[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF HARVARD UNIVERSITY AND BROOKHAVEN NATIONAL LABORATORY AND THE MEDICAL LABORATORIES OF THE COLLIS P. HUNTINGTON MEMORIAL HOSPITAL OF HARVARD UNIVERSITY][1]

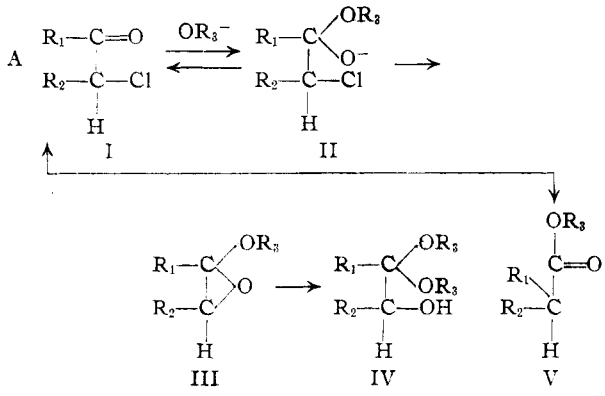
The Alkaline Rearrangement of α-Haloketones. II. The Mechanism of the Faworskii Reaction

BY ROBERT BERNER LOFTFIELD[2]

When 2-chlorocyclohexan-1-one-1,2-C^{14} is treated with sodium isoamyloxide, the major reaction product is isoamylcyclopentanecarboxylate. A clean-cut degradation procedure has been developed for distinguishing among the carbonyl-, the α- and the β-carbon atoms of this compound. It is found that the α- and β-carbon atoms possess equal radioactivities.

None of the five mechanisms which have been proposed for this reaction would have predicted this result. After establishing that the observed results are not due to an artifact such as halogen migration, we find that the only mechanism which fits the facts must involve the formation of a symmetrical intermediate, *viz.*, a cyclopropanone derivative. Theorizing that rearrangements of α-haloketones to acid derivatives proceed through a cyclopropanone intermediate with rare exceptions, we are able to predict correctly the products obtained from a large variety of polyhaloketones and to correlate structure and reaction conditions with the proportion of rearrangement *vs.* substitution products.

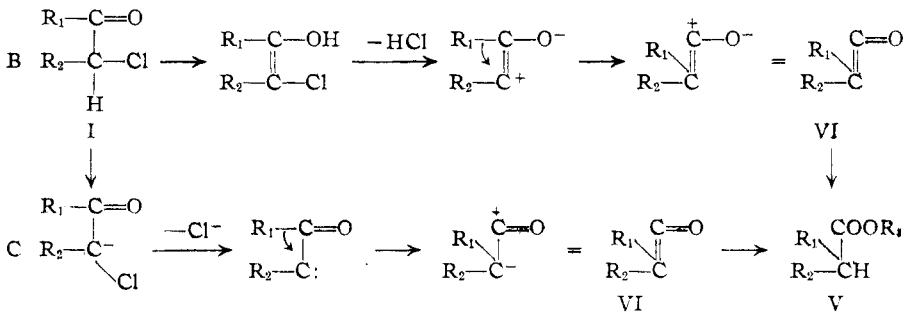
Since the pioneer work of Faworskii[3] considerable effort has been expended in elucidating the mechanism by which α-haloketones are converted by base into carboxylic acids with the same number of



carbon atoms. Although a wide variety of di- and trihaloketones reacts in what is grossly an analogous process, most investigation has been concerned with the monohaloketones. Depending on whether the base is hydroxide ion, alkoxide ion or an amine, the product is an acid salt, an ester or an amide. Generally there is concomitant production of hydroxy ketone or its acetal.

Faworskii[4a] and later Aston[4b] suggested a mechanism to account for the major products. In this (equation A), alkoxide attack on the carbonyl produces an epoxide-ether III, which then reacts further to give either IV or V. The formation of III is certainly reasonable and quite recently an epoxide-ether of this type has been isolated from the action of sodium methoxide on α-bromopropiophenone by Temnikova[5a] and Stevens.[5b] Mousseron[6] has isolated a number of alkoxy-ketones by the action of sodium alkoxides on 2-chlorocyclohexanone. The conversion of III to IV is likewise not unexpected and has been observed in the first of these cases.[5b] However, the path by which III could become V under these conditions is not apparent and, in fact, Stevens could obtain no evidence for rearrangement of his epoxide-ether to an acid or ester.

Richard[7] suggested the intermediate formation of a ketene derivative VI by elimination of hydrogen chloride from the enol of I (scheme B). (VI could also be derived by 1,1-elimination of hydrogen chloride (C) from I by a process analogous to that of the Hofmann rearrangement which occurs under similar reaction conditions.) Richard's chief evidence for the ketene intermediate was a transient color and the presence in his products of a ketene dimer. Examples of the rearrangement are known in which the formation of a ketene is impossible (*e.g.*, α-chlorodicyclohexyl ketone[8a] yields 1-cyclohexylcyclohexane-1-carboxylic acid) and have been interpreted as disposing of any ketene mechanism.



Another mechanism has received considerable support from its close analogy to the well established course of the benzilic acid rearrangement (D).[8]

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(2) Now working under a grant from the American Cancer Society, Inc., to the Massachusetts General Hospital. Address: Medical Laboratories of the C. P. Huntington Memorial Hospital, Massachusetts General Hospital, Boston, Massachusetts.

(3) Faworskii, *J. Russ. Phys. Chem. Soc.*, **26**, 559 (1894); **27**, 8 (1895); **46**, 1097 (1914); **50**, 582 (1920); *J. prakt. Chem.*, [2] **51**, 533 (1895). An extensive review of this reaction has been prepared by Jacquier (*Bull. soc. chim.*, D 35 (1950)).

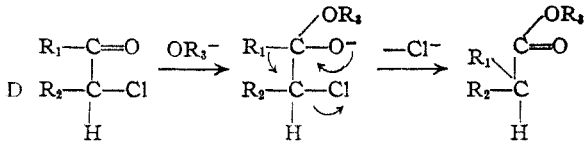
(4) (a) Faworskii, *J. prakt. Chem.*, **88**, 641 (1913); (b) Aston, *et al.*, THIS JOURNAL, **62**, 2590 (1940); **64**, 360 (1942).

(5) (a) Temnikova and Kropacheva, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **19**, 1917 (1949); *C. A.*, **44**, 1929 (1950); (b) Stevens, Malik and Pratt, THIS JOURNAL, **72**, 4758 (1950).

(6) Mousseron, Jacquier and Fountain, *Compt. rend.*, **231**, 864 (1950).

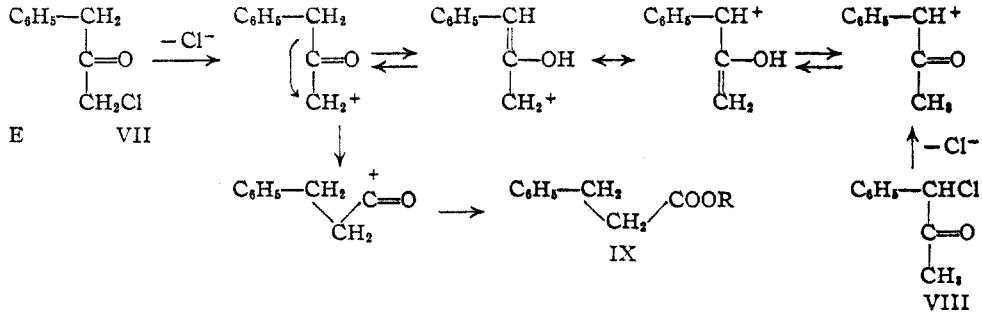
(7) Richard, *ibid.*, **197**, 1943 (1933).

