

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA, MINNEAPOLIS 14, MINN.]

The Reaction of Alkylmercuric Iodides with Non-halogen Acid^{1a}BY MAURICE M. KREEVOY AND RICHARD L. HANSEN^{1b}

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A study of the relative reactivities of alkylmercuric iodides toward aqueous non-halogen acids gives the following order of reactivities: cyclo-C₃H₅- >> CH₃- > C₂H₅- > *n*-C₃H₇- > iso-C₃H₇- > *t*-C₄H₉-. These results, along with the thermodynamic quantities of activation, are consistent with a rate-determining step in which the carbon-mercury bond is broken and the new carbon-hydrogen bond is made. For the open-chain compounds the former process is nearly complete while the latter is just beginning in the transition state. The entropy of activation and the solvent isotope effect for the cyclopropyl case suggest certain quantitative differences.

In a previous paper² the reaction of methylmercuric iodide with aqueous perchloric and sulfuric acids was discussed and a mechanism advanced. This work has now been extended to other saturated alkylmercuric iodides. The original conclusions are supported and extended.

Results

As before, the reactions were carried out in sealed ampoules and the progress of the reaction was followed spectrophotometrically. Since a very large excess of acid was present and approximately one mole of mercuric iodide was produced from each two moles of substrate, eq. 1 was used to evaluate pseudo first-order rate constants, k_1 .²

$$k_1 = \frac{2.303}{2(t - t_0)} \log \frac{(D_\infty - D_0)}{(D_\infty - D_t)} \quad (1)$$

Ethyl, *n*-propyl and cyclopropylmercuric iodides gave approximately linear plots of $\log \{(D_\infty - D_t)/(D_\infty - D_0)\}$ vs. t . A typical example of this sort of plot has been shown.² These compounds were shown to be insensitive to molecular oxygen under the present conditions. Rate constants obtained for them were reproducible with an average deviation of less than 10% in all cases and the reliability of the measurements is thought to be comparable with those for methylmercuric iodide.² Isopropyl- and *t*-butylmercuric iodide, on the other hand, both gave mercuric iodide quite rapidly in the absence of acid unless atmospheric oxygen was rigorously excluded. In the presence of both atmospheric oxygen and acid, isopropylmercuric iodide gave mercuric iodide several powers of ten faster than in the presence of acid alone.³ Atmospheric oxygen was, therefore, excluded from the reaction mixtures involving these compounds. The plots obtained from these reactions show much more scatter than those described above, and the rate constants are correspondingly less reliable. A typical example is shown in Fig. 1. The scatter is presumably due to residual traces of oxygen. *N*-Hexylmercuric iodide was also studied briefly, but only an approximate rate constant could be obtained because of the limited solubility of this compound in water.

(1) (a) This work was supported in part by the Air Force Office of Scientific Research, through contract no. AF 49(638)711, in part by the National Science Foundation, through grant no. N.S.F.-G5434, and in part by the Graduate School of the University of Minnesota. Reproduction in whole or in part is permitted for any purpose of the United States Government. (b) Sun Oil Co. fellow 1958-1959; du Pont Co. fellow, summer, 1959.

(2) M. M. Kreevoy, *J. Am. Chem. Soc.*, **79**, 5927 (1957).

(3) The reaction with oxygen will be discussed in future publications.

The reaction of isopropylmercuric iodide with acid in the presence of oxygen shows an extremely anomalous temperature dependence.³ The fact that a normal plot of $\log (k_2/T)$ vs. $1/T$ was finally obtained strongly supports the view that the rate reported is that of the normal acid cleavage, uninfluenced by oxygen. This view is further supported by the regularity of the series methyl, ethyl, isopropyl, *t*-butyl. The evidence is weaker in the case of the *t*-butyl compound, resting entirely on the regularity of the series, because we were unable to study the reaction as a function of temperature. Also the sensitivity to oxygen was even greater in the case of the *t*-butyl compound. Consequently, while it is most unlikely that the tabulated rate for the *t*-butyl compound is significantly low, it is possible that it may be somewhat too high.

