returned to total reflux. When equilibrium was again attained, the process was repeated. Individual samples of one to three grams of liquid were taken and the refractive index determined. Samples of nearly constant boiling point and equal refractive index were combined. The yields of the octylbenzenes recorded in Table II are based on the weight of the liquid where the refractive index varies by no more than 0.001 unit (the 2,3,4-trimethyl-3-phenylpentane was repeatedly distilled through a Vigreux column until pure). The physical constants were determined on the largest combined sample of constant refractive index. In Fig. 1, the fractions of constant refractive index were obtained by combining a number of samples of the same refractive index.

Surface tensions were determined by the drop-weight method. The correction factor was calculated according to the "International Critical Tables."[16]

Summary

Eight tertiary octyl alcohols have been condensed with benzene to produce the corresponding tertiary octylbenzenes. The physical constants of the latter have been determined.

3,4-Dimethyl-3-hexanol has been synthesized by two methods.

[16] "I. C. T.," 1928, Vol. IV, p. 435.

EAST LANSING, MICHIGAN RECEIVED AUGUST 25, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Allylic Chlorides. IV. Relative Reactivities with Potassium Iodide in Acetone[1]

BY LEWIS F. HATCH, LEON B. GORDON AND JOHN J. RUSS[2]

A number of different reactions has been used to demonstrate marked differences in relative reactivity between various types of organic halides. Of these methods, the most satisfactory bimolecular (S_N2) reaction for alkyl chlorides is the metathetical reaction between the chloride and potassium iodide in dry acetone.[3] This reaction usually proceeds at an easily measured rate for most chlorides, at readily obtainable temperatures, and without side reactions.

Although this reaction has been used to compare the relative reactivities of a large number of alkyl chlorides, it was not until 1941 that the reaction was utilized in a study of the relative reactivities of several allylic chlorides.[4] The reaction proved to be entirely satisfactory for this type of chloride.

Recent work[5] on the cuprous chloride catalyzed acid hydrolysis of the isomeric 1,3-dichloropropenes has shown that geometrical configuration has a marked influence on the rate of reaction. The present investigation was undertaken to reinvestigate the reaction between allylic chlorides and potassium iodide and to determine if the previously noted effect of geometrical configuration on the hydrolysis reaction also applied to a bimolecular metathetical reaction.

Materials

Potassium Iodide.—C. P. potassium iodide was recrystallized from water and dried three hours at 120°. It failed to give a positive test for iodate ion.

Acetone.—The actone used boiled at 56.6° and did not color anhydrous copper sulfate in one hour. It retained a faint pink color of potassium permanganate for thirty minutes and liberated neither iodine nor hydriodic acid from 0.04 molar potassium iodide when kept in the dark.

1-Chloro-1-propene.—A mixture of *cis*- and *trans*-1-chloro-1-propene[6] was distilled to obtain a fraction with a boiling range of 33–34°. This fraction, being intermediate in boiling range between the two isomers (*cis* 32.0–32.2°; *trans* 36.7°), contained both isomers.

Allyl Chloride.—Allyl chloride boiling at 44.9° was obtained by distillation from crude allyl chloride[7] with a boiling range of 44.5–45.1°. It was used without further purification.

2-Bromo-3-chloro-1-propene.—2-Bromo-3-chloro-1-propene, obtained from Halogen Chemicals of Columbia, S. C., was distilled at 150 mm. pressure. The fraction used had the following constants: b. p. 61.6° (150 mm.); $n^{25}D$ 1.4968; d^{25}_4 1.6290; *MR* (calcd.) 28.22, (obsd.) 27.61.

2,3-Dichloro-1-propene.—2,3-Dichloro-1-propene[6] with a boiling range of 93–94° was distilled at 150 mm. pressure and a fraction boiling at 48.0° was used.

Methallyl Chloride.—Methallyl chloride[7] was redistilled and a fraction boiling at 72.1° was used.

1,3-Dichloropropene.—In the still bottoms remaining from the distillation of crude allyl chloride, prepared by the high temperature substitutive chlorination of propylene, there remains an appreciable quantity of higher boiling material containing a dichloride fraction consisting of approximately 63% 1,3-dichloropropene (*cis* and *trans*), 35% 1,2-dichloropropane and 2% 2,3-dichloro-1-propene. This material[7,8] was separated by distillation into fractions containing the low and high boiling isomers of 1,3-dichloropropene. These fractions were redistilled at 150 mm. pressure and the following data were obtained: low boiling 1,3-dichloropropene, b. p. 57.0°, $n^{20}D$ 1.4673; high boiling 1,3-dichloropropene, b. p. 64.7°, $n^{20}D$ 1.4745.

