[CONTRIBUTION FROM THE ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

The Preparation and Properties of Oxaziranes

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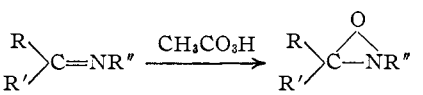
The preparation of a wide variety of oxaziranes by oxidation of the appropriate imine with peracetic acid is discussed. These compounds represent a previously unknown heterocycle, a carbon–nitrogen–oxygen three-membered ring. The evidence for assignment of this structure is reviewed, and a general survey is made of some of the reactions characteristic of oxaziranes. Depending upon the particular structure involved, acid hydrolysis of oxaziranes may give either aldehydes and β-alkylhydroxylamines (possibly *via* the nitrones) or else aldehydes, ketones and primary amines. The latter reaction involves structural rearrangement of the 2-substituent in some cases. The treatment of oxaziranes with ferrous salts causes a one-electron transfer reaction and results in either reductive dealkylation or else isomerizations *via* free radical chain reactions. Again depending upon the structure, the observed products may be either an isomeric amide, a dealkylated amide plus hydrocarbons or else a mixture of aldehyde, ketone and ammonia. Upon pyrolysis, oxaziranes may give the isomeric nitrones, the isomeric amides (often with structural rearrangement) or else products derived from a mixture of aldehydes, ketones and ammonia.

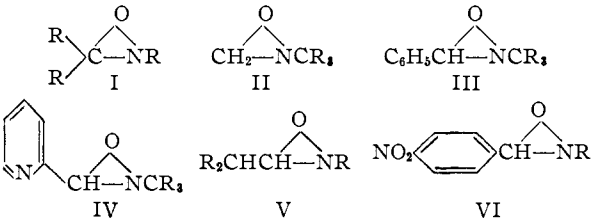
The existence of a three-membered carbon–nitrogen–oxygen ring has frequently been postulated in the older literature largely as a means of solving certain structural problems. A notable example where this hypothesis has been involved is in the case of the nitrones. In the last few decades, however, with the advent of modern structural theory as well as a considerable amount of experimental work concerning these compounds, the oxazirane structure has been discarded entirely. Indeed no compounds having a well-authenticated oxazirane structure appear to have been described in the literature.

In connection with our investigation of the reactions of organic peracids, it was observed that these reagents react smoothly with a wide variety of imines to give compounds whose structures have been unequivocally established as oxaziranes, and a preliminary report of this work has been published.[2] These compounds are in some respects comparable to organic peroxides and indeed they may be assayed by iodometric procedures. They are extremely reactive materials, and their chemistry is in many respects quite unusual.

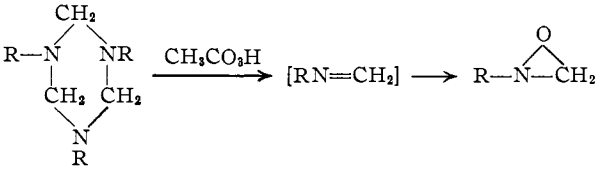


The Preparation of Oxaziranes.—For laboratory purposes the oxaziranes were most conveniently synthesized by addition at 10–20° of an essentially anhydrous solution of peracetic acid in methylene chloride to the imine dissolved in the same solvent. The peracetic acid normally was prepared at ice-bath temperatures by reaction of acetic anhydride with 90% hydrogen peroxide in the presence of a catalytic amount of sulfuric acid. The reagent was then diluted with methylene chloride and allowed to react with the azomethine under appropriate experimental conditions. Yields of the oxaziranes generally were of the order of 50–80%, depending on the properties and stability of the particular compound obtained. The oxaziranes were in most cases distillable liquids boiling slightly above the imine from which they were derived. In general, they were sufficiently stable for distillation in a spinning band column under reduced pressure, provided pot temperatures were not allowed above 100°.

