A review of the reactions of azene intermediates has been reported recently by Abramovitch and Davis.[10]

In the previous work the decomposition of 2-azidobenzylideneamines was shown to result in the attack of the azene at the nitrogen atom of the azomethine linkage, whereas, in the present system, the cyclization occurred at the carbon atom. Although the data is certainly incomplete, there is no evidence to indicate that the azene has a substantially greater affinity for either the carbon or the nitrogen atoms of the azomethine linkage in these systems.

Experimental[11,12]

N-(2-Aminophenyl)succinimide.—A solution of 44.0 g. (0.2 mole) of N-(2-nitrophenyl)succinimide[7] in 400 ml. of N,N-dimethylformamide was hydrogenated with 4.0 g. of 10% palladium on charcoal on a Parr shaker for 2 hr. The mixture was filtered free of catalyst and the solvent was removed at reduced pressure. The solid residue was triturated with ethanol yielding 35.0 g. (90%) of N-(2-aminophenyl)succinimide, m.p. 236–238° (lit.[7] m.p. 230–232°).

N-(2-Azidophenyl)succinimide (I).—A solution of 19.0 g. (0.1 mole) of N-(2-aminophenyl)succinimide in 100 ml. of concentrated hydrochloric acid and 500 ml. of water was cooled to −5°. The amine was diazotized by the slow addition of 7.5 g. of sodium nitrite in 50 ml. of water. A solution of 8.0 g. of sodium azide in 50 ml. of water was added to the solution. The precipitate was collected and dried yielding 20.0 g. (93%) of N-(2-azidophenyl)succinimide. An analytical sample was prepared by recrystallization from ethanol yielding white plates, m.p. 142°. An absorption band at 2140 cm.−1 characteristic of the azido[13] group was observed in the infrared.

2-Azidoaniline (II).—A hydrolysis procedure similar to that described for N-(2-azidophenyl)phthalimide was used. A

(10) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).

(11) All melting points are uncorrected.

(12) Analysis were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Mr. S. Hotta of this laboratory.

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 15.

mixture of 5.0 g. of N-(2-azidophenyl)succinimide and 500 ml. of 10% sodium hydroxide solution was stirred at 65° for 2 hr. The mixture was cooled and extracted twice with 200 ml. of methylene chloride. The methylene chloride extract was dried with sodium sulfate and treated with decolorizing charcoal. The methylene chloride was removed at reduced pressure leaving 3.0 g. (97%) of crude 2-azidoaniline. The crude yellow-brown 2-azidoaniline was purified by dissolving repeatedly in a small amount of methanol and reprecipitating by the addition of water. Bright yellow needles melting at 61–63° (lit.[9] m.p. 63–63.5°) were obtained. These crystals darkened on prolonged exposure to the atmosphere and turned dark brown after 12 hr. Slightly lower yields were obtained when 22 g. (0.1 mole) of N-(2-azidophenyl)succinimide was hydrolyzed in the same quantity of base.

An azido[13] absorption band at 2130 cm.−1 was observed in the infrared.

All the benzylidene-2-azidoanilines employed in this study were prepared by condensation of 2-azidoaniline with the appropriate benzaldehyde. The azides prepared in this manner are summarized in Table I. A typical example is given below.

4-Nitrobenzylidene-2-azidoaniline (VI).—To a solution of 2.0 g. of crude 2-azidoaniline in 50 ml. of ethanol, 2.0 g. of 4-nitrobenzaldehyde and a few drops of acetic acid were added. The mixture was heated for a few minutes. Upon cooling 3.5 g. (88%) of golden-colored 4-nitrobenzylidene-2-azidoaniline crystallized. An analytical sample was prepared by recrystallization from ethanol, m.p. 132°.

Thermal decompositions of all the azides were carried out in 1,2-dichlorobenzene under essentially the same conditions. The results are summarized in Table II. Pyrolysis of 4-chlorobenzylidene-2-azidoaniline is described below as a representative example.

2-(4-Chlorophenyl)benzimidazole.—A solution of 2.0 g. of 4-chlorobenzylidene-2-azidoaniline in 100 ml. of 1,2-dichlorobenzene was heated to 140°. The temperature was maintained at 140–145° for 3 hr. The solvent was then removed at reduced pressure. The solid, greenish residue was triturated with a benzene-hexane mixture yielding 1.7 g. (96%) of 2-(4-chlorophenyl)benzimidazole, m.p. 288–294°. An analytical sample was prepared by recrystallization from ethanol, m.p. 296°.