The reaction rate was studied as a function of acid concentration for all the compounds except *n*-hexyl- and *t*-butylmercuric iodide. In all cases a somewhat less-than-linear dependence on the stoichiometric acid concentration was found.² Following Bunnett,⁴ a plot of the quantity $\log k_1 + H_0$, vs. $\log \alpha_{H_2O}$ is shown in Fig. 2 for ethylmercuric iodide in sulfuric acid. The plot is approximately linear with slope 11.7. The Hammett acidity function values, H_0 , were those of Paul and Long.⁵ They pertain to 25°, but they are not thought to be excessively temperature sensitive.⁵ The activity of water, α_{H_2O} , was extrapolated to 90° from the data of Harned and Owen.⁶ An exactly analogous plot using the data for the reaction of methylmercuric iodide with sulfuric acid at 100° has a slope of 11.5.² In other cases, data were too scanty or too imprecise to justify making the plot.

The reactivities of the various alkylmercuric iodides are compared in Table I. Second-order rate constants, k_2 , were obtained by dividing first-order rate constants by the exact acid concentration. In those cases where k_2 was studied as a function of acid concentration, its value at 1.00 *M* acid was taken from the experimental curve. Experimental ΔH^* values were used to interpolate or extrapolate to 110°. (Extrapolation was required only in the case of cyclopropylmercuric iodide and *t*-butylmercuric iodide. In the latter case a typical ΔH^* also had to be used, as no experimental value was available.) Several

(4) J. F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960).

(5) M. A. Paul and F. Long, *Chem. Revs.*, **57**, 1 (1957).

(6) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, 1958 p. 574.

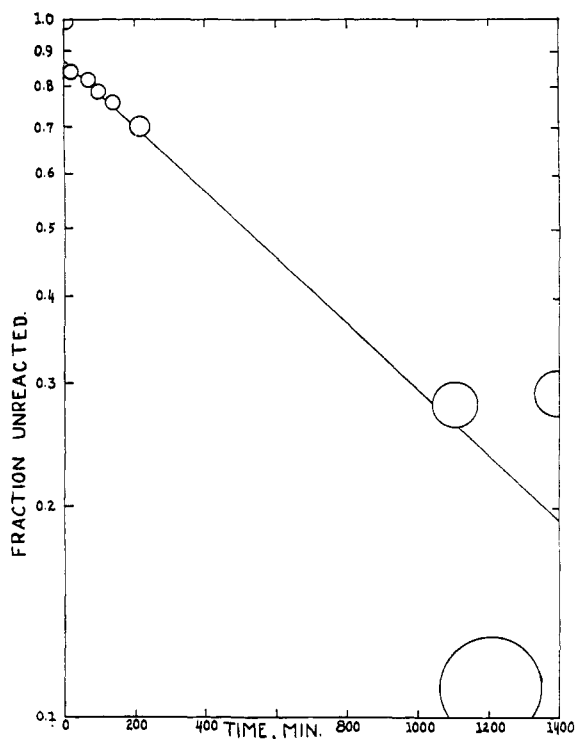


Fig. 1.—Typical first-order rate plot for reactions which are oxygen sensitive; from an experiment with *t*-butylmercuric iodide.

of the compounds were treated only with perchloric acid. Since methylmercuric iodide reacted 1.71 times faster with sulfuric than with perchloric acid, second-order rate constants obtained with the latter only were multiplied by 1.71.

TABLE I
RATES AT 1 M ACID

Substituent	k_2^a
CH ₃	1.72×10^{-5b}
C ₂ H ₅	6.8×10^{-6}
<i>n</i> -C ₃ H ₇	3.8×10^{-6c}
<i>n</i> -C ₆ H ₁₁	$\sim 2 \times 10^{-6e,d}$
<i>i</i> -C ₃ H ₇	2.2×10^{-6d}
Cyclo-C ₃ H ₅	$1.3 \times 10^{-2e,d}$
<i>t</i> -C ₄ H ₉	$\sim 1.4 \times 10^{-7e-g}$

^a All the reaction mixtures contained 2% methanol except those for *t*-butylmercuric iodide which contained 6% methanol. ^b Obtained by interpolating the data of ref. 2. ^c k_2 was assumed not to vary with changes in acid concentration. ^d The data were obtained with perchloric acid and the factor of 1.71 was used to convert to a common acid. ^e This datum was obtained at 123°. A "normal" activation enthalpy, 23 kcal. mole⁻¹, was assumed in converting to 110°.