As mentioned previously, it was possible to convert a wide variety of imines to their oxaziranes. Indeed the oxazirane synthesis is a remarkably general reaction limited largely by the stability of the parent imine under acidic conditions and the stability of the oxazirane obtained. Typical examples of easily prepared oxaziranes are trialkyloxaziranes (I), 2-*t*-alkyloxaziranes (II), 2-*t*-alkyl-3-phenyloxaziranes (III), 2-*t*-alkyl-3-(2-pyridyl)-oxaziranes (IV), 2-alkyl-3-(dialkylcarbinyl)-oxaziranes (V), 2-alkyl-3-*p*-nitrophenyloxaziranes (VI), 2-alkyloxaziranes and 2-alkenyl-3,3-dialkyloxaziranes.[3] In all of the cases cited here the parent imines are also readily available.



It is interesting to note that the conversion of imines to oxaziranes is a reasonably selective oxidation and may be carried out in the presence of functional groups which normally react with peracids. Also 1,3,5-trialkylperhydro-*s*-triazines obtained from condensation of formaldehyde and primary amines can be oxidized to oxaziranes. Under these conditions the acidic reagent apparently depolymerizes the triazine to the imine which is then converted to the oxazirane.



The oxidation of the bifunctional imine derived from glyoxal and *t*-butylamine was also of some

(1) Rohm and Haas Co., Research Laboratories, 5000 Richmond Street, Philadelphia 37, Pa.

(2) W. D. Emmons, THIS JOURNAL, **78**, 6208 (1956). A recent report also has appeared in the patent literature which describes the reaction of peracids with imines: H. Krimm, K. Hamann and K. Bauer, U. S. Patent 2,784,182, March 5, 1957.

(3) The numbering of the oxazirane ring is 

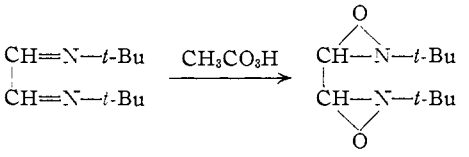
TABLE I

PROPERTIES OF OXAZIRANES, RR'C(O)NR''

R	R'	R''	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	B.p. °C.	B.p. Mm.	Active oxygen, %	$n^{20}D$
H	H	*t*-Bu	59.37	59.70	10.97	11.30	13.85	13.82	46	52–54	75	93.8	1.4150
H	H	*t*-Oct	68.74	68.70	12.18	11.58	8.90	9.65	69	70–72	6	99.2	1.4445
C_6H_5	H	*t*-Bu	74.54	75.01	8.53	8.58	7.90	7.78	71	61–63	0.3	95.6	1.5081
C_6H_5	H	*t*-Oct	77.21	77.00	9.93	10.16	6.00	6.16	67[a]				1.5019
p-$O_2NC_6H_4$	H	*i*-Pr	57.68	57.91	5.81	6.26	13.46	13.06	60[b]	46–48	(m.p.)	92.0	
p-$O_2NC_6H_4$	H	Et	55.66	55.69	5.19	5.31	14.43	13.59	97[b]	34–35	(m.p.)	99.3	
p-$O_2NC_6H_4$	H	*t*-Bu	59.44	59.53	6.35	6.60	12.60	13.08	78[b]	65–66	(m.p.)	99.4	
i-Pr	H	*t*-Bu	67.09	67.35	11.97	12.16	9.78	9.20	71	68–70	39	99.8	1.4152
i-Pr	H	*n*-Bu	67.09	67.20	11.97	12.15	9.78	9.69	65	65–67	10	91.5	1.4178
n-BuCH(Et)	H	*n*-Bu	72.30	72.45	12.64	12.64	7.03	6.70	83[c]			98.7	1.4350
i-Pr	H	$C_6H_5CH(CH_3)$	75.35	74.92	8.96	8.80	7.32	7.16	80[d]			99.7	1.4956
i-Bu	Me	*n*-Pr	68.74	68.29	12.18	12.40	9.87	9.42	73	61	8	93.6	1.4267
p-$O_2NC_6H_4$	H	*t*-Oct	64.72	64.70	7.97	7.86	10.07	9.96	66[b]	54–56	(m.p.)	96.9	
Me	*i*-Pr	*n*-Pr	67.09	66.79	11.97	11.97	9.78	8.95	64	60	15	94.7	1.4222
n-Bu	H	H	59.37	59.58	10.96	11.09	13.84	13.10	74[f]	43	20	98.1	1.4178
i-Pr	H	*t*-Oct	72.31	71.59	12.64	12.50	7.02	7.12	78[a]			99.6	1.4385
Me	Et	Allyl	66.11	66.13	10.30	10.60	11.00	10.92	49	51	6	91.2	1.4413
Et	Et	Et	65.07	65.19	11.70	11.30	10.84	10.84	56	62	19	97.7	1.4225
Me	Me	*n*-Hex	68.74	68.44	12.18	12.10	8.90	8.52	14	58	3	94.7	1.4278
i-Pr	H	*i*-Bu	67.08	66.89	11.97	11.94	9.78	9.27	50	53	12	92.0	1.4150
Et	Et	$C_6H_5CH(CH_3)$	76.06	75.80	9.33	9.39	6.82	6.61	91[g]			90.1	1.5038
α-Pyridyl	H	*t*-Bu	67.83	67.48	7.92	8.04	15.72	14.93	75	68–70	0.4	96.1	1.5010

