131° (3.5 mm.); λ_{max}^{EtOH} 225 mμ, ε 9830; $\lambda_{max}^{CCl_4}$ 5.85, 6.12 μ.

Addition to 2,3-dimethylbutadiene was carried out by heating in a sealed tube at 170° for 24 hours in the presence of a little hydroquinone a mixture of 12.7 g. of 2,3-dimethyl-1,3-butadiene and 28.3 g. of the above benzyl ester. The adduct was obtained as a liquid, b.p. 125–130° (0.1 mm.), in 72% yield, $\lambda_{max}^{CCl_4}$ 5.85 μ.

The benzyl ester was hydrogenolyzed to ***trans*-1-chloro-2,4,5-trimethyl-4-cyclohexenecarboxylic acid (XXII)** by reducing a solution of 0.7 g. of ester in 14 ml. of cyclohexane in the presence of 0.113 g. of 10% palladium-on-charcoal. Absorption of hydrogen at atmospheric pressure was complete in 28 minutes. Isolation gave 0.226 g. (50%) of acid, m.p. 103–105.5°. Two sublimations at a bath temperature of 70° (3 mm.) gave the analytical sample of XXII, m.p. 102.4–103.1°.

Anal. Calcd. for $C_{10}H_{14}O_2Cl$: C, 59.26; H, 7.46. Found: C, 59.66; H, 7.38.

The acid was converted into its **acid chloride** by refluxing for 8.5 hours a mixture of 5.01 g. of acid and 2 ml. of distilled thionyl chloride in 10 ml. of dry benzene. This gave complete conversion (disappearance of 5.9 μ maximum and appearance of 5.6μ acid chloride band) while oxalyl chloride or thionyl chloride in benzene at 25°, or oxalyl chloride in refluxing benzene, gave only partial conversion. The acid chloride was transformed into the diazoketone by adding the crude acid chloride from above (*ca.* 0.247 mole) to an ether solution of diazomethane prepared from 15.1 g. (0.147 mole) of N-nitrosomethylurea. The solution was kept at room temperature for 12 hours and was then evaporated at 20 mm. leaving an oil, the infrared spectrum of which showed complete conversion to diazoketone (disappearance of 5.6 μ band and appearance of the characteristic peaks at 4.8 and 6.2 μ). The diazoketone was changed into the corresponding dichloroketone by dissolving it, without further purification, in 25 ml. of anhydrous ether and adding a solution of 1.2 g. of anhydrous hydrogen chloride in 13 ml. of ether. After allowing to stand at room temperature for 20 hours, removal of the ether left an oil the infrared spectrum of which showed complete disappearance of the diazoketone bands. Distillation from an oil-jacketed flask at a bath temperature of 170° (3 mm.), gave 4.88 g. (84% from the acid XXII) of dichloroketone as a light yellow oil.

Reduction to XXIII was carried out by refluxing for 16 hours a solution of 4.88 g. (0.0208 mole) of dichloroketone in 20 ml. of absolute ethanol and 80 ml. of benzene to which had been added two drops of glacial acetic acid and 3.72 g. (0.0246 mole) of sodium iodide. The orange red solution was diluted with ether and was washed with water until halide stopped being extracted (silver nitrate test). The ether–benzene solution was shaken with 10% sodium bisulfite[40] until the aqueous layer no longer liberated iodine upon the cautious addition of 30% hydrogen peroxide to an aliquot. Ten washings with *ca.* 40-ml. portions of bisulfite solution were required. The organic layer was washed with water and saturated salt solution and was then dried. Removal of solvents and distillation gave 2.47 g. (50% over-all from the acid XXII) of *trans* 1-chloro-1-acetyl-2,4,5-trimethyl-4-cyclohexene (XXIII), b.p. 97–99° (4.5–5.5 mm.), $n^{25}D$ 1.4882. The infrared spectrum of this authentic sample was identical with that of the ketone from the Diels–Alder addition to 3-chloro-3-pentene-2-one, described above.

Anal. Calcd. for $C_{11}H_{17}OCl$: C, 65.82; H, 8.54. Found: C, 66.13; H, 8.48.

Rearrangement of the Haloketone to *cis*-1,2-Dimethylcyclohexanecarboxylic Acid (XXIV).—To a stirred suspension of dry sodium benzyloxide (from 0.92 g. of sodium) in anhydrous ether, under nitrogen, was added 1.4 g. of chloroketone X in portions, while maintaining the temperature at 15–20°. The mixture was stirred for another 12 hours at room temperature and, after addition of 10 ml. of water, it was refluxed under nitrogen for 48 hours. The solution was washed with ether, acidified, and extracted with ether. Drying of this ether extract, removal of the solvent and distillation gave 44% of the liquid acid XXIV which was distilled from an oil-jacketed flask at a bath temperature of 160–170° (8 mm.).

The anilide, m.p. 113.8–115.8°, was obtained in 42% yield from the acid. The infrared spectrum (KBr) had λ3.04, 6.10, 6.28, 7.95(weak), 8.56(weak), 8.71 μ but no absorption at 11.4–11.6 μ. The analytical sample, recrystallized from cyclohexane, had m.p. 115.6–116.1°; λ_{max}^{EtOH} 243 mμ, ε 17,350.