The rate was studied as a function of temperature for ethyl, *n*-propyl-, isopropyl- and cyclopropylmercuric iodide at constant acid and substrate concentrations. In all cases plots of $\log(k_2/T)$ vs. $(1/T)$ were linear within the uncertainty of the measurements. (As previously mentioned, the uncertainty was quite considerable in the case of isopropylmercuric iodide.) The enthalpies of activation were obtained by the method of least squares⁷ from the slopes of such plots. The free

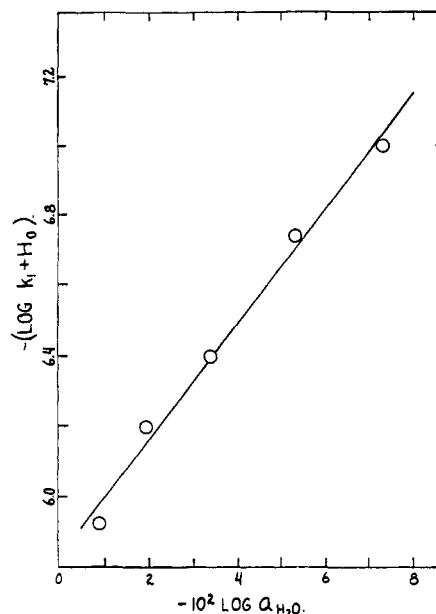


Fig. 2.—Bunnett plot for the reaction of ethylmercuric iodide with sulfuric acid.

energies of activation were obtained in the usual way² from second-order rate constants taken from the plots at the mid-point of the temperature range. Entropies of activation were obtained from the thermodynamic equalities.⁸ The thermodynamic quantities of activation are listed in Table II, along with the temperature range studied, the

TABLE II
THERMODYNAMIC PROPERTIES OF ACTIVATION

R	Temp. range °C.	No. of points	ΔH^* , kcal. mole ⁻¹	ΔS^* , cal. mole ⁻¹ deg. ⁻¹	(H ₂ SO ₄), mole l. ⁻¹
CH ₃	92-161	6	22.3 ± 0.3^a	-23.3 ± 1^b	1.0
C ₂ H ₅	92-147	5	22.8 ± 1.7	-25 ± 4	2.0
<i>n</i> -C ₃ H ₇	111-147	2	$23 \pm \sim 3^c$	$-23 \pm \sim 9^c$	2.0
Cyclo-C ₃ H ₅	40-101	5	20.9 ± 1.4	-11 ± 4	0.014 ^d
Iso-C ₃ H ₇	100-156	9	25.0 ± 2.4	-21 ± 6	.14 ^d

^a Taken from ref. 2. ^b Recalculated from the data of ref. 2. ^c Since the rate constant was available at only two temperatures, the uncertainties were estimated on the basis of those observed with other compounds. ^d Perchloric acid.

number of measurements made, the acid concentration used, and the probable errors of the thermodynamic quantities. For completeness, Table II also includes the results for methylmercuric iodide. A numerical error seems to have been made in the previous calculation of ΔS^* for methylmercuric iodide,² and a recalculated value is given in Table II.

Because of the strikingly higher rate and rather different thermodynamic properties of activation exhibited by cyclopropylmercuric iodide, the solvent isotope effect on its cleavage rate was determined from three experiments in water and two experiments in water containing 95.5 atom per cent. deuterium. In both cases the tempera-

(7) C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 38-40.

(8) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 275.