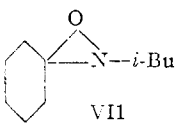
[a] The yield refers to crude product. The analytical sample was purified by flash distillation at a pot temperature of 165° and a pressure of 0.01 mm. [b] Recrystallized at low temperature from petroleum ether. [c] The yield refers to crude product which was sufficiently pure for most purposes. The analytical sample was chromatographed over silica gel with methylene chloride. [d] Flash distilled at a pot temperature of 165° (0.01 mm.). [f] Yield of crude product. [g] Yield and analytical data were obtained on the crude product.

interest in that two crystalline isomeric oxaziranes (presumably *meso*- and *dl*-forms) were obtained and separated by chromatography. The infrared



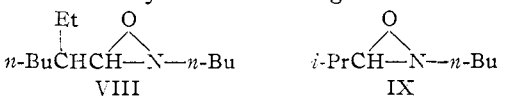
spectra of these two isomers were identical except in the fingerprint region, and they both had the typical properties of oxaziranes. A summary of the oxaziranes prepared along with their physical constants and analytical data may be found in Table I. Each oxazirane prepared was an active oxygen compound and was assayed by an iodometric procedure with potassium iodide in aqueous acetic acid.

The stability of the oxazirane ring is markedly influenced by its substituent groups. Thus without exception all of the 2-*t*-alkyloxaziranes prepared were stable compounds. They were readily distilled and could be kept for several months at laboratory temperatures without detectable decomposition. In similar fashion all of the trialkyloxaziranes with the exception of 2-isobutyl-3,3-pentamethyleneoxazirane (VII) were also stable compounds. The latter material was relatively unstable, however, and while it could be distilled



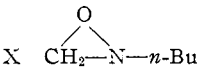
VII

without any significant decomposition, its active oxygen titer dropped from 97 to 32% after standing one month at room temperature. 2,3-Dialkyloxaziranes were also rather unstable. Thus, the active oxygen assay of VIII dropped from 96 to 54% in two weeks at room temperature. In similar fashion IX dropped from 95 to 2% in the iodometric assay after standing two months at



VIII IX

room temperature. Finally the least stable compound prepared was 2-*n*-butyloxazirane (X) which after three days had dropped in purity to 63% and