1,3-Dichloro-2-methyl-1-propene.—The isomeric 1,3-dichloro-2-methyl-1-propenes were prepared from methallyl chloride.[9] The methallyl chloride was chlorinated to 1,2,3-trichloro-2-methylpropane using sulfuryl chloride. The trichloride was dehydrochlorinated and hydrolyzed to a mixture of the 3-chloro-2-methyl-2-propen-1-ols which were separated using a Podbielniak Hypercal distillation column. The chloroalcohols were converted to the corresponding dichlorides using concentrated hydrochloric acid.

---

[1] Presented in part at the Texas Regional Meeting of the American Chemical Society, Dallas, Texas, December 13, 1946.

[2] Present address: Magnolia Petroleum Company, Dallas, Texas.

[3] (a) Conant and Kirner, THIS JOURNAL, **46**, 232 (1924); (b) Conant and Hussey, *ibid.*, **47**, 476 (1925); (c) Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925).

[4] Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

[5] Hatch and Roberts, THIS JOURNAL, **68**, 1196 (1946).

[6] Obtained from Research Chemicals, San José, California.

[7] Furnished us for this investigation by Shell Development Co., Emeryville, California.

[8] These isomers are now available from Shell Chemical Co., San Francisco, California.

[9] Hatch, Russ and Gordon, THIS JOURNAL, **69**, 2614 (1947).

TABLE I

RELATIVE REACTIVITIES OF ALLYLIC CHLORIDES: REACTION WITH POTASSIUM IODIDE IN ACETONE AT 20°

1-Chloro-1-propene[a]	Time, hr.	6.00	8.00				
	% reacted	0.0	0.0				
	k	0.00	0.00				
				Av. k	0.000		
Allyl chloride	Time, hr.	3.00	4.50	5.00	6.00	7.00	7.50
	% reacted	22.4	34.6	41.5	44.1	50.0	50.7
	k	0.187	0.212	0.243	0.221	0.230	0.217
				Av. k	0.218[b]		
2-Bromo-3-chloro-1-propene	Time, hr.	3.00	3.50	4.00	4.50	5.00	
	% reacted	24.4	25.9	27.8	30.9	33.2	
	k	0.208	0.191	0.183	0.186	0.181	
				Av. k	0.190		
2,3-Dichloro-1-propene	Time, hr.	2.00	3.00	4.00	5.00	6.00	7.00
	% reacted	13.1	18.9	24.3	30.1	35.7	38.5
	k	0.155	0.154	0.155	0.161	0.166	0.156
				Av. k	0.158		
Methallyl chloride	Time, hr.	3.00	4.00	5.00			
	% reacted	38.0	43.8	52.4			
	k	0.362	0.328	0.343			
				Av. k	0.344[c]		
1,3-Dichloropropene (High boiling)	Time, hr.	3.00	4.50	4.75	5.00	6.00	7.00
	% reacted	55.6	69.4	71.8	74.5	78.3	84.6
	k	0.607	0.625	0.635	0.654	0.614	0.654
				Av k.	0.632		
1,3-Dichloropropene (Low boiling)	Time, hr.	1.00	1.50	2.00	2.50	3.25	3.50
	% reacted	55.3	72.3	79.3	85.9	91.0	91.9
	k	1.87	2.04	1.84	1.92	1.76	1.81
				Av. k	1.87		
1,3-Dichloro-2-methyl-1-propene (High boiling)	Time, hr.	0.50	1.00	1.50	2.00	2.25	2.50
	% reacted	37.7	56.6	70.0	77.2	78.3	80.8
	k	2.14	1.94	1.91	1.78	1.64	1.60
				Av. k	1.84		
1,3-Dichloro-2-methyl-1-propene (Low boiling)	Time, hr.	0.25	0.50	0.75	1.00	1.25	
	% reacted	62.0	80.4	88.5	92.4	92.8	
	k	9.06	7.91	7.10	6.45	5.27	
				Av. k	7.16		
1,1,3-Trichloro-2-methyl-1-propene	Time, hr.	0.50	1.00	1.50			
	% reacted	83.6[d]	95.4	97.5			
	k	Not calculated					

[a] A mixture of the *cis* and *trans* isomers. [b] Tamele, Ott, Marple and Hearne (*Ind. Eng. Chem.*, **33**, 119 (1941)) give $k = 0.226$. [c] Tamele, Ott, Marple and Hearne give $k = 0.354$. [d] Probably low.