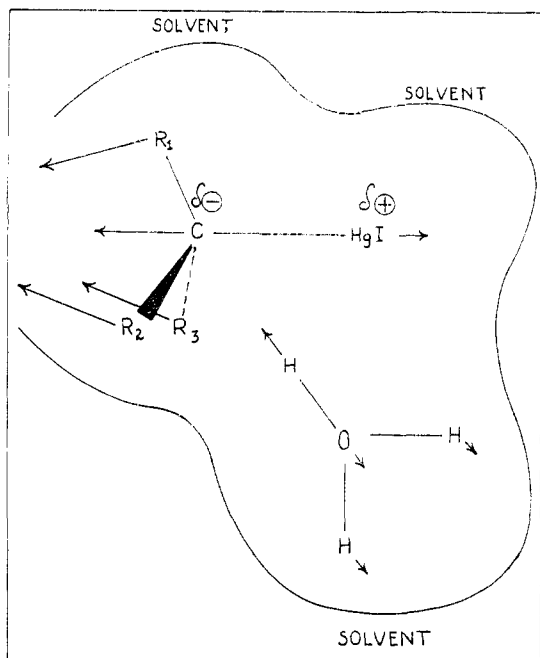


Fig. 3.—The transition state for the acid cleavage of alkylmercuric iodides. The arrows approximate the direction and relative magnitudes of the atomic motions along the reaction coordinate.

ture was 63.8° and $0.0136 M$ perchloric acid was used. The ratio k_2^H/k_2^D is 1.7 ± 0.3 .

Discussion

From the results obtained with methylmercuric iodide,² it was concluded that the cleavage of alkylmercuric iodides by non-halogen acids is a one-step reaction in which the old carbon-mercury and oxygen-hydrogen bonds are broken and the new carbon-hydrogen bond is formed. It was suggested, however, that the formation of the new carbon-hydrogen bond lags behind the breaking of the old carbon-mercury bond, so that the carbon atom bears a substantial part of a unit negative charge in the transition state. Recent work on the stereochemistry of electrophilic displacement reactions^{9,10} and the older work on the geometry of H_3^{\oplus} ¹² make it seem very likely that the carbon, the mercury and the incoming proton define some sort of a triangle. The proposed transition state is shown in Fig. 3.

As previously indicated,² a nearly linear dependence of rate on the stoichiometric acid concentration is consistent with a rate-determining proton transfer. The slope of the plots of $\log k_1 + H_0$ vs. α_{H_2O} is higher than any of those reported by Bunnett.⁴ The conclusion that the transition state requires more solvation than the starting state seems well founded, however. It is consistent with the postulated transition state and in accord with the substantial negative entropies of activation. The reduction in rate accompanying the ramification of the alkyl group may be due to

(9) S. Winstein and T. Traylor, *J. Am. Chem. Soc.*, **78**, 2597 (1956).

(10) H. B. Charman, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2530 (1959).

(11) F. R. Jensen, *J. Am. Chem. Soc.*, **82**, 2469 (1960).

(12) J. Hirschfelder, *J. Chem. Phys.*, **6**, 795 (1938).

to the increasingly electron-supplying character of those groups.¹⁵ Or, if the preferred bond angles about a carbon-like carbon are smaller than 109° , it may be due to an increased crowding of the attached groups. It seems quite likely that the preferred bond angles about a carbanion-like carbon are somewhat less than 109° .¹⁴ More alkylmercuric iodides of more widely varying polar characteristics will have to be studied to evaluate the relative importance of these two effects.

The order of reactivity $Me > Et > i\text{-Pr} > t\text{-Bu}$ is the same as that observed by Kharasch and co-workers¹⁵ and different from that observed by Winstein and Traylor¹⁶ and by Dessy and co-workers.¹⁷

Although their reliability leaves something to be desired, the similarity of the entropies of activation for the open-chain compounds strongly suggests that there are no drastic changes in transition state structure from one member of the series to another. It also suggests that there is no great loss of internal freedom in the alkyl group of the transition state. The standard entropies of the larger alkylmercuric halides must be substantially larger than that of methylmercuric iodide so that they would give rise to increasingly more negative entropies of activation if their structure became more rigid in the transition state.¹⁸