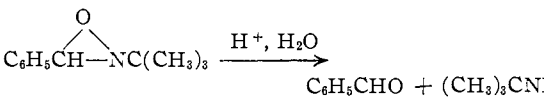


after eight days had decomposed completely. Some oxaziranes appear to be too unstable to be isolated by conventional techniques. Thus, efforts to prepare 2-phenyl- and 2-benzyloxaziranes were unsuccessful in that a very unstable product was obtained. 3-Phenyloxaziranes other than those with a 2-*t*-alkyl substituent also could not be obtained, possibly because of the extreme sensitivity to acid-catalyzed hydrolysis of the imine[4] or possibly because of the facile decomposition of the oxazirane after it was formed. Indications are that in this reaction some oxazirane is produced, but it was not possible to separate it from the major contaminant, benzaldehyde.

(4) Peracetic acid prepared from 90% hydrogen peroxide and acetic anhydride contains a small amount of water.

Proof of Structure of the Oxazirane Ring.—The proof of structure of the oxaziranes is based on the following facts: (1) analytical data, (2) their quantitative hydrolysis in some cases to aldehydes and β-alkylhydroxylamines, (3) a comparison of their physical and chemical properties with those of the isomeric nitrones where applicable, (4) their thermal isomerization to the isomeric nitrones under anhydrous conditions and finally (5) the partial resolution of 2-*n*-propyl-3-methyl-3-isobutyloxazirane. In addition most of their chemical reactions are readily interpreted by the oxazirane structure.

A major portion of the structural work was done with 2-*t*-butyl-3-phenyloxazirane since its hydrolysis and reduction products could be conveniently characterized. Treatment of this compound with aqueous methanolic sulfuric acid[5] gave a 93% yield of benzaldehyde and an 82% yield of β-*t*-butylhydroxylamine. Similarly, 2-*t*-octyl-3-phenyloxazirane gave β-*t*-octylhydroxylamine in 86% yield and benzaldehyde in 91% yield. The availability of these hydroxylamines permitted the synthesis of the two isomeric nitrones in good yield by condensation with benzaldehyde.



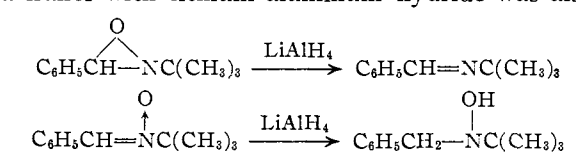
$$C_6H_5CHO + RNHOH \longrightarrow C_6H_5CH{=}\overset{\uparrow O}{N}R$$

XI, R = *t*-Bu; XII, R = *t*-Oct

These nitrones were both solids, were not active oxygen compounds and had very different physical and chemical properties from the isomeric oxaziranes. Unlike the oxaziranes, they formed salts in aqueous acid. In common with the oxaziranes, however, they readily were hydrolyzed back to benzaldehyde and the *t*-alkylhydroxylamine by aqueous sulfuric acid. Altogether six nitrones were prepared, and in every case the marked difference in properties between the nitrones and the isomeric oxaziranes was observed.

One of the most striking differences in these two isomeric classes of compounds was found in the ultraviolet spectra. Table II illustrates these differences for three pairs of the isomeric compounds. A considerable amount of data has been published on the electronic spectra of nitrones[6] but none have been reported on the N-*t*-alkylbenzaldoximes of interest here. The highly conjugated nitrones show, of course, extensive absorption in the ultraviolet whereas the oxazirane ring, as anticipated on the basis of its structure, does not appear to have any characteristic absorption.

The behavior of the isomeric nitrones and oxaziranes with lithium aluminum hydride was also

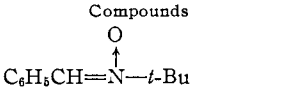
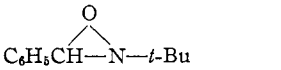
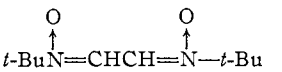
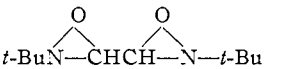
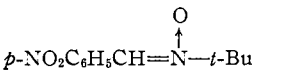
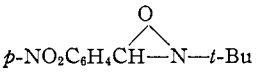


(5) Hydrochloric acid cannot be used in this hydrolysis since oxaziranes under acidic conditions oxidize chloride ion to chlorine.