(8) (a) Tschoubar, *ibid.*, **228**, 580 (1949); (b) Tschoubar and Sackur, *ibid.*, **208**, 1020 (1939).

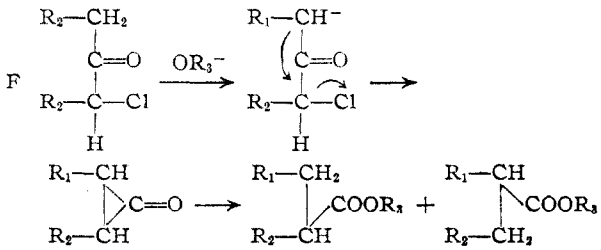


Mechanisms A, B, C and D all predict different acids from the two isomeric mono-haloketones in the course of the rearrangement. Since this is not the case, Richard[9] proposed "synionic isomerism" (*i.e.*, chlorine migration from the α- to the α'-carbon atom). It is, of course, well established that in acetic acid solution containing hydrogen bromide various 2,2-dibromo-3-keto steroids rearrange to the 2,4-dibromo isomers.[10] Furthermore, work in this Laboratory indicates that the reaction of 2-bromocyclohexanone with sodium alkoxide yields large amounts of 1-hydroxycyclopentane-1-carboxylic acid. This is most easily explained by assuming disproportionation of the monobromoketone to give some dibromoketone which in turn is known to give the hydroxy acid.[11] Thus the "synionic" rearrangement is not to be dismissed *a priori*.

McPhee and Klingsberg[12] repeated and extended Richard's work, observing that α-phenyl-α'-chloroacetone (VII) and α-phenyl-α-chloroacetone (VIII) both give β-phenylpropionic acid IX, the former more rapidly and in higher yield. Discounting the "synionic isomerism," they suggested mechanism E to provide a common intermediate leading to a single product.



The last type of mechanism (F) to be discussed here involves initial removal of the α'-hydrogen followed by the intermediate formation of a cyclopropanone.[13]



Wallach[14] suggested a cyclopropanone intermediate in the rearrangement of dibromoketones only to reject it for rather involved reasons. Similarly, Tschoubar[8b] considered that her success in rearranging α-chlorocyclohexyl phenyl ketone constituted evidence for Mechanism D and against F. Altogether there are several reported cases of rearrangement taking place in which α'-hydrogen is not available. On the other hand, this mechanism does account for the same product acids being formed from isomeric α-chloroketones (VII and VIII yield IX) without invoking prior migration of the halogen.

It is apparent that none of the suggested mechanisms is entirely consistent with the facts. We felt that it would be desirable to examine a single case in which the course of the reaction is not influenced by the impossibility of forming one of the postulated intermediates for only such a case can be considered general. Thus the work of Tschoubar[8a] with α-chlorodicyclohexyl ketone does not alter the possibility that mechanism B or C is operative in other, or even in most, cases. The same is true for mechanism F with respect to those cases in which a cyclopropanone intermediate is impossible.

Method

2-Chlorocyclohexanone-1,2-C^{14} (IX) was prepared by way of 2-chloro-1-cyclohexanone-1-C^{14} using the synthesis outlined in Fig. 1. Sodium cyanide-C^{14} [15] reacted with pentamethylene dibromide to give the dinitrile which was hydrolyzed without isolation to pimelic acid. Calcium pimelate was pyrolyzed to yield 1-cyclohexanone-1-C^{14}. For chlorination of this ketone on a 10-g. scale we found chlorourea[16] to be an excellent reagent. Because chlorocyclohexanone is insoluble in the aqueous chlorinating phase, there is no appreciable polychlorination and the rate of the reaction is conveniently followed by iodometric titration of aliquots. Reduction of the ketone to the chlorohydrin was accomplished by the method of Winstein[17] in which a large excess of aluminum isopropoxide and isopropyl alcohol is refluxed with the ketone for a very short while. The product was a mixture of 55% *trans*-chlorocyclohexanol and 45% *cis*.[18] Treatment with sodium hydroxide afforded the corresponding oxide which when treated with ethereal hydrogen chloride at −40° was reconverted to the *trans*-chlorohydrin. 2-Chloro-1-cyclohexanone-1,2-C^{14} was then obtained by oxidation of the alcohol with bichromate and sulfuric acid at 20°. The ketone was identified by its boiling point (69–71° at 6 mm.) and melting point (18–20°; reported 23°). Like authentic chlorocyclohexanone it formed a dinitrophenylosazone (m.p. 236–238°)[19]; it reacted

(9) Richard, *Compt. rend.*, **200**, 1944 (1935).
(10) Djerassi, THIS JOURNAL, **69**, 2404 (1947).
(11) Wallach, *Ann.*, **414**, 296 (1918).
(12) McPhee and Klingsberg, THIS JOURNAL, **66**, 1132 (1944).
(13) Loftfield, *ibid.*, **72**, 632 (1950).
(14) Wallach and Grote, *Ann.*, **414**, 294 (1918).

(15) Prepared by reaction of carbon-14 dioxide, potassium and ammonia at 620°; Loftfield, *Nucleonics*, Vol. I, No. 3, p. 54 (1947). The barium C-14 carbonate was obtained on allocation from the Isotopes Division of the U. S. Atomic Energy Commission.
(16) Godchot, *Compt. rend.*, **180**, 444 (1925).
(17) Winstein, Jacobs, Henderson and Florsheim, *J. Org. Chem.*, **11**, 150 (1946).
(18) Bartlett, THIS JOURNAL, **57**, 224 (1935).
(19) Adkins and Rossow (*ibid.*, **71**, 3836 (1949)), report an osazone of this formula (m.p. 218–219°) from the reaction of dinitrophenylhydrazine on 2-methoxycyclohexanone.

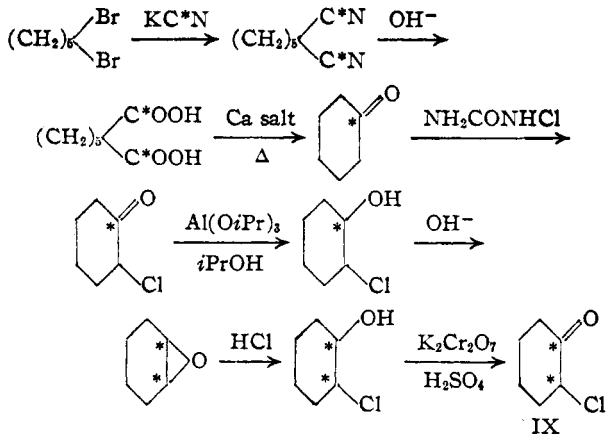
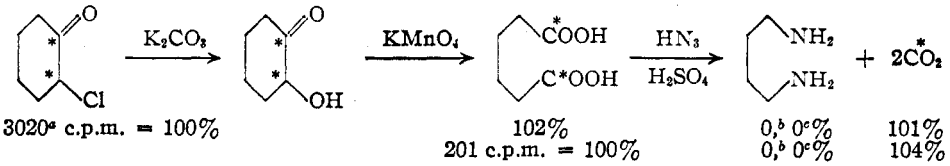


Fig. 1.

the high chlorine analysis (87% of calculated) eliminate hydroxycyclohexanone as a significant contaminant.