The following physical data were obtained: low boiling 1,3-dichloro-2-methyl-1-propene: b. p. 130° (741 mm.); $n^{25}{}_{\mathrm{D}}$ 1.4698; $d^{25}{}_4$ 1.1629; *MR* (calcd.) 29.94, (obsd.) 29.97. High boiling 1,3-dichloro-2-methyl-1-propene: b. p. 132.0° (754 mm); $n^{25}{}_{\mathrm{D}}$ 1.4740; $d^{25}{}_4$ 1.1667; *MR* (calcd.) 29.94, (obsd.) 30.08.

1,1,3-Trichloro-2-methyl-1-propene.—1,1,3-Trichloro-2-methyl-1-propene was obtained from Halogen and Perfume Chemicals, Columbia, S. C., and was distilled at 150 mm pressure. A center fraction gave the following constants: b. p. 101.0° (150 mm); $n^{25}{}_{\mathrm{D}}$ 1.4933; $d^{25}{}_4$ 1.3211; *MR* (calcd.) 34.81, (obsd.) 35.08.

Experimental

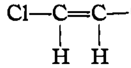
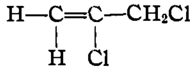
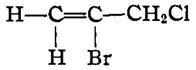
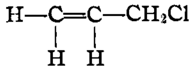
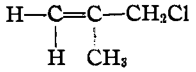
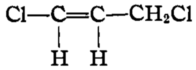
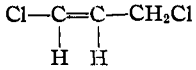
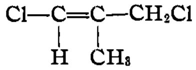
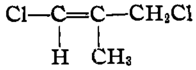
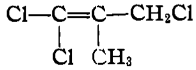
The rate studies were carried out in 16 × 150 mm. Pyrex tubes maintained at 20.00 ± 0.01° in a constant temperature bath. The procedure used was the same as that described by Tamele, *et al.*[4], and the same equation was used to calculate the specific reaction rate constant, k. The data obtained are given in Table I.

Discussion

Table II lists the allylic chlorides for which rate constants were obtained. These compounds are listed in the increasing order of their relative reactivity with the rate constant of allyl chloride taken as unity. Allyl chloride was taken as unity because all the other allylic chlorides may be considered as derived from it by replacing one or more hydrogen atoms.

TABLE II

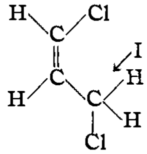
RELATIVE REACTIVITIES OF ALLYCLIC CHLORIDES WITH KI IN ACETONE

Compound		Relative reactivities
 $\mathrm{Cl{-}\underset{H}{\underset{\mid}{C}}{=}\underset{H}{\underset{\mid}{C}}{-}CH_3}$	*cis* and *trans*	0.00
 $\mathrm{H{-}\underset{H}{\underset{\mid}{C}}{=}\underset{Cl}{\underset{\mid}{C}}{-}CH_2Cl}$		0.72
 $\mathrm{H{-}\underset{H}{\underset{\mid}{C}}{=}\underset{Br}{\underset{\mid}{C}}{-}CH_2Cl}$		0.87
 $\mathrm{H{-}\underset{H}{\underset{\mid}{C}}{=}\underset{H}{\underset{\mid}{C}}{-}CH_2Cl}$		1.00
 $\mathrm{H{-}\underset{H}{\underset{\mid}{C}}{=}\underset{CH_3}{\underset{\mid}{C}}{-}CH_2Cl}$		1.58
 $\mathrm{Cl{-}\underset{H}{\underset{\mid}{C}}{=}\underset{H}{\underset{\mid}{C}}{-}CH_2Cl}$	High boiling	2.90
 $\mathrm{Cl{-}\underset{H}{\underset{\mid}{C}}{=}\underset{H}{\underset{\mid}{C}}{-}CH_2Cl}$	Low boiling	8.58
 $\mathrm{Cl{-}\underset{H}{\underset{\mid}{C}}{=}\underset{CH_3}{\underset{\mid}{C}}{-}CH_2Cl}$	High boiling	8.45
 $\mathrm{Cl{-}\underset{H}{\underset{\mid}{C}}{=}\underset{CH_3}{\underset{\mid}{C}}{-}CH_2Cl}$	Low boiling	32.8
 $\mathrm{Cl{-}\underset{Cl}{\underset{\mid}{C}}{=}\underset{CH_3}{\underset{\mid}{C}}{-}CH_2Cl}$		>33