Free-Radical Chemistry of Peptide Bonds. I. Dealkylation of Substituted Amides[1]

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Potassium persulfate in aqueous dipotassium hydrogen phosphate dealkylated N-substituted and N,N-disubstituted amides to amides and N-alkylamides, respectively, in moderate yields. The dealkylated group appeared in the reaction mixture as the corresponding aldehyde or ketone. In addition to dealkylation, formamides were oxidized to carbon dioxide and ammonia. We believe these dealkylations proceed *via* radical attack on the carbon α to the amide nitrogen.

The chemically induced free-radical attack on model systems related to proteins in aqueous solutions has received little attention. Reaction of N,N-dimethylacetamide with peracetic acid in water solution[3] gave N-acetoxymethyl-N-methylacetamide in 13% yield and four hydroxamic acid derivatives. The reaction of simple amino acids with aqueous potassium persul-

fate[4] gave aldehydes containing one less carbon atom than the starting amino acid and quantitative yields of ammonia and carbon dioxide. The action of alkaline persulfate on tryptophan[5] yielded a complex mixture of products including anthranilic acid, 3-hydroxyanthranilic acid, and o-aminophenol.

Potassium persulfate was chosen for study of free-radical attack on model compounds containing the peptide bond, because its mode of decomposition and free-radical attack of other organic compounds[6] is well

(1) Presented before the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964.

(2) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, Albany, Calif.

(3) W. Walter, M. Steffen, and K. Heyns, *Chem. Ber.*, **94**, 2462 (1961).

(4) K. Lang, *Z. Physiol. Chem.*, **241**, 68 (1936).

(5) E. Boyland, P. Sims, and D. C. Williams, *Biochem. J.*, **62**, 546 (1956).

(6) D. A. House, *Chem. Rev.*, **62**, 185 (1962).

established. Dipotassium hydrogen phosphate was used to maintain the pH at 4.9–4.6 during the reaction.

Discussion and Results

The reaction of potassium persulfate with several amides of varying substitution in aqueous dipotassium hydrogen phosphate was investigated in an oxygen-free system.

The products resulting from the reaction of persulfate with several acetamides are listed in Table I. Although acetamide was not attacked by persulfate, all N-

TABLE I
THE REACTION OF PERSULFATE WITH ACETAMIDES[a]

Amide reactant	Amide recovered, %	Aldehyde[b] or ketone	Dealkylated amide
Acetamide	>90	. .	. .
N-Methyl-	56	30	25
N,N-Dimethyl-	None	68	73
N-Ethyl-	41	48	24
N,N-Diethyl-	None	57	39
N,N-Diisopropyl-[c]	None	42	33
N-t-Butyl-	62[d]	. .	. .

[a] At 65–90°. [b] Isolated as the 2,4-dinitrophenylhydrazone. [c] The volume of water in this reaction was doubled to dissolve the amide. [d] Carbon dioxide evolution (4%) and a small quantity of tar were also found.

substituted and N,N-disubstituted acetamides except N-t-butylacetamide were dealkylated to acetamide and N-substituted acetamides, respectively. The alkyl group lost through dealkylation was found in the reaction mixture as the corresponding aldehyde or ketone.

the reaction products found, and little influence on the yields.

It is well established[6] that aqueous solutions of persulfate decompose by first-order kinetics to yield sulfate- and hydroxyl-free radicals. Attack of N-methyl in N,N-dimethylamides by free radicals also has been observed.[3,7–9] This suggests that the dealkylations proceed via radical attack on the carbon α to the amide nitrogen.

The observed exothermicity, high reaction rate, and reaction products are consistent with the following chain process which is analogous to the oxidation of methanol by persulfate.[10,11]

$$S_2O_8^{-2} \longrightarrow 2\ SO_4^-$$

$$SO_4^- + H_2O \longrightarrow HSO_4^- + OH\cdot$$

$$SO_4^- + \underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}-CH_3 \longrightarrow HSO_4^- + \underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}-CH_2\cdot$$

or

$$OH\cdot + \underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}-CH_3 \longrightarrow H_2O + \underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}-CH_2\cdot$$

$$\underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}-CH_2\cdot + S_2O_8^{-2} \longrightarrow \underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}CH_2OSO_3^- + SO_4^-$$

$$\underset{\underset{CH_3}{|}}{R\overset{O}{\overset{\|}{C}}N}-CH_2OSO_3^- \xrightarrow[H^+]{H_2O} R\overset{O}{\overset{\|}{C}}NHCH_3 + H\overset{O}{\overset{\|}{C}}H + HSO_4^-$$