The very rapid cleavage of the cyclopropylmercury bond has previously been observed by Dessy and co-workers,¹⁷ and is in accord with the foregoing picture of the transition state. The orbital used by the cyclopropyl group to make exocyclic bonds has less p-character and more s-character than that used by an open-chain substituent,¹⁹ and is, therefore, more electron withdrawing. The cyclopropyl group also may be more able to delocalize a negative charge than an open-chain alkyl group.²⁰ In addition, if the preferred bond angles in the transition state are smaller than those in the starting state, the activation process will be aided by a release of strain. Using the harmonic oscillator approximation and the force constant suggested by Westheimer,²¹ this release of strain would amount to some 5 kcal. mole⁻¹ if the preferred bond angles in the transition state were 100° .

If all these things took place without altering the transition state solvation, the observed effect would be almost entirely in the enthalpy of activation. In fact, more than half of the observed

(13) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 590.

(14) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p. 120.

(15) (a) M. S. Kharasch and S. Swartz, *J. Org. Chem.*, **3**, 405 (1939);

(b) M. S. Kharasch and A. Flenner, *J. Am. Chem. Soc.*, **54**, 674 (1932).

(16) S. Winstein and T. Traylor, *ibid.*, **81**, 2683 (1959).

(17) R. E. Dessy, G. F. Reynolds and Jin-Young Kim, *ibid.*, **81**, 2683 (1959).

(18) H. M. Humphreys and L. P. Hammett, *ibid.*, **78**, 521 (1956). It is likely that the entropy of isopropylmercuric iodide in dilute aqueous solution is ~ 10 cal. mole⁻¹ deg.⁻¹ higher than that of methylmercuric iodide.

(19) C. A. Coulson, "Valence," Oxford University Press, Oxford, England, 1952, p. 205.

(20) E. T. Trachtenberg and G. Odian, *J. Am. Chem. Soc.*, **80**, 4018 (1958).

(21) F. H. Westheimer, ref. 13, p. 523.

effect is in the entropy of activation. To account for this, the oxygen-carbon distance in the cyclopropyl transition state must be smaller than that in the open-chain transition states, and the carbon-hydrogen-oxygen bond more nearly symmetrical. This raises the enthalpy of activation by increasing the non-bonded repulsions but makes the entropy more positive by releasing solvent. From such a picture it is predicted that the solvent isotope effect, k_H/k_D , should be larger in the cyclopropyl case than in the open-chain cases. The oxygen-hydrogen stretching frequency in the transition state would probably be reduced more than the bending frequencies would be raised.²² Such an effect is observed, k_H/k_D , is 1.7 for cyclopropylmercuric iodide as compared to 1.0 for methylmercuric iodide.² It is also predicted that the Bunnett w should be substantially smaller than for the open-chain compounds.⁴ That prediction has not yet been tested.

Experimental²³

Materials.—Ethylmercuric iodide was prepared from ethylmercuric chloride, obtained through the courtesy of Eli Lilly and Co. The chloride was crystallized once from ethanol and sublimed under reduced pressure to give a white, crystalline material, m.p. 193–194. Purified ethylmercuric chloride was treated with 90% of the theoretical amount of potassium iodide in methanol after which the ethylmercuric iodide was precipitated by adding water. The product was crystallized from methanol and then sublimed under reduced pressure to give a white, crystalline product, m.p. 185–186° (sealed capillary), reported²⁴ m.p. 186°.

n-Propylmercuric iodide was prepared from *n*-propylmagnesium iodide and mercuric iodide by the method of Marvel, Gauerke and Hill.²⁵ After three sublimations at 60° and 0.4 mm., the product was white and crystalline and had a m.p. of 110–111°. *n*-Propylmercuric iodide is reported to melt at 113°.^{24,25}

n-Hexylmercuric iodide was prepared in the same way as ethylmercuric iodide and was purified by crystallization from methanol; m.p. 105–107°, reported²⁴ m.p. 110°.