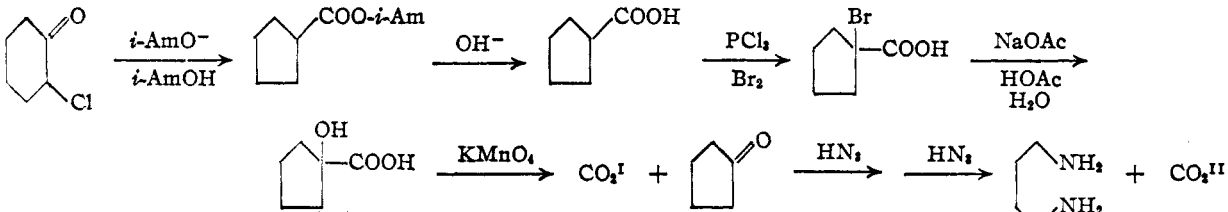
In order to establish the location of the chlorine in the recovered ketone, the adipic acid obtained from it was treated with hydrazoic acid and sulfuric acid and the resultant carbon dioxide and putrescin assayed for their radioactivity (degradation series 1 and 2; Fig. 2).

The isoamyl ester obtained from the Faworskii reaction was hydrolyzed to the free acid which was brominated in nearly quantitative yield with phosphorus trichloride and bromine. This α-bromo acid gave only cyclopentene carboxylic acid using a variety of reagents. However, by dissolving it in an aqueous acetone solution of sodium acetate and acetic acid, the bromocarboxylate anion was produced under acidic conditions where elimination is minimized. Participation of the α-carboxylate anion[21] followed by solvolysis led to excellent yields of 1-hydroxycyclopentane-1-carboxylic acid. The acid is smoothly oxidized to cyclopentanone and carbon dioxide[I]. The ketone on successive Schmidt reactions was converted to carbon dioxide[II] and putrescin (degradation series 3 and 4; Fig. 3).



Series 1	3020[a] c.p.m. = 100%		102%	0,[b] 0[c]%	101%
Series 2			201 c.p.m. = 100%	0,[b] 0[c]%	104%

Fig. 2.—[a] As dinitrophenylosazone. [b] As putrescin dihydrochloride. [c] As picrate. The first figure in each series is the "molecular radioactivity" obtained as follows. The compound in question was converted quantitatively into carbon dioxide (usually by wet combustion; method to be published). From this an "infinitely thick" precipitate of barium carbonate of 2 cm.[2] was prepared and counted in a nucleometer. The number of counts observed per minute (less background) was multiplied by the number of carbon atoms to give "molecular radioactivity." Subsequent figures in each series are percentages which relate the molecular radioactivity of each compound to that of the first compound in the series.



Series 3	1050 c.p.m. = 100%	52%	48,[d] 48[e]%	24,[b] 24[c]%	24%
Series 4	3024 c.p.m. = 100%	49	51, 49	25,	25
Series 5	650 c.p.m. = 100%	100	0, 0	.. ..	..
Series 6	1644 c.p.m. = 100%	0	97, 91	0, 0	91

Fig. 3.—[b] As putrescin dihydrochloride. [c] As putrescin picrate. [d] As semicarbazone. [e] As dinitrophenylhydrazone.

with aqueous potassium carbonate to give hydroxycyclohexanone (m.p. 129–131°). The infrared spectra indicated a purity of approximately 90%.

This ketone was then treated with sodium isoamyloxide in isoamyl alcohol under conditions where half-life of the reaction is several minutes. Because less than one equivalent of base was used it was possible to extract the salt with water and separate unreacted chlorocyclohexanone and isoamyl cyclopentanecarboxylate by fractional vacuum distillation.

The recovered ketone was not nearly as pure as the starting material, being contaminated by a substance or substances of the same boiling point (89–90° at 14 mm.). The impurity was probably the same in quantity but greater in proportion due to reaction of 80% of the chloroketone. Nevertheless, the ketone was identified as being present by preparation of the osazone (in yield corresponding to 45% purity), by infrared analysis (which indicated 48% purity) and by isotope-dilution techniques. In the latter case 238 mg. of the impure ketone was diluted with 1720 mg. of authentic chloroketone and the mixture hydrolyzed with potassium carbonate solution to hydroxycyclohexanone[20] and oxidized to adipic acid. The molecular radioactivity of this adipic acid compared to that obtained from undiluted impure ketone showed that the ketone was 48% pure. The absence of a hydroxyl band in the infrared spectra and

(20) Kötz, Blenderman, Rosenbusch and Sirringhaus, *Ann.*, **400**, 55 (1913).

It was necessary to establish that there was no ambiguity in the assignment of radioactivity from the degradation products to the positions of cyclopentanecarboxylic acid. To this end, 2-chlorocyclohexane-1-one-1-C[14] was rearranged to the acid and degraded. The exclusive appearance of the radioactivity in the carbon dioxide[I] indicates that the carbonyl carbon of the chlorocyclohexanone becomes the carboxyl carbon and that in turn this appears only in carbon dioxide[I] all without measurable randomization (Degradation Series 5; Fig. 3). Cyclopentane-1-carboxylic acid-1-C[14] was prepared[22] by pyrolysis of calcium adipate 1-C[14] to cyclopentanone-1-C[14] and reduction to cyclopentanol-1-C[14]. This was converted through the *p*-bromobenzenesulfonate to the iodide, the Grignard compound of which

(21) Grunwald and Winstein, THIS JOURNAL, **70**, 841 (1948).

(22) When we attempted to prepare this acid by the reaction sequence cyclopentanol-1-C[14] $\xrightarrow{PBr_3}$ cyclopentyl bromide $\xrightarrow{NaCN}$ cyclopentyl cyanide $\xrightarrow{NaOH}$ cyclopentane carboxylic acid, the usual degradation revealed 20% of the total radioactivity in the putrescin. This very likely means that the first of these reactions involves a carbonium ion sufficiently free to permit a "hydride ion" migration. Roberts (THIS JOURNAL, **72**, 4237 (1950)) has observed little or no rearrangement in metathetical reactions of this type. However, the cases he examined would have involved tertiary → secondary or primary carbonium ions. As he points out, his cases may be unfavorable for this reason.

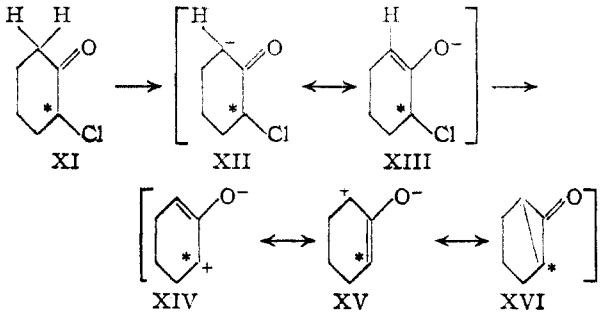
was carbonated with ordinary carbon dioxide. The radioactivity figures are conclusive in showing that the α-carbon atom appears entirely as the carbon dioxide[11] in this degradation (degradation series 6; Fig. 3).