Because several of the compounds contain a vinyl halogen as well as an allylic chlorine, it was necessary to determine if a vinyl chlorine reacts with potassium iodide in acetone at 20°. 1-Chloro-1-propene was used as the test compound, for it was available as a mixture of the *cis* and *trans* isomers. It was desirable to use a mixture of geometrical isomers because geometrical configuration might cause some difference in reactivity. A mixture of these two isomers did not give a measurable reaction in eight hours, and it has been assumed that only the allylic chlorine reacts in those compounds containing both types of halogen.

The influence of the relative electronegativity of the atom or group on the number 2 carbon ($\overset{1}{\mathrm{C}}{=}\overset{2}{\mathrm{C}}{-}\overset{3}{\mathrm{C}}$) is not great, but nevertheless definite. The rate of reaction increases with a decrease in the relative electronegativity of the group or atom in the order: $\mathrm{CH_3} > \mathrm{H} > \mathrm{Br} > \mathrm{Cl}$. This effect would be expected if the reaction takes place through an attack of the iodide ion on the carbon atom opposite the point of attachment of the allylic chlorine. The influence of a negative group on the number 2 carbon in this position is to cause the allylic carbon to become relatively less positive and consequently to exert less attraction for the negative iodide ion.

The nature of the effect of a substituent on the number 1 carbon is more involved than for substituents on the number 2 carbon because of the role played by geometrical configuration. This effect may be through steric hindrance or electrostatic interference or both. A group with a large negative field in the *cis* position would offer electrostatic impedance to the approach of the negative iodide ion. In *cis*-1,3-dichloropropene, for example, it is assumed that the allylic chlorine is oriented in a position away from the vinyl chlorine. If this were true, the iodide ion must approach the carbon through the negative field of the vinyl chlorine.



A scale model of this molecule also indicates that there would be considerable steric hinderance to the approach of the iodide ion. The *trans* isomer should have a greater reactivity than the *cis* isomer, provided the other group (H in this case) is relatively less negative than chlorine and smaller in size. With 1,1,3-trichloro-2-methyl-1-propene the activating influence of another vinyl chlorine apparently is somewhat greater than the deactivating effect of a chlorine in the *cis* position. This compound is somewhat more reactive than *trans*-1,3-dichloro-2-methyl-1-propene.

The two isomers of both 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene have distinctly different rates of reaction with the *low* boiling isomer in each case being the *more* reactive. If the foregoing reaction mechanism applies, it would seem that the *low* boiling isomer of 1,3-dichloropropene and of 1,3-dichloro-2-methyl-1-propene is the *trans* isomer and the high boiling isomer the *cis* form.

This conclusion is the same as that drawn by Hatch and Roberts[5] from the fact that the *low* boiling isomer of 1,3-dichloropropene reacts more *slowly* in its cuprous chloride catalyzed acid hydrolysis. Andrews and Kepner,[10] however, have pointed out that the data presented to substantiate this conclusion are amenable to other interpretations.

The only previously reported investigation of the relative reactivities of allylic chlorides with potassium iodide is that of Tamele and co-workers[4] on allyl and methallyl chlorides, crotyl chloride and 1-chloro-2-methyl-2-butene. With neither of the latter two compounds is it possible to determine from the data given if the compound used was the *cis* or the *trans* isomer or a mixture of the two. A confirmation of their conclusions as to the influence of the position of the methyl group must await the establishment of configuration and the determination of the reaction rate of both isomers of each compound. This investigation is now in progress.

---

[10] Andrews and Kepner, THIS JOURNAL, 69, 2230 (1947).

Acknowledgment.—The authors wish to thank both the University of Texas Research Institute and the Research Corporation for their support of these and related researches on allylic chlorides.

Summary

The reaction of allylic chlorides with potassium iodide in acetone has been used to elucidate the influence of substitutents on both the number 1 and number 2 carbons and also of geometrical isomerism on the relative reactivity of the allylic chlorine.

The greater the relative electronegativity of the group on the number 2 carbon, the less is the activity of the allylic chlorine toward iodide ion. The differences in reactivity, however, are small.

Because the reaction of potassium iodide with allylic chlorides is an S_N2 type reaction, either a relatively negative group or a relatively large group, or both, in the *cis* position on the number 1 carbon would inhibit the reaction.