Isopropylmercuric iodide was prepared in the same way as *n*-propylmercuric iodide, and purified by sublimation; m.p. 123–124° (sealed capillary). It has been reported to melt at 125°.²⁶

Cyclopropylmercuric iodide was prepared in essentially the same way as ethylmercuric iodide from a 58-mg. sample of cyclopropylmercuric chloride that was furnished by Prof. R. E. Dessy of the University of Cincinnati; m.p. 183–184° (sealed capillary). Cyclopropylmercuric iodide does not seem to have been reported previously (although the chloride has been thoroughly characterized²⁷). The present sample was entirely consumed by the kinetic measurements so that no analytical data could be obtained.

t-Butylmercuric iodide was prepared in the same way from *t*-butylmercuric chloride and purified by crystallization from methanol. The material decomposes before melting if the m.p. is taken in the usual way. By introducing it into the bath in a sealed capillary just below its m.p., a m.p. of 93–94° was obtained.

Anal. Calcd. for C₄H₉HgI: C, 12.49; H, 2.36; Hg, 52.16; I, 33.00. Found²⁸: C, 12.74; H, 2.39; Hg, 52.27; I, 32.82.

t-Butylmercuric chloride was prepared from *t*-butylmagnesium chloride and mercuric chloride by the method of Kharasch,¹⁵ except that the ethereal solution of the

product was not washed with 1% sulfuric acid—such a wash caused extensive decomposition in our hands; m.p. 117–119° dec.

The ultraviolet spectra of all the foregoing alkylmercuric iodides were recorded on a Beckman DK-2 far ultraviolet spectrophotometer between 1900 and 3000 Å. Each shows a peak (or shoulder) around 2000 Å. and a weaker peak (or shoulder) around 2250 Å. This pair of peaks seems to be characteristic of this type of compound and its presence in cyclopropylmercuric iodide helps to characterize the latter. Table III shows the peak positions and extinction coefficients in aqueous solution.

TABLE III
ULTRAVIOLET PEAKS OF ALKYL MERCURIC IODIDES

Compound	λ_{\max}^a (Å.)	ϵ_{\max}^a 10 ⁻⁴	λ_{\max}^b Å.	ϵ_{\max}^b 10 ⁻⁴
CH ₃ HgI	1970(sh)	2.3	2230(sh)	0.8
C ₂ H ₅ HgI	2090	1.8	2280(sh)	1.2
<i>n</i> -C ₃ H ₇ HgI	2070	1.9	2270(sh)	1.2
Iso-C ₃ H ₇ HgI	2150	1.9	2300(sh)	1.7
Cyclo-C ₃ H ₅ HgI	2070	1.4	2260(sh)	1.1
<i>t</i> -C ₄ H ₉ HgI	1960(sh)	1.7	2260	1.4

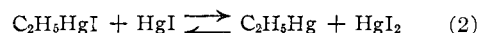
^a For the short wave length maximum. ^b For the long wave length maximum.

Kinetic Techniques.—All the reagents used have been previously described, as have the kinetic techniques used for all the compounds except *n*-hexylmercuric iodide.² The latter was insufficiently soluble to give a large enough change in optical density for the ampoule technique, so a more dilute solution of substrate was made up in aqueous acid and transferred to a spectrophotometer cell. The spectrophotometer cell was held at 92° by an aluminum block submerged in a conventional thermostat and the cell was removed, briefly, at intervals, to make measurements. The rate constants obtained in this way had a reproducibility of only $\pm 25\%$ (as compared to $\pm 10\%$ for the ampoule technique) so it was not used with any of the other compounds.

For isopropyl- and *t*-butylmercuric iodides, as mentioned above, oxygen was found to have a profound influence on the rate of production of mercuric iodide. Each ampoule was, therefore, bubbled with oxygen-free nitrogen for three minutes before it was sealed, and a blanket of nitrogen was maintained over the opening during the sealing process. Increasing the bubbling period to 5 minutes or decreasing it to 2 minutes had no observable effect on the results.

Most of the reaction mixtures studied contained 2% methanol, introduced with the substrates, since the latter were in methanolic solution. Because of the solubility difficulties with *t*-butylmercuric iodide, its reaction mixtures contained 6% methanol.