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15. Found: C, 77.91; H, 9.24.

Authentic *cis*-1,2-Dimethylcyclohexanecarboxylic Acid (XXIV).—A mixture of 3.0 g. (0.03 mole) of tiglic acid, m.p. 63.5–65° (reported m.p. 64.5°), and 9 ml. (*ca.* 0.10 mole) of 1,3-butadiene was heated in a sealed tube in the presence of a little hydroquinone for 27 hours at 190–200°. Distillation of the reaction mixture from an oil-jacketed flask gave 2.66 g. of a liquid acid mixture (containing tiglic acid) at a bath temperature of 160° (0.5 mm.). Hydrogenation of the unsaturated adduct mixture in ethyl acetate with 0.1 g. of platinum oxide resulted in an uptake of 585 ml. of hydrogen (calculated 386 ml.) showing the presence of considerable tiglic acid in the adduct mixture. Distillation at bath temperature of 110–120° (8 mm.) gave 0.77 g. of acid XXIV which gave its anilide, m.p. 115.4–116.6°, in 44% yield. The melting point was not depressed on admixture with the anilide from the chloroketone rearrangement above.

Rearrangement of the Haloketone XI to *trans*-1,2-Dimethylcyclohexanecarboxylic Acid (XXV).—The rearrangement was carried out in the same manner as in the case of X above, using sodium benzyloxide in ether. Distillation of the acid, after saponification, gave 30% of the liquid acid XXV. This distilled at a bath temperature of 150–160° (9 mm.) and was transformed in 48% yield into its anilide, m.p. 81.4–82.6° after recrystallization from cyclohexane; λ_{max}^{EtOH} 243 mμ, ε 17,950; λ_{max}^{KBr} 3.04, 6.10, 6.28 and 11.5 μ, but no absorption at 7.92, 8.55 and 8.70 μ. The melting point of a mixture with the epimeric anilide from XXIV was depressed to 73.8–90°.

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15. Found: C, 77.85; H, 9.11.

Rearrangement of *trans*-1-Acetyl-1-chloro-2,4,5-trimethyl-4-cyclohexene (XXIII) to *trans*-1,2,4,5-Tetramethyl-4-cyclohexenecarboxylic Acid (XXVI).—Rearrangement of 1.52 g. of XXIII (from the chloropentenone XIII) was carried out with dry sodium benzyloxide in ether as with X above. The acid obtained after hydrolysis was semi-solid and showed no absorption bands at 9.0 and 9.6 μ which are characteristic of the epimeric *cis*-acid (*vide infra*). The crude acid was sublimed at a bath temperature of 70–75° (1 mm.) to yield 0.92 g. of acid, m.p. 63–78°. This was dissolved in a mixture of 5% benzene and 30–60° petroleum ether and chromatographed on a 13 × 3 cm. column of 30 g. of a 1:1 mixture of 100 mesh silicic acid–Celite, using air pressure. Petroleum ether eluted 0.28 g., m.p. 77–80°. This was sublimed to give 0.235 g., m.p. 77.4–79.4°. Further eluates (petroleum ether–10% benzene to petroleum ether–75% benzene) were combined (0.521 g.), after removal of some neutral lactone ($\lambda_{max}^{CHCl_3}$ 5.68 μ) from the later fractions, and rechromatographed on 32 g. of silicic acid (11 × 3 cm. column) after solution in 1:2 cyclohexane–pentane. The collected fractions were sublimed to give

(40) P. L. Julian and W. J. Karpel, THIS JOURNAL, **72**, 362 (1950).

0.329 g., m.p. 76–79.2°. The total yield was 44% from XXIII. The analytical sample of XXVI after two more sublimations at 70° (2 mm.) had m.p. 80.0–81.6°, ϵ_{212}^{EtOH} 1510; $\lambda_{max}^{CCl_4}$ 5.92, 7.95 μ; λ_{max}^{KBr} 8.05 μ.

Anal. Calcd. for $C_{11}H_{18}O_2$; C, 72.49; H, 9.96. Found: C, 72.73; H, 9.82.

Rearrangement of the chloroketone XXIII made from *trans*-2-chlorocrotonic acid was carried out separately and in the same manner as above, except that the benzyl ester was isolated (b.p. 114–116° (0.1 mm.), $n^{28}D$ 1.5158) before hydrolysis and submitted to hydrogenolysis to produce the corresponding acid, m.p. 65–72°. Sublimation and chromatography on silicic acid gave 20–28% of acid XXVI, m.p. 76.8–80.7°, undepressed on mixing with that described above.