(6) M. J. Kamlet, *J. Org. Chem.*, **22**, 576 (1957).

TABLE II

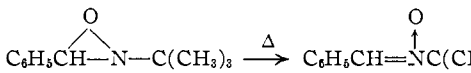
ULTRAVIOLET SPECTRA OF ISOMERIC NITRONES AND OXAZIRANES[a]

Compounds	λ_{max}, mμ	ϵ_{max}
	295	16,700
	249	930
	336	20,800
	None	
	252; 362	11,400; 15,800
	268	11,900

[a] All spectra were determined in ethanol except that the *p*-nitrophenyl compounds were run in acetonitrile.

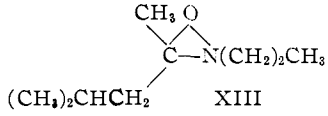
illuminating. Reduction of 2-*t*-butyl-3-phenyloxazirane in ether gave a 91% yield of N-benzylidene-*t*-butylamine. The corresponding nitrone, however, gave under comparable conditions a 77% yield of N-benzyl-N-*t*-butylhydroxylamine. The latter amounts to a 1,3-reduction of the nitrone system and appears to be a general reaction of nitrones.[7] In similar fashion 2-*t*-octyl-3-phenyloxazirane and its isomeric nitrone were reduced to give, respectively, a 77% yield of N-benzylidene-*t*-octylamine and a 41% yield of N-benzyl-N-*t*-octylhydroxylamine. In contrast to the above results the reduction of 2-*t*-octyloxazirane yielded only N-methyl-*t*-octylamine (73%). The fact that the latter reduction does not stop at the imine stage may be explained readily by either steric or electronic factors and is indeed not surprising. The reduction does, however, clearly establish the carbon skeleton of the oxazirane under consideration. The reaction between 2-*t*-butyl-3-phenyloxazirane and potassium iodide in aqueous acetic acid was also examined on a preparative scale and here, too, the only product obtained was N-benzylidene-*t*-butylamine (75% yield). The isomeric nitrone under comparable conditions showed no reaction other than some hydrolysis.

Additional insight into the relationship between isomeric nitrones and oxaziranes was provided by the thermal conversion of an oxazirane into the nitrone. Thus 2-*t*-butyl-3-phenyloxazirane when heated under reflux in acetonitrile for three days was converted quantitatively into the nitrone. Indeed it is interesting to note that a nitrone may properly be regarded as an "electronic tautomer" of its isomeric oxazirane and this facile isomerization is not surprising.



(7) O. Exner, *Collection Czechoslov. Chem. Communs.*, **20**, 202 (1955).

One of the more salient points concerning the oxazirane ring is that it has an asymmetric carbon atom. In fact it is interesting to note that one of the major reasons that the oxazirane three-membered ring structure was discarded for nitrones was the failure to resolve these compounds. Accordingly a major effort was undertaken to resolve an oxazirane. The initial work was done with 2-*t*-butyl-3-phenyloxazirane. An excess of this compound when boiled in methylene chloride with brucine converted the alkaloid to its insoluble N-oxide in essentially quantitative yield. The oxazirane was, of course, reduced to N-benzylidene-*t*-butylamine, and in principle this reaction seemed an ideal one to effect a partial resolution of the oxazirane. Unfortunately, however, all efforts to resolve the oxazirane by this method were unsuccessful. The same reaction, however, was applied to 2-*n*-propyl-3-methyl-3-isobutyloxazirane (XIII), and partial resolution ($\alpha^{22}D$ $-3.94°$) of the recovered oxazirane was obtained. The successful resolution of the latter compound may well be dependent on its greater steric requirements around the oxazirane ring.