With ethylmercuric iodide it was noted that the optical density at 2700 Å. showed a slow decline after reaching a maximum somewhat short of 10 half-lives. A decline of about 25% was observed over a period of about 30 half-lives in one case. This decline is understandable if the optical density contributed by 2 moles of HgI⁺ is smaller than that contributed by 1 mole of HgI₂,^{2,29} and if the reaction shown in eq. 2 has a finite equilibrium constant.



Assuming that this equilibrium constant is finite and that only ethylmercuric iodide reacts, a more exact rate law was derived,³⁰ which reduces to eq. 1 in the limit $K \rightarrow \infty$. This rate law was too complicated for routine use. It was shown that the maximum reached by the mercuric iodide concentration is within $\sim 5\%$ of that it would reach with $K = \infty$ if K is 400. (Consideration of related equilibrium constants suggests 400 as the most likely value of K .³⁰) The measured optical density would be even closer to that for $K = \infty$ because HgI⁺ also contributes something to the optical density. These results correspond to the experimental observation that the optical density does approach that predicted if half a mole of mercuric iodide and no

(22) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Chap. 3.

(23) All m.p.'s are corrected.

(24) K. H. Slotta and K. R. Jacobi, *J. prakt. Chem.*, **120**, 249 (1929).

(25) C. S. Marvel, C. G. Gauerke and E. L. Hill, *J. Am. Chem. Soc.*, **47**, 3009 (1925).

(26) M. Goret, *Bull. sci. pharmacol.*, **29**, 297 (1922).

(27) R. E. Dessy, private communication.

(28) By Clark Microanalytical Laboratories, Urbana, Ill.

(29) M. M. Kreevoy, *J. Am. Chem. Soc.*, **81**, 1009 (1959).

(30) R. L. Hansen, Ph.D. thesis, University of Minnesota, 1960, p. 23.

other absorbing species are produced from each mole of substrate. It was, therefore, concluded that K is of the order of 10^2 - 10^3 and that the use of eq. 1 to calculate rate constants does not introduce serious difficulties.

Product Spectra.—For all the substrates except isopropylmercuric iodide, the product spectra were essentially those expected if each mole of starting material had produced one-half mole of mercuric iodide. The isopropylmercuric iodide product mixtures seemed to contain some substance absorbing strongly at the shorter wave lengths, although the optical density at 2700 Å. was appropriate. When 2 ml. of product solution was mixed with 1 ml. of 0.4 M sodium iodide, the characteristic spectrum of HgI_4^{--} was

obtained, with a peak of the expected intensity at 3220 Å. An identical spectrum was obtained from 2 ml. of mercuric chloride solution of an appropriate concentration mixed with 1 ml. of 0.4 M sodium iodide. These findings support the stoichiometry originally proposed² and justify the use of eq. 1 to obtain rate constants.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,¹ SOUTHERN RESEARCH INSTITUTE, BIRMINGHAM 5, ALA.]

Synthesis of Potential Anticancer Agents. XXVI. The Alkylation of 6-Chloropurine²

BY JOHN A. MONTGOMERY AND CARROLL TEMPLE, JR.

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A new procedure has been developed for the preparation of 9-alkylpurines by the alkylation of 6-chloropurine with a variety of substituted alkyl halides in dimethyl sulfoxide. A lesser amount of the 7-alkylpurines was obtained. These N-substituted-6-chloropurines were converted to a number of derivatives for anticancer screening.

The anticancer activity of 9-alkyl-6-chloro-9H-purines and 9-alkyl-9H-purine-6(1H)-thiones³ made it desirable to find a shorter route to these compounds. This was particularly true for the synthesis of 8-C¹⁴-labeled purines of this type needed for biological studies, since the original synthesis does not lend itself to the conservation of C¹⁴. An obvious method of accomplishing this purpose is the direct alkylation of 6-chloropurine, especially since 6-chloropyrimidine-8-C¹⁴ has been prepared in this Laboratory.