Since the low boiling geometrical isomers of both 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene react more readily than the high boiling isomers, the low boiling isomers have tentatively been assigned the *trans* structure.

RECEIVED JUNE 16, 1947

[CONTRIBUTION FROM LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Pteroic Acid Derivatives. I. Pteroyl-α-glutamylglutamic Acid and Pteroyl-α,γ-glutamyldiglutamic Acid

BY J. H. MOWAT, B. L. HUTCHINGS, R. B. ANGIER, E. L. R. STOKSTAD, J. H. BOOTHE, C. W. WALLER
J. SEMB AND Y. SUBBAROW

In the course of the degradation of the fermentation *L. casei* factor[1] this compound was found to contain three molecules of glutamic acid in contrast to the liver *L. casei* factor (pteroylglutamic acid) which contained only one molecule of glutamic acid.

The synthesis of the fermentation *L. casei* factor became of particular interest when Lewisohn and his associates[2] reported that the substance caused regression of spontaneous breast tumors in mice.

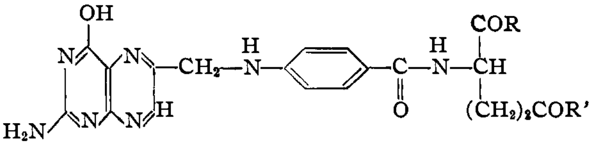
This communication describes the synthesis of one of the two possible isomers of pteroyldiglutamic acid and one of the five possible isomers of pteroyltriglutamic acid. These compounds were prepared during the course of our work on the structure and synthesis of the fermentation *L. casei* factor.

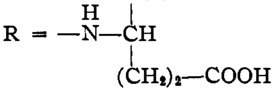
In the preparation of pteroyl-α-glutamylglutamic acid (I) the dipeptide α-glutamylglutamic acid[3] was treated with *p*-nitrobenzoyl chloride and after reduction of the nitro group the resulting *p*-aminobenzoyl-α-glutamylglutamic acid was condensed with 2,4,5-triamino-6-hydroxypyrimidine and 2,3-dibromopropionaldehyde by the procedure of Waller, *et al.*[4]

The purified product was only slightly active when assayed with *Lactobacillus casei* or *Streptococcus faecalis R*. The low activity with *Lactobacillus casei* indicated that the fermentation *L. casei* factor probably contained at least one gamma-linkage in the peptide side chain. It therefore seemed desirable to prepare pteroyl-α,γ-glutamyldiglutamic acid (II).

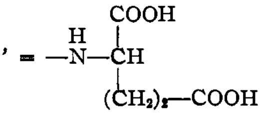
This substance was prepared by condensing diethyl glutamate[5] with the γ-acid chloride of carbobenzoxy-α-glutamyldiethylglutamate[3] to give carbobenzoxy-α,γ-glutamyldiglutamic acid tetraethyl ester. The carbobenzoxy group was removed in the usual manner with hydrogen and palladium charcoal catalyst in the presence of acetic acid, giving the acetate of α,γ-glutamyldiglutamic acid tetraethyl ester which was then converted to the *p*-nitrobenzoyl derivative. After reduction of the nitro group, the resulting *p*-aminobenzoyl-α,γ-glutamyldiglutamic acid was condensed with 2,4,5-triamino-6-hydroxypyrimidine and 2,3-dibromopropionaldehyde by the procedure of Waller, *et al.*[4]

The crude product, pteroyl-α,γ-glutamyldiglutamic acid, was not available in quantities sufficient for a satisfactory purification but the biological assay of both the crude and the partially purified material did not differ appreciably from that of pteroyl-α-glutamylglutamic acid and it



I 

$$R = \underset{\displaystyle (CH_2)_2—COOH}{\overset{\displaystyle COOH}{—\overset{H}{N}—CH}} \qquad R' = —OH$$

II 

$$R \text{ and } R' = \underset{\displaystyle (CH_2)_2—COOH}{\overset{\displaystyle COOH}{—\overset{H}{N}—CH}}$$

---

[1] Hutchings, *et al.*, THIS JOURNAL, **70**, 10 (1948).

[2] Lewisohn, C. Leuchtenberger, R. Leuchtenberger and Keresztesy, *Science*, **104**, 436 (1946).

[3] Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

[4] Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).

[5] Chiles and Noyes, *ibid.*, **44**, 1798 (1922).