Discussion

Mechanisms A, B, C, D, E and F are *a priori* all possible in the rearrangement of chlorocyclohexanone, that is to say, substitution and steric factors in chlorocyclohexanone do not preclude rearrangement according to any of these paths. Of these mechanisms, the first four would all lead to the prediction that carbon atom 2 (carrying the chlorine) would become exclusively the α-carbon of the acid unless there is prior migration of the chlorine to carbon 6. *The location of the radioactivity is unchanged in the recovered chlorocyclohexanone (series 1 and 2) but is divided equally between the α- and β-positions of the product acid (series 3 and 4).* This means that whatever reaction leads to randomization is irreversible and that Mechanisms A, B, C and D must be rejected.

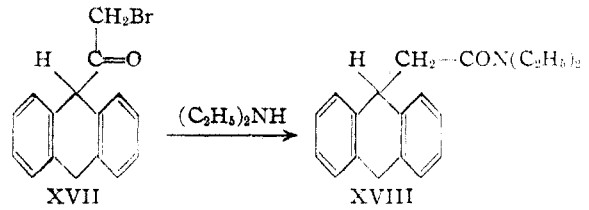
It may be argued that having removed chlorine irreversibly, a mechanism similar to one of the first four might be consistent with the facts since the ion formed could make the two α-positions equivalent. This is the relationship that E bears to D. However, it is apparent that such a hypothesis is unjustifiable in that it gives no rôle to the base which is essential to the reaction. In any event, it seems more likely that halogen migrations take place by nucleophilic attack on the halogen (leaving a carbanion) rather than by electrophilic attack as suggested by mechanism E.

One alternative which remains is the cyclopropanone intermediate (XIV–XVI); Mechanism F.[22a]



In this picture it is clear that, far from being derived from a common intermediate, substitution products such as IV and rearrangement products V are derived from entirely different paths initiated by base attack at the carbonyl carbon or at the α′-hydrogen, respectively. The second order rate constant measured from disappearance of ethoxide ion for the reaction of 0.1 *N* sodium ethoxide in ethanol with 0.1 *N* chlorocyclohexanone at 0° is approximately 9 liters moles^{-1} minutes^{-1}. Under these conditions the major product is ethyl cyclopentanecarboxylate (65–70%). The second order rate constant for the base-catalyzed rate of enolization of acetone in water at 0° is 1.7.[23] Considering the differences in solvent and degree of enolization of cyclohexanone *vs.* acetone, it is not possible to conclude much from these figures except that the ionization reaction (XI → XII) is either rate determining or at least not much faster than the subsequent reactions.[24] If this is the case with α-chlorine, it would almost surely be the case with bromine or iodine and the over-all rate should not be markedly influenced by the nature of the halogen. On the other hand, comparison of I ⇄ II → III with the established mechanism for closure of epoxide rings from halohydrins[25] suggests a considerable reversible formation of ion II, with II → III as rate determining. Under such circumstances, the nature of the halogen is extremely influential in increasing the over-all rate I → III (→ IV). Thus, the net effect of replacing α-chlorine by bromine is to decrease the proportion of rearrangement products V to substitution products IV. We have observed that under similar conditions (ethanolic sodium ethoxide at 0°), much more cyclopentanecarboxylic ester is obtained from α-chlorocyclohexanone than from α-bromocyclohexanone.

It also follows that if the α′-hydrogen is more easily or less easily removed, the amount of rearrangement will be greater or less, respectively. Thus 9-ω-bromoaceto-9,10-dihydroanthracene XVII in which the α′ hydrogen is activated by two phenyl groups gives almost a 50% yield of the rearranged amide XVIII with no stronger base than diethylamine.[26] It is noteworthy that a



number of phenanthrene and anthracene compounds related to XVII but lacking the 9-hydrogen give only normal substitution products.[27] On the other hand, the rate of base-catalyzed ionization of the tertiary α-hydrogen of *p*-menthone[28] in ethyl alcohol is approximately sixty times slower than that of acetone in water and three hundred times slower than the reaction of chlorocyclohexanone with base in ethanol. If this large difference may be extended to the tertiary α-hydrogen in bromomethyl cyclohexyl ketone XIX and the primary α-hydrogens in methyl bromocyclohexyl ketone XX it becomes easy to explain the observed difference of these two compounds in their reaction

(22a) NOTE ADDED IN PROOF.—Aston and Newkirk (THIS JOURNAL 73, 3900 (1951)) favor an intermediate (their IIIra and IIIrc) obtained by unspecified means which is essentially the dipolar formulation of a cyclopropanone. Except when sterically impossible, their intermediates would be considered as resonance forms contributing to the stability of the cyclopropanone intermediate.

(23) Bartlett, THIS JOURNAL, 56, 967 (1934).

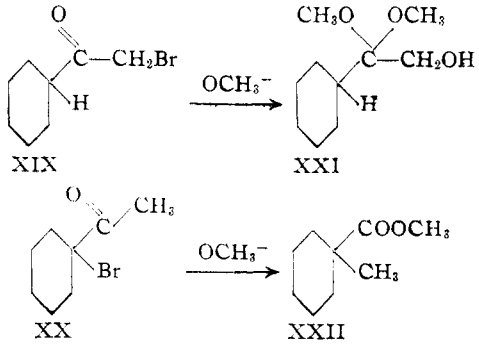
(24) The possibility of a concerted reaction to form the cyclopropanone is not excluded.

(25) McCabe and Warner, THIS JOURNAL, 70, 4031 (1948).

(26) May and Mosettig, *ibid.*, 70, 1077 (1948). Dr. William Dauben of the University of California has investigated this reaction with XVII carbonyl C-14 and finds the C-14 in the carbamide group of XVIII, confirming our assumption that XVII → XVIII involves a skeletal rearrangement (private communication).

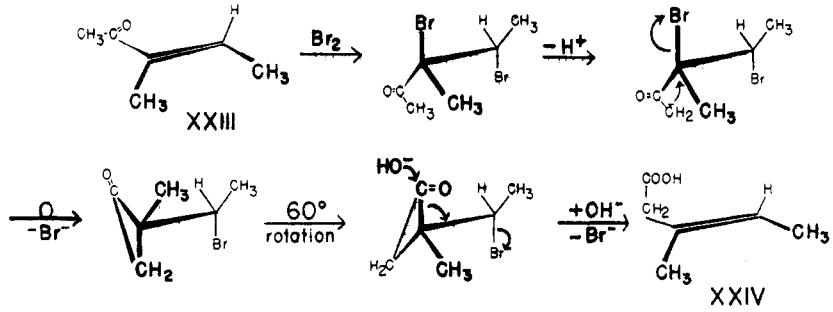
(27) May and Mosettig, *J. Org. Chem.*, 11, 1, 10, 15 (1946); THIS JOURNAL, 70, 688 (1948).

(28) Tubandt, Mohs, Tubandt and Weinhausen, *Ann.*, 377, 284 (1910).