There are no examples of the alkylation of 6-chloropurine in the literature,^{4,6} although purine itself has been methylated in the 9-position by the use of dimethyl sulfate and diazomethane.¹⁴

(1) Affiliated with the Sloan-Kettering Institute.

(2) This work was presented at the Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., November 4, 1959. It was supported by funds from the C. F. Kettering Foundation and from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(3) H. E. Skipper, J. A. Montgomery, J. R. Thomson and F. M. Schabel, Jr., *Cancer Research*, **19**, 425 (1959).

(4) In a preliminary account of her work on N-methylpurines, Elion mentioned the methylation and conversion of 6-chloropurine to 7-methyl-7H-purine-6(1H)-thione and 9-methyl-9H-purine-6(1H)-thione. No description of the N-alkyl-6-chloropurines is given.⁵

(5) G. B. Elion in G. W. E. Wolstenholme and C. M. O'Connor, eds., "The Chemistry and Biology of Purines," (A Ciba Foundation Symposium), J. and A. Churchill, Ltd., London, 1957, p. 39.

(6) A number of 6-chloropurine nucleosides⁷⁻¹² have been prepared by application of the mercuri procedure¹³ to this purine. The procedure failed with the less reactive iodoethane.

(7) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1959).

(8) H. M. Kissman and M. J. Weiss, *J. Org. Chem.*, **21**, 1053 (1956).

(9) L. Goodman, J. W. Marisco and R. B. Augier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

(10) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, *J. Org. Chem.*, **22**, 954 (1957).

(11) R. E. Schaub, M. J. Weiss and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 4692 (1958).

(12) F. J. McEvoy, B. R. Baker and M. J. Weiss, *ibid.*, **82**, 209 (1960).

(13) J. Davoll and B. A. Lowy, *ibid.*, **73**, 1650 (1951); J. J. Fox, N. Yung, J. Davoll and G. B. Brown, *ibid.*, **78**, 2117 (1956).

(14) H. Bredereck, H. Ulmar and H. Waldmann, *Chem. Ber.*, **89**, 12 (1956).

Other attempted methylation procedures have failed.¹⁵

Although 6-chloropurine could be methylated with iodomethane in dilute aqueous sodium hydroxide, ethylation of purine or 6-chloropurine with iodoethane under the same conditions was not successful. However, when dimethyl sulfoxide and potassium carbonate were used with iodoethane, reaction took place and 6-chloro-9-ethyl-9H-purine (I) was obtained in 50% yield along with a small amount of 6-chloro-7-ethyl-7H-purine (II). The presence of both isomers was detected by paper chromatography, and the identity of the isomers was established by ultraviolet spectroscopy. Although the spectra of the two 6-chloropurines are very similar, they are easily converted to the corresponding 6-dimethylaminopurines (Ia and IIa) whose spectra are quite different (see Table I). This difference in 6-dimethylamino-7- and -9-alkylpurines was originally observed by Baker, Schaub and Joseph¹⁶ in connection with the synthesis of puromycin.

TABLE I
ULTRAVIOLET SPECTRA

Compound	$\text{pH } 1$		$\text{pH } 7$	
	λ_{max} , $m\mu$	$\epsilon \times 10^{-3}$	λ_{max} , $m\mu$	$\epsilon \times 10^{-3}$
6-Dimethylamino-9-ethyl-9H-purine (Ia) ^a	270	17.5	277.5	18.0
6-Dimethylamino-7-ethyl-7H-purine (IIa) ^a	290	19.8	295	17.4
6-Chloro-9-ethyl-9H-purine (I) ^b	265	9.5	266	9.4
6-Chloro-7-ethyl-7H-purine (II)	267	8.0	270	8.1
6-Chloro-7-methyl-7H-purine ^c	268	8.4	271	8.5

^a See Ref. 16. ^b See Ref. 18. ^c R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957).

This synthetic method was first applied to the synthesis of 6-chloro-9-ethyl-9H-purine-8-C¹⁴ from which 9-ethyl-9H-purine-6(1H)-thione-8-C¹⁴ was

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(16) B. R. Baker, R. E. Schaub and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954).