Authentic *cis*-1,2,4,5-Tetramethyl-4-cyclohexenecarboxylic Acid (XXVII).—A mixture of 1.0 g. (0.101 mole) of tiglic acid and 2.0 ml. (0.0177 mole) of 2,3-dimethyl-1,3-butadiene was heated in a sealed tube at 180° for 24 hours, in the presence of a little hydroquinone. Distillation from an oil-jacketed flask yielded 1.25 g. of solid at a bath temperature of 110–120° (0.3 mm.). This had m.p. 78–86° and was a mixture of tiglic acid and adduct XXVII, as shown by ultraviolet measurement (tiglic acid has λ_{max}^{EtOH} 217 mμ, ϵ 9840). The mixture was chromatographed on 1:1 silicic acid–Celite and the resulting solid was sublimed twice to yield the analytical sample, m.p. 86.0–87.0° (depressed to 48–65° on admixture with XXVI); ϵ_{212}^{EtOH} 1890; $\lambda_{max}^{CCl_4}$ 5.92, 8.05μ; λ_{max}^{KBr} 8.05, 9.0 and 9.6 μ. The yield of acid XXVII was 45%.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.52; H, 9.89.

NEW YORK 27, N. Y.

[CONTRIBUTION FROM THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

Synthesis and Reactions of Glycidonitriles. Transformation into α-Haloacyl Compounds and Aminoalcohols

BY GILBERT STORK, W. S. WORRALL AND J. J. PAPPAS

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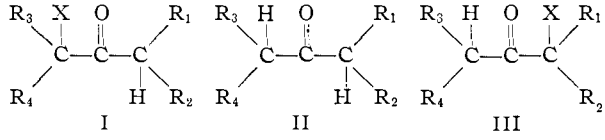
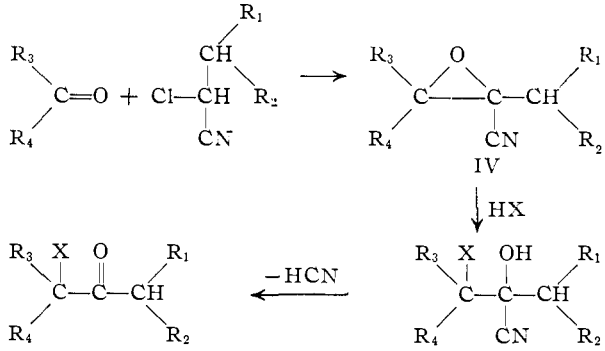
It is shown that the condensation of a ketone with an α-halonitrile is at least as general as the well-known Darzens glycidic ester synthesis. The glycidonitriles can be transformed into α-haloketones, α,β-unsaturated carbonyl compounds and aminoalcohols.

Studies in this Laboratory on the Favorskiĭ rearrangement[1] made it quite clear that the synthesis of haloketones of type I (R_1, R_2, R_3 = H or alkyl) is not at present very satisfactory. Direct halogenation of the parent ketone (*cf.* II) suffers from two major drawbacks: It is necessary to utilize a source of positive halogen which may not be compatible with the presence of certain functional groups in the molecule (*e.g.*, double bonds, phenolic rings), and although the *major* product is often predictable, mixtures of the two possible α-haloketones, I and III, often result.



I II III

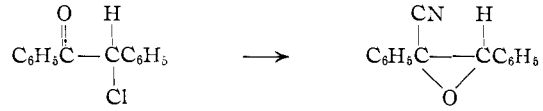
This paper is concerned with the development of an alternative method which may be illustrated as follows: Should it be possible to synthesize glycidonitriles (IV) from ketones or aldehydes and α-



IV

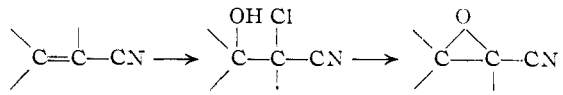
halonitriles, opening of IV with HX would lead as usual to a chlorohydrin *which in this case would also be a cyanohydrin* and, consequently, could be transformed into the corresponding ketone by abstraction of the elements of hydrogen cyanide.[2] It will be noted that in this scheme the halogen can only appear on one specific carbon atom and that its source is actually a halide ion rather than an electrophilic halo compound.

We will now turn our attention to the synthesis of glycidonitriles. We first note that these substances are not new: they have been prepared previously by one of two methods. The reaction of many α-haloketones with cyanide ion leads to α-epoxynitriles.[3]



This particular synthesis is obviously of no interest for our purpose.

It has also been found possible in certain cases to add the elements of HOCl to α,β-unsaturated nitriles. Treatment with base then leads to glycidonitriles.[4]



This sequence suffers from the number of operations required and from the lack of a simple general synthesis of α,β-unsaturated nitriles.

(1) G. Stork and I. J. Borowitz, THIS JOURNAL, **82**, 4307 (1960).

(2) *Cf.* P. Delbaere, *Bull. soc. chim. Belg.*, **51**, 1 (1942).

(3) *Cf.* E. P. Kohler and F. W. Brown, THIS JOURNAL, **55**, 4299 (1933); R. Justoni and M. Terruzzi, *Gazz. chim. ital.*, **78**, 155 (1948).

(4) R. Gerbaux, *Acad. roy. Belg. Classe Sci., Mem.* **18**, No. **4**, 3 (1939); *Chem. Zentr.*, **113**, I, 1621 (1942); L. Moelants, *Bull. soc. chim. Belg.*, **52**, 53 (1943).