XIX XXI XX XXII

with sodium methoxide.[29] In XX a proton is removed more rapidly than the epoxide is formed; in XIX the reverse is true. Since the rate of removal of the tertiary proton by ethoxide ion in *p*-menthone is markedly increased by changing to a benzene or ether solvent,[28] we may have a partial explanation for Aston's observation that in many cases the yield of rearrangement product is greatest when no alcohol is present.[4b]



XXIII XXIV

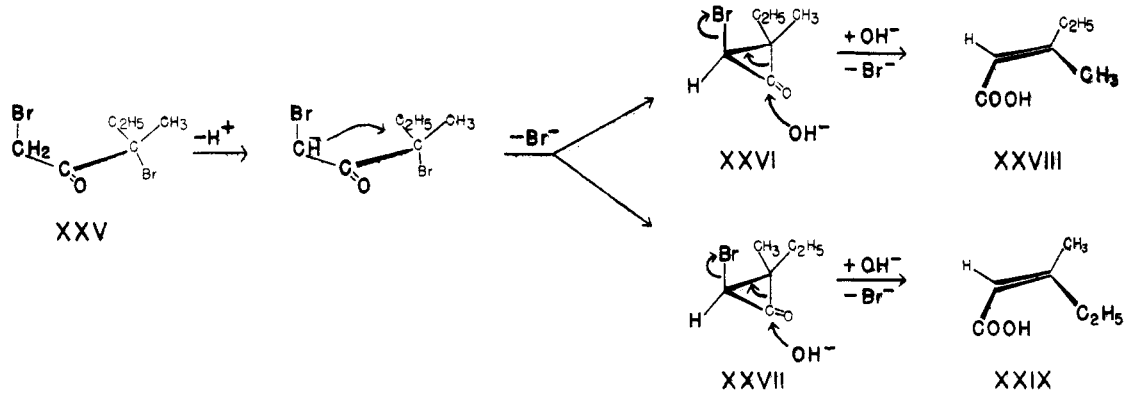
Having established the probable correctness of Mechanism F in one case, we find abundant correlative evidence in more complicated reactions. Thus it would be predicted that bromination of *trans*-3-methyl-3-penten-2-one XXIII would yield a dibromide which would undergo a rearrangement as shown to *trans*-β-methyl-β,γ-pentenoic acid (XXIV). Wagner[30] has, in fact, obtained pure *trans* XXIV starting with XXIII of unspecified but probably *trans* geometry. In each of several α,β-dibromoketones that he studied the β,γ-unsaturated acid was the initial product as this theory would require.

The α,α′-dibromide of racemic methyl *s*-butyl ketone XXV would be expected to give roughly equal amounts of two cyclopropanone derivatives XXVI and XXVII depending on which α-hydrogen was removed in the first step. It is apparent that just as XXVI will open to give *trans*-β-methyl-α,β-pentenoic-acid XXVIII, XXVII will give a nearly equal amount of the *cis* isomer XXIX. The products of this reaction have been investigated by Wagner[31] who isolated 22% and 29% yields of XXVIII and XXIX, respectively. None of the β,γ-unsaturated isomer was found in the rearrangement of any of several α,α′-dibromoketones that he investigated.

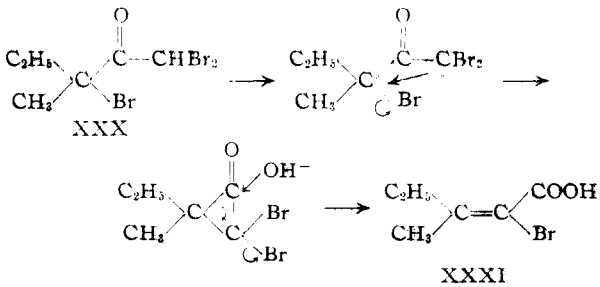
By an entirely analogous process, the α,α,α′-trihaloketones[32] XXX would be expected to give the α-halo-α,β-unsaturated carboxylic acid derivatives which are isolated XXXI.

Similarly the α,α-dichloroketones prepared from unsymmetrically substituted acetylenes XXXII by addition of hypochlorous acid are undoubtedly mixtures which on the basis of our theory would give a mixture of two unsaturated acids as Faworskii observed.[4a]

The chief objection to this theory must rest on the fact that several cases are known in which rearrangement proceeds although a cyclopropane



XXV XXVI XXVIII XXVII XXIX



XXX XXXI

intermediate is impossible. Thus Cope and Graham[33] report that XXXIV is obtained by the

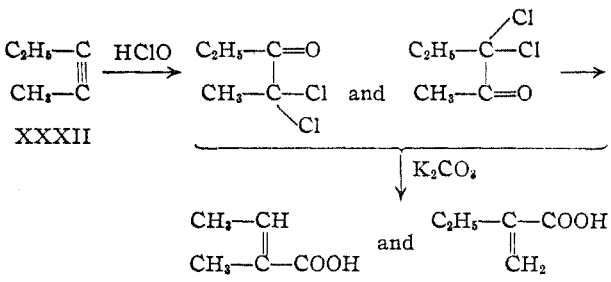
(29) Wagner and Moore, THIS JOURNAL, **72**, 2884 (1950). It is noteworthy that in the analogous cyclopentyl methyl ketones of the steroid series both isomer α-chloroketones rearrange to give the same tertiary ester (Plattner and Heusser, *Helv. Chim. Acta*, **31**, 603 (1948); **32**, 270 (1949)). In this case steric factors may operate to hinder the competing carbonyl attack or epoxide formation.

(30) Wagner, THIS JOURNAL, **71**, 3214 (1949).

(31) Wagner and Moore, *ibid.*, **72**, 974 (1950).

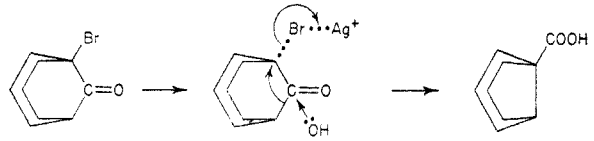
(32) Wagner and Moore, *ibid.*, **72**, 3655 (1950).

(33) Cope and Graham, *ibid.*, **73**, 4702 (1951).



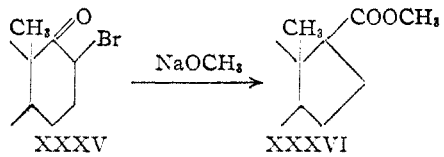
XXXII

action of base or silver nitrate on XXXIII. Their postulated push-pull type mechanism is most reasonable and may support Stevens'[34] suggestion



XXXIII XXXIV

that the rearrangement (8% yield) of α-chlorocyclohexyl phenyl ketone[8b] by solid sodium hydroxide in ether proceeds by way of a similar mechanism. An entirely analogous scheme may be used to account for the 3% yield of XXXVI obtained after two days of treating 17b-bromo-D-homoandrostane-3(β)-ol-17-one acetate XXXV with sodium methoxide in dioxane.[35]



XXXV XXXVI

Experimental

Pimelic Acid-1-C_2^{14}.—A mixture of 4.60 g. (20 mmoles) of pentamethylene dibromide, 2.60 g. (40 mmoles, 5.7 millicuries) of potassium C-14-cyanide, 8 cc. of water and 2 cc. of methanol was refluxed two days with stirring to prevent bumping. Another 1.5 g. of potassium cyanide was added and the reaction contined for one more day. **The pimelic nitrile-1-C_2^{14}** was not isolated; instead it was found preferable to add 3.0 g. of potassium hydroxide in 6.0 cc. of water, and to reflux eight hours after removing the methanol by distillation. The salts were brought into solution by adding 80 cc. of water. After extraction with ether, the aqueous phase was acidified with hydrochloric acid and continuously extracted with ether 12 hours. Concentration and addition of petroleum ether gave 3.20 g. (100% based on pentamethylene dibromide) of pimelic acid-1-C_2^{14}, m.p. 98–101°.