TABLE II
THE REACTION OF PERSULFATE WITH FORMAMIDES[a]

Amide reactant	Amide recovered, %	Formaldehyde[b]	Carbon dioxide[c]	Ammonia[d]	Demethylated amide
Formamide	None	. .	100	61	. .
N-Methyl-	42	14	32	35	[e]
N,N-Dimethyl-	None	40	14	21	40

[a] At 65–90°. [b] Isolated as its 2,4-dinitrophenylhydrazone. [c] Trapped by Ascarite absorbent. [d] Calculated from analysis of reaction mixture for ammonia nitrogen. [e] Formamide formed was further oxidized to carbon dioxide and ammonia.
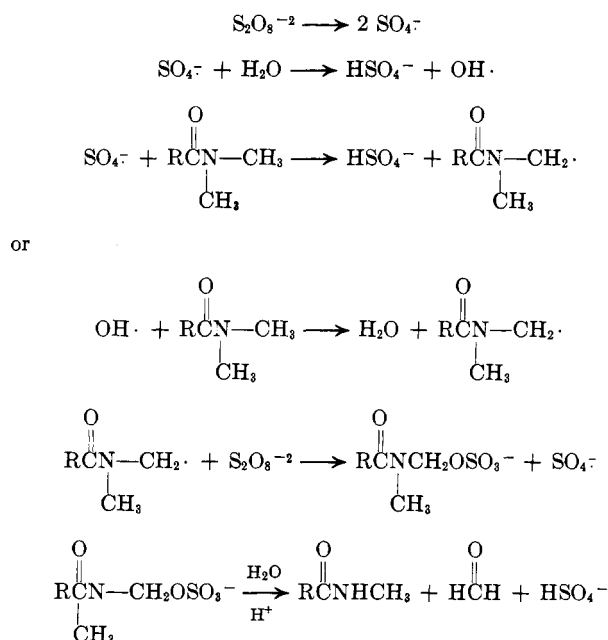
The reaction of persulfate with formamide, N-methylformamide, and N,N-dimethylformamide yield a more complicated mixture of products. The results of these reactions are listed in Table II. Formamide was oxidized to carbon dioxide and ammonia. N-Methylformamide yielded carbon dioxide, ammonia, and formaldehyde as products, whereas N,N-dimethylformamide gave N-methylformamide in addition to the above products. It is thought that any formamide resulting from the demethylation of N-methylformamide is further oxidized by persulfate to carbon dioxide and ammonia.

The products from the reaction of persulfate with the five N,N-dimethylamides studied are found in Table III. In each instance, no starting amide was recovered, and the major products are demethylated amide and formaldehyde. With the exception of N,N-dimethylformamide, the nature of the R-group attached to the amide carbonyl appears to have no influence on

In the formamide series, radicals apparently also attack formyl hydrogen to yield carbon dioxide and

TABLE III
REACTION OF PERSULFATE WITH N,N-DIMETHYLAMIDES[a]

Amide reactant	Formaldehyde[b]	Demethylated amide
N,N-Dimethylformamide[c]	40	40
N,N-Dimethylacetamide	68	73
N,N-Dimethylpropionamide	70	58
N,N-Dimethylbutyramide	47	44
N,N-Dimethylbenzamide	44	37

[a] At 65–90°. [b] Isolated as its 2,4-dinitrophenylhydrazone. [c] Carbon dioxide (14%) and ammonia (21%) were also formed.

(7) C. H. Bamford and E. F. T. White, J. Chem. Soc., 1860 (1959).

(8) C. H. Bamford and E. F. T. White, ibid., 4490 (1960).

(9) K. Schwetlick, Angew. Chem., 72, 208 (1960).

(10) P. D. Bartlett and J. D. Cotman, J. Am. Chem. Soc., 71, 1419 (1949).

(11) We are indebted to the referee for pointing out this analogy.

ammonia. Substitution of methyl groups on the form-amide nitrogen appears to stabilize the formyl hydrogen against radical attack.

Experimental

All melting points are corrected and were taken on a Fisher-Johns apparatus.[12] Infrared spectra were determined using a Perkin-Elmer Infracord 137 spectrophotometer. Analyses for ammonia nitrogen were performed by H. M. Wright of this laboratory.