1-Cyclohexanone-1-C^{14}.—The above pimelic acid (3.20 g., 20 mmoles) was dissolved in 60 cc. of water and the solution was made slightly alkaline to phenolphthalein with sodium hydroxide. After the addition of 5.0 g. (45 mmoles) of calcium chloride in 20 cc. of water, the suspension was concentrated to a volume of 30 cc. on the steam-bath, and filtered hot with suction. The **calcium pimelate-1-C_2^{14}** was dried *in vacuo* over phosphorus pentoxide to a weight of 4.60 g. (theory requires 3.96 g. for the anhydrous salt). This salt was packed into a 10 × 200 mm. Pyrex tube with a 6-mm. delivery tube. The tube was gradually heated in an oven to about 500° and the distillate was collected in a test-tube cooled in ice-water. A solution of 4.0 g. of sodium bisulfite in 6 cc. of water was added to the distillate, the crystal mass cooled in ice overnight, filtered and washed with ether. The resultant 1-cyclohexanone-1-C^{14} sodium bisulfite compound weighed 3.15 g. Second and third crops of reduced specific radioactivity were obtained by addition of 1.0-g. portions of ordinary cyclohexanone to the mother liquors.

2-Chloro-1-cyclohexanol-1-C^{14}.—Two grams of the above bisulfite compound was shaken with 5.0 g. of potassium carbonate, 20.0 cc. of water and 20.0 g. of ordinary cyclohexanone. The upper phase was separated and stirred gently in a water-bath at 24° with 10 cc. of acetic acid and 100 cc. (0.24 mole) of chlorourea[16] solution (prepared by absorbing 105 g. of chlorine in a stirred suspension of 150 g. of water, 150 g. of calcium carbonate and 300 g. of urea, filtering through Filteraid, and diluting to 600 cc. with water; titer, 2.4 moles per liter). After five hours, intermittent titration of aliquots of the aqueous phase indicated an abrupt change in the rate of chlorination. Benzene (50 cc.) was added, the upper phase was washed three times with water, shaken with sodium sulfate, filtered and boiled briefly to dry. In some runs this benzene solution was distilled giving less than 2.0 g. of cyclohexanone and 22.0 g. (77%) of **2-chloro-1-cyclohexanone-1-C^{14}**, b.p. 89–90° (14 mm.), m.p. 20–24°. In general, the dry benzene solution was added to a refluxing solution of 50 g. of aluminum isopropoxide in 700 cc. of absolute isopropyl alcohol.[17] After 12 minutes of refluxing, the flask was chilled in ice and the solvent removed by distillation at 15 mm. To the very thick sirup were added 30 cc. of concentrated hydrochloric acid and 200 g. of cracked ice. The mixture was extracted twice with 50 cc. of ether, the extracts washed with saturated sodium chloride solution, dried over sodium sulfate and distilled. **2-Chloro-1-cyclohexanol-1-C^{14}** thus obtained boiled at 78–82° (12 mm.) and weighed 17.5 g. (60% from cyclohexanone). Titration by the method of Bartlett[18] indicated the presence of 54% of the *trans* isomer.

1,2-Cyclohexeneoxide-1-C^{14}.—The above chlorohydrin (3.3 g.) was mixed with 62.5 of mixed *cis*- and *trans*-chlorohydrin (total *trans*-2-chlorocyclohexanol was 40.3 g.). This was stirred ten minutes with 16.1 g. of sodium hydroxide in 25 cc. of water and 60 cc. of ethanol. Twenty grams of potassium carbonate was added, the mixture was filtered, and the filtrate was distilled *in vacuo*. Redistillation from potassium hydroxide at atmospheric pressure gave 20.4 g. (70%) of cyclohexene oxide, b.p. 129–134°.

***trans*-2-Chloro-1-cyclohexanol-1,2-C^{14}.**—All of the above cyclohexene oxide was diluted with 30 cc. of absolute ether and cooled to −40°. The solution was saturated with anhydrous hydrogen chloride while cold. After warming to room temperature, the ether and excess hydrogen chloride were removed by water-pump vacuum, and 25.0 g. (89%) of chlorocyclohexanol obtained by vacuum distillation, b.p. 86–87° (17 mm.), m.p. 26–28°. Titration indicated the compound was free from the *cis* isomer.[18]

2-Chloro-1-cyclohexanone-1,2-C^{14}.—A mixture of 25.0 g. of the above chlorohydrin, 18.0 g. of potassium dichromate and 15 cc. of water was vigorously stirred at 20–22° while a solution of 25.0 g. of sulfuric acid in 15 cc. of water was added in 1-cc. portions at ten-minute intervals. Fifty cc. of water was added and stirring was continued overnight at room temperature. After the addition of 200 cc. of water and 10 cc. of concentrated hydrochloric acid the ketone was extracted with two 75-cc. portions of benzene, washed twice with water, once with saturated sodium chloride solution, dried over sodium sulfate and distilled at 6 mm. giving 1.0 g., b.p. <62°; 3.1 g., b.p. 62–69°; 14.4 g. (58%), b.p. 69–71°. The last fraction had m.p. 13–19°; infrared absorption at 5.80 μ corresponded to at least 90% purity.

Anal. Calcd. for C_6H_9OCl: C, 54.35; H, 6.84; Cl, 26.7. Found: C, 54.45; H, 7.01; Cl, 26.2.

The Faworskii Rearrangement.—A solution of 13.8 g. of the above 1-chloro-2-cyclohexanone-1,2-C^{14} in 10 cc. of isoamyl alcohol was added to a solution of 1.8 g. of sodium in 44 cc. of absolute isoamyl alcohol (b.p. 128–129°) at −5°. A precipitate of salt formed after 20 seconds and then the mixture warmed spontaneously to about 40°. It was then left overnight in the refrigerator. Twenty cc. of water was added, the upper layer was separated, filtered, and distilled through an efficient concentric tube column at 14 mm. The

(34) Stevens and Farkas, Abstracts of the 118th Meeting of the American Chemical Society, Sept. 3–8, 1950, p. 51N.

(35) Prins and Shoppee, *J. Chem. Soc.*, 494 (1946).

following fractions were obtained: A, 0.25 g., b.p. 86–89°; B, 1.60 g., b.p. 89–90°; C, 0.60 g., b.p. 90–108°; D, 6.80 g., b.p. 108–109°.

Fraction B: Recovered Chlorocyclohexanone (degradation series 1 and 2; Fig. 2).—*Anal.* Calcd. for C_6H_9OCl: C, 54.35; H, 6.84; Cl, 26.7. Found: C, 55.66; H, 8.17; Cl, 23.3. Forty-two mg. of this material dissolved in carbon tetrachloride absorbed exactly as much light of 5.80 μ (ketone band) as did 20 mg. of authentic pure 2-chlorocyclohexanone. When 51 mg. of fraction B and 3 cc. of ethanol were refluxed five minutes with 76 mg. of 2,4-dinitrophenyl hydrazine and 3 drops of concentrated hydrochloric acid, and allowed to stand overnight, 32 mg. (20%) of the dinitrophenylosazone, m.p. 236–238°, was obtained. If 25 mg. of authentic chlorocyclohexanone was treated in the same way, 40 mg. (45%) of the osazone (cyclohexanedione bis-dinitrophenylhydrazone), m.p. and mixed m.p. with above 236–238° was obtained.[19] *Anal.* Calcd. for $C_{18}H_{16}O_8N_8$: C, 45.77; H, 3.41. Found: C, 45.98; H, 3.33. A mixture of 1.72 g. of chlorocyclohexanone, 4.0 g. of potassium carbonate, 20 cc. of water, and 237 mg. of Fraction B was stirred overnight.[20] Extraction with ether and repeated recrystallizations yielded 0.80 g. of **2-hydroxy-1-cyclohexanone-1,2-C^{14}**, m.p. 127–129°. This was dissolved in 100 cc. of water at 40° and 2.40 g. of potassium permanganate was added. The excess permanganate was destroyed with methyl alcohol and the mixture filtered by suction. After acidification with hydrochloric acid and continuous ether extraction we obtained **adipic acid** which after recrystallization from water and from ether–petroleum ether weighed 0.81 g. and had m.p. 153.0–153.5°. (Undiluted Fraction B (0.65 g.) when treated by the same procedure behaved in a similar way except that we did not succeed in getting the hydroxyketone in a crystalline form. On oxidation 0.25 g. of adipic acid was produced.) To a solution of 251 mg. (1.72 mmoles) of adipic acid in 0.6 cc. of concentrated sulfuric acid was added a solution of 6 mmoles of hydrazoic acid in 3 cc. of benzene. The evolved carbon dioxide was trapped in a series of carbonate-free sodium hydroxide solutions. After 16 hours at room temperature, the benzene was removed in a stream of nitrogen, 30 cc. of water was added, and the solution was digested on a steam-bath with 7.0 g. of barium carbonate. When the liquid no longer contained sulfate it was filtered through charcoal, acidified with hydrochloric acid and evaporated to dryness. The **putrescin dihydrochloride** twice recrystallized from ethanol–water weighed 107 mg. and had m.p. *in vacuo* 283–285°. It formed a **picrate** m.p. 272°.

Fraction D; Isoamyl Cyclopentanecarboxylate.—B.p. (14 mm.) 108–109°; $n^{26}D$ 1.4413; d^{25}_{20} 0.9239. *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.52; H, 11.10. A solution of 5.4 g. of this ester, 10 cc. of ethanol, 5 cc. of water and 1.5 g. of sodium hydroxide was refluxed three hours. The ethanol was distilled off and the alkaline solution was extracted once with ether. After acidification, with hydrochloric acid, the **cyclopentanecarboxylic acid** was extracted with ether and distilled giving 2.50 g., b.p. 103–105° (8 mm.). This acid (2.30 g.), bromine (1.10 cc.) and phosphorus trichloride (0.20 g.) were heated to 100° for one hour in a sealed tube. After opening the tube most of the hydrogen bromide and excess bromine were removed at 50° by water-pump vacuum. The residue, **1-bromocyclopentanecarboxylic acid**, was dissolved in a mixture of 30 cc. of acetone, 30 cc. of water, 2.5 cc. of acetic acid and 2.0 g. of sodium acetate and allowed to stand 16 hours at room temperature. After removal of the acetone by distillation, the solution was acidified to *p*H 2 with hydrochloric acid and continuously extracted with ether. The extract was concentrated to dryness, dissolved in ethyl acetate, filtered through charcoal, and diluted with petroleum ether to give 1.60 g. of **1-hydroxycyclopentanecarboxylic acid**, m.p. 105.5–106°.

Degradation Series 3 and 4.—In a flask equipped for distillation a solution of 813 mg. of the hydroxy acid and 20 mg. of potassium permanganate in 5 cc. of water was warmed to 50°. A stream of nitrogen bubbling through the solution carried the released carbon dioxide to a carbonate-free sodium hydroxide trap. Another 20 mg. of potassium permanganate was added and a second sample of carbon dioxide was collected. Then 1.5 g. of phthalic acid and 600 mg. more of the hydroxy acid were added in 40 cc. of water. The contents of the flask were heated to boiling, and while water was distilling over, 700 mg. of potassium permanganate in 20 cc. of water was added dropwise. A total of 5.4 cc. of distillate was obtained containing **cyclopentanone**. One-tenth of this distillate was used to prepare cyclopentanone dinitrophenylhydrazone, recrystallized twice from ethyl alcohol, m.p. 146–147°. Another tenth of the distillate served to make cyclopentanone semicarbazone recrystallized twice from water, m.p. 207–208°.

The remainder of the aqueous solution of ketone was cooled to 0° and saturated with hydrogen chloride.[36] Sodium azide (1.0 g.) was added to the cold solution and the temperature allowed to rise to 25°. After four hours the temperature was raised to 90° and held there four hours. The solution was evaporated to dryness in a stream of nitrogen. The residues were extracted twice with hot absolute ethanol and the extracts concentrated to dryness. The 0.8 g. of **δ-aminovaleric acid hydrochloride** thus obtained was dissolved in 1.5 cc. of concentrated sulfuric acid and warmed *in vacuo* to remove the hydrogen chloride. Ten mmoles of hydrazoic acid in 5 cc. of benzene was added and a series of sodium hydroxide traps connected to collect the effluent carbon dioxide. After 12 hours at room temperature, the reaction was warmed gradually to 50° for about one hour. The benzene was removed in a nitrogen stream, 30 cc. of water was added, and the solution digested with 11 g. of barium carbonate. **Putrescin hydrochloride** (420 mg.) and **putrescin picrate** were isolated as described above.

Cyclopentanol-1-C^{14}.—Potassium cyanide-C^{14} and tetramethylene dibromide reacted as was described above for cyclohexanone-1-C^{14} to give adipic acid-1-C$_2^{14}$ and from it the cyclopentanone-1-C^{14} bisulfite compound. A solution of 13.0 g. of this in 50 cc. of ether was added dropwise to a stirred solution of 4.0 g. of lithium aluminum hydride in 100 cc of ether. After decomposing the excess hydride with hydrochloric acid, distillation gave 11.2 g. of cyclopentanol b.p. 54–55° (22 mm.).

Cyclopentane-1-C^{14}-1-carboxylic Acid.—To a solution of 7.8 g. of cyclopentanol in 50 cc. of dry pyridine at 0° was added 25 g. of pure *p*-bromobenzenesulfonyl chloride. After standing overnight in ice, the mixture was poured into excess dilute hydrochloric acid and extracted with carbon tetrachloride. After drying over potassium carbonate the extract was concentrated and the ester recrystallized from ether–petroleum ether. After two recrystallizations the **cyclopentyl-1-C^{14}-1-*p*-bromobenzene sulfonate** weighed 20.4 g. and had m.p. 45.5–46.0°. *Anal.* Calcd. for $C_{11}H_{13}O_3SBr$: C, 43.30; H, 4.30. Found: C, 43.38; H, 4.40. This ester decomposes in a few days at room temperature. The ester was dissolved in 60 g. of acetone containing 15 g. of sodium iodide and left overnight under nitrogen. The salt was filtered off and washed with petroleum ether. The filtrate and washings were poured into 200 cc. of ice-water containing 1.0 g. of sodium bisulfite. After two extractions with petroleum ether, 9.8 g. of **1-C^{14}-cyclopentyl iodide**, b.p. 57–58° (17 mm.), was obtained. This was dissolved in 100 cc. of dry ether and added over four hours to a stirred suspension of 1.5 g. of magnesium turnings in 50 cc. of ether. After the Grignard solution was cooled to −5°, carbon dioxide was passed through the stirred mixture. Dilute sulfuric acid was added, the ether phase was washed with water, and then extracted with sodium hydroxide solution. After washing the base extract with ether, the free cyclopentanecarboxylic acid was obtained by acidification and distillation; 2.0 g., b.p. 111–112° (17 mm.). This material was degraded in Series 6.