Reaction of Potassium Persulfate with Amides.—Into a 500-ml. three-necked round-bottom flask equipped with a gas-inlet tube, reflux condenser, thermometer, and magnetic stirring bar was placed 0.1 mole of amide, 27.0 g. (0.1 mole) of potassium persulfate, 34.8 g. (0.2 mole) of dipotassium hydrogen phosphate, and 250 ml. of distilled water. In experiments using N,N-diisopropylacetamide, 500 ml. of water was used. The reflux condenser was fitted with a gas-outlet tube leading to a calcium chloride drying tube followed by two tubes containing Ascarite sodium hydrate asbestos absorbent. Nitrogen was bubbled through the solution for 1 hr., and the reaction system was swept with a stream of nitrogen throughout the course of the reaction. On heating to 65° with stirring, a rapid exothermic

reaction took place, raising the temperature to 85–90° at which the reaction mixture was maintained for 30 min. The water was removed from the reaction mixture by distillation.

In experiments where an aldehyde or ketone was a product, the water distillate was treated with 2,4-dinitrophenylhydrazine dissolved in dilute sulfuric acid. The resulting 2,4-dinitrophenyl-hydrazone was removed by filtration and recrystallized from 95% ethanol. In each case, the purified 2,4-dinitrophenylhydrazone's melting point and infrared spectrum were compared with those of an authentic sample.

The residue in the reaction flask was extracted with several small portions of hot 95% ethanol. The ethanol was distilled to yield an oil. Distillation of this oil at 20 mm. yielded any demethylated amide and/or unreacted amide present. Each amide was characterized by comparing its boiling point and infrared spectrum with those of an authentic sample of amide. In the case of N-t-butylacetamide, recovery was made by sublimation.

The carbon dioxide evolved during the reaction was determined by the weight uptake of Ascarite absorbent. The yield of ammonia was determined by analyzing the crude reaction mixture for ammonia nitrogen.

Each dealkylation was performed two or more times, and the yields of products were found reproducible within a few per cent. In control experiments, recoveries of known quantities of amides and aldehydes were 70% or greater by the methods of isolation used in these dealkylations. The product yields based on starting material for the dealkylations are listed in Tables I, II, and III.

(12) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

Dissociation Constants of the Cyanohydrins of Alkylcyclohexanones

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The dissociation constants of the cyanohydrins of a series of 2-, 3-, and 4-alkylcyclohexanones and 2,6-dialkyl-cyclohexanones show the effect of interactions with the cyanohydrin for groups larger than methyl in the α-position. The effect is smaller in the β- and absent in the γ-position.

The possible interaction between an equatorial α-alkyl group and the oxygen atom of the carbonyl group in cyclohexanone has been termed the 2-alkyl ketone effect. The suggestion[2] that an equatorial methyl group in the 2-position interacting with the carbonyl group destabilizes the alkyl group by 1.0 kcal./mole with respect to the axial conformation has not been confirmed by recent studies.[3] Larger groups, such as ethyl and isopropyl, apparently show such an effect.[3] However, a 2-t-butyl group distorts the ring into a twist-chair conformation,[3,4] and recent data[5] suggest that even a 2-methyl group may produce some twisting of the ring. The origin of the increased reactivity of cyclohexanone over acyclic ketones has recently been attributed[6] to the stabilization by α-axial carbon–hydrogen bonds, relative to carbon–carbon bonds. The amount of stabilization is estimated as 1 kcal./mole and this stabilization is lost on methyl substitution. A 3-

alkyl ketone effect has also been postulated,[2,7] arising from the fact that in cyclohexanone there are only two axial substituents on one side of the molecule and an alkyl substituent can be accommodated on one of these positions without greatly increasing the nonbonded interactions.

In a previous study[8] 3- and 4-methylcyclohexanone were found to have slightly smaller dissociation constants than cyclohexanone (see Table I); this was interpreted as being due to equatorial interference between the methyl group and the neighboring equatorial hydrogen atoms. The higher alkylcyclohexanones studied in the present work all had larger K_D-values than cyclohexanone itself (see Table I).

For the 2-alkyl compounds, an ethyl group had a slightly larger effect than methyl, and this increased greatly for isopropyl and t-butyl. However, increasing the number of methylene groups in an unbranched chain, as in n-propyl and n-butyl, resulted in little increase in the dissociation constants. Two α-methyl (2,6-dimethyl) groups had little effect, although two α-isopropyl groups lead to a large increase in K_D. The data for 3-alkyl substitution showed a slight increase in dissociation constant with increasing size of the sub-

(1) Operated by the University of Puerto Rico under Contract No. At-(40-1)-1833 for the Atomic Energy Commission.

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(3) (a) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, 83, 994 (1961); (b) B. Rickborn, *ibid.*, 84, 2414 (1962); (c) C. Djerassi, P. A. Hart, and C. Beard, *ibid.*, 86, 85 (1964).

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