Rearrangement of Bromocyclohexanone.—When 12.5 g. of the bromoketone was treated with sodium ethoxide in 120 cc. of ethanol at 0°, the total yield of acidic material (after hydrolysis) was about 1.0 g. This was not pure cyclopentanecarboxylic acid. Under the same conditions, 13.5 g. of the chloroketone gave 7.5 g. of cyclopentanecarboxylic acid, b.p. 117–118° (25 mm.). By treating 17.7 g. (0.1 mole) of the bromoketone with 0.1 mole of sodium ethoxide in 250 cc. of dry ether it was possible to isolate, after hydrolysis, 2.3 g. (21%) of cyclopentanecarboxylic acid of the b.p. 94–96° (7 mm.) and 2.0 g. of 1-hydroxycyclopentane-1-carboxylic acid, b.p. 154° (7 mm.), m.p. 104.0–104.5°.

Kinetic Determination.—Equal volumes of 0.2 *N* solutions of sodium ethoxide in ethanol and 1-chlorocyclohexanone in ethanol were cooled to 0° in an ice-bath. After mixing the two solutions, aliquots were removed by syringe at

(36) Smith, THIS JOURNAL, 70, 320 (1948).

intervals of a minute or more, transferred to flasks containing a measured excess of perchloric acid in ethanol and back-titrated. The second order rate constant varied from 8.6 to 10.0 with no obvious trend.

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The Preparation of Crystalline 6-Desoxy-L-glucose (L-Epirhamnose) from D-Gluco-D-*gulo*-heptose

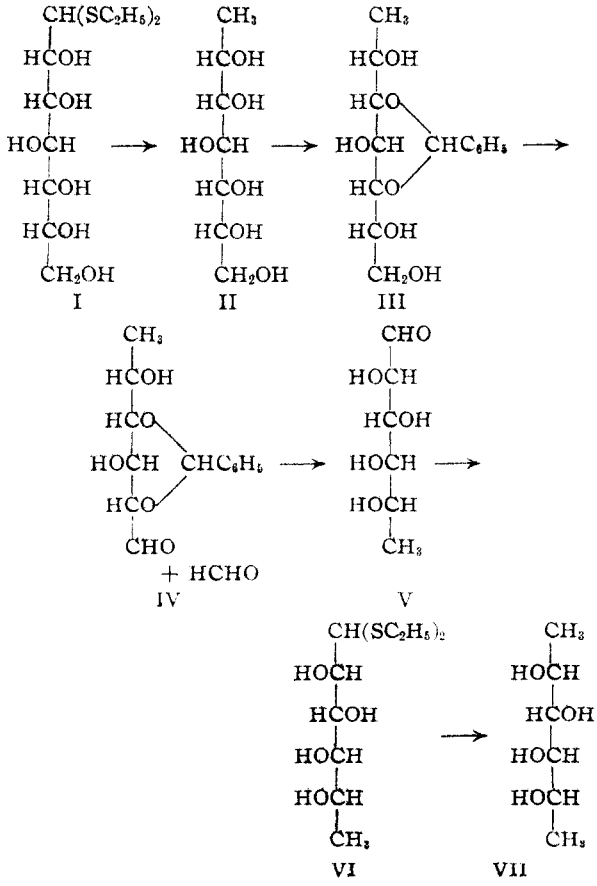
BY EMMANUEL ZISSIS, NELSON K. RICHTMYER AND C. S. HUDSON

The steps here described for the preparation of 6-desoxy-L-glucose are the reductive desulfurization of D-gluco-D-*gulo*-heptose diethyl mercaptal to 1-desoxy-D-gluco-D-*gulo*-heptitol, a condensation with benzaldehyde and the oxidative cleavage with lead tetraacetate of the 3,5-benzylidene derivative of the desoxyheptitol, followed by subsequent removal of the benzylidene group by hydrolysis. The free sugar crystallized as an α form, mutarotating from $[\alpha]^{20}D$ −99.7 to −29.9° in water. Reductive desulfurization of 6-desoxy-L-glucose diethyl mercaptal yielded 1,6-didesoxy-L-glucitol (synonym, 1,6-didesoxy-D-gulitol), which was characterized through its crystalline acetyl and benzylidene derivatives.

6-Desoxy-D-glucose occurs in nature as a component of several glycosides, and it has been obtained synthetically through the reduction of a glucose derivative containing a bromine atom in place of the hydroxyl group on carbon 6. The sugar was crystallized as early as 1911 by Votoček.[1] The enantiomorphous 6-desoxy-L-glucose (isorhamnose; epirhamnose),[2] on the other hand, has been known until now only as a sirup with $[\alpha]D$ about −30°; its preparation was accomplished by Fischer and Herborn[3a] and by Votoček and Mikšič[3b] through the sodium amalgam reduction of L-epirhamnonic lactone which, in turn, was obtained by epimerization of L-rhamnonic lactone in aqueous pyridine.

For our new procedure the starting material was D-gluco-D-*gulo*-heptose, which was converted first to the known diethyl mercaptal (I), and then, by reductive desulfurization with Raney nickel, to 1-desoxy-D-gluco-D-*gulo*-heptitol (II). Upon reaction of the last-named substance with benzaldehyde and concentrated hydrochloric acid, a monobenzylidene derivative was obtained in 84% yield. The formation of a monobenzylidene derivative of II was to be expected, for Fischer[4] had found that the closely related gluco-*gulo*-heptitol produced only a monobenzylidene derivative, and that in nearly quantitative yield; later, Hann, Ness and Hudson[5] proved by periodate oxidation that the benzylidene group was attached at carbons 3 and 5 of the heptitol molecule. Similarly, our substance was shown to be the analogous 3,5-benzylidene derivative III, for upon oxidation with lead tetraacetate it consumed only one molar equivalent of oxidant and the resulting product (besides formaldehyde) was a sirupy, six-carbon aldehyde that must have been 2,4-benzylidene-6-desoxy-L-glucose (IV); its mild acid hydrolysis then yielded the desired 6-desoxy-L-glucose (V).

The 6-desoxy-L-glucose thus obtained crystallized without difficulty and like the antipodal 6-desoxy-D-glucose it was presumably an α form as judged by the course of its mutarotation in water. Final $[\alpha]^{20}D$ values of −29.9 and −30.1° (*c*, 2) were observed for samples of both needle and prism



(1) E. Votoček, *Ber.*, **44**, 819 (1911).

(2) It may be of interest to note that thevetose, the 3-methyl ether of 6-desoxy-L-glucose, occurs in nature as a constituent of several cardiac glycosides from *Thevetia neriifolia* Jussieu, *Tanghinia venenifera* Poir. and *Cerbera Odollam* Gaertn. The synthesis of thevetose from L-glucose has been described by F. Blindenbacher and T. Reichstein [*Helv. Chim. Acta*, **31**, 1669 (1948)]; pertinent references to the earlier literature are given in their publication.

(3) (a) E. Fischer and H. Herborn, *Ber.*, **29**, 1961 (1896); (b) E. Votoček and J. Mikšič, *Bull. soc. chim. France*, [4] **43**, 220 (1928).

(4) E. Fischer, *Ann.*, **270**, 64 (1892); *Ber.*, **27**, 1524 (1894).

(5) R. M. Hann, A. T. Ness and C. S. Hudson, THIS JOURNAL, **68**, 1769 (1946).