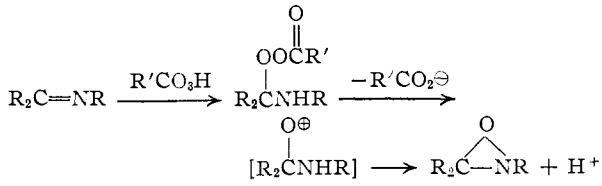
XIII

In any event the resolution of this compound together with the evidence previously presented establishes the oxazirane structure for these materials beyond any reasonable doubt.

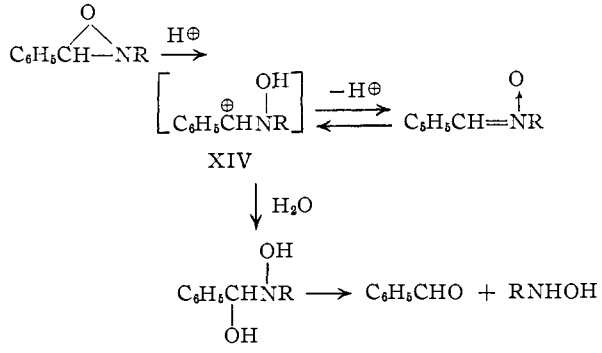
Nuclear magnetic resonance spectra were also obtained from 2-*t*-butyl-3-phenyloxazirane and 2-*t*-butyloxazirane. The former compound had three absorption peaks with chemical shifts, $(H_{H_2O} - H_0)/H_{H_2O}$, equal to $+0.28$ (phenyl protons), -0.01 (oxazirane proton) and -0.40 (*t*-butyl protons). In the latter compound the oxazirane protons were found at -0.09 and the *t*-butyl protons at -0.38 unit. The oxazirane ring proton absorption was also split into two peaks under high resolution as might be expected for two slightly different protons (*cis* and *trans* to the alkyl group on a near tetrahedral nitrogen atom). This is in accord with the oxazirane structure and suggests that inversion of the N-alkyl group does not take place rapidly at room temperature in this compound.

It is also of some interest to speculate briefly concerning the nature of the oxidation of imines to oxaziranes. It is quite possible that this reaction is analogous to the epoxidation of olefins with peracids and involves a similar cyclic transition state.[8] An equally attractive if less obvious possibility is that the imine reaction proceeds through addition of the peracid to the azomethine followed by heterolysis of the O–O bond. This would result in the formation of an electron-deficient oxygen atom which could be stabilized by ring closure to form the oxazirane ring with subsequent loss of a proton. This formulation of the reaction is, of course, somewhat similar to the Baeyer–Villiger oxidation of ketones to esters by peracids.

The Reactions of Oxaziranes with Acidic Reagents.—The reaction of the 2-*t*-alkyl-3-phenyloxaziranes with aqueous acid already has been described in the preceding section. This reaction is of some importance from a practical point of view since it makes β-*t*-alkylhydroxylamines readily



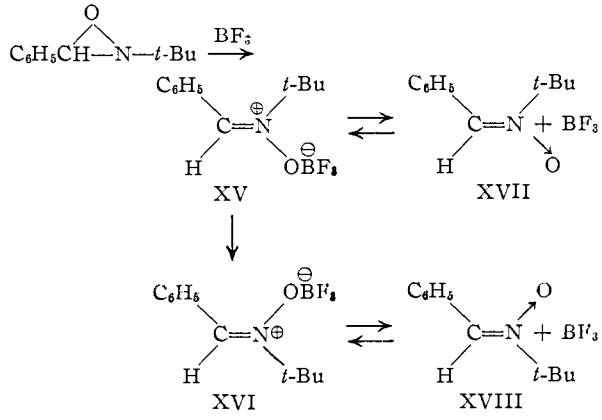
available, and these compounds are of some value as synthetic intermediates. It is also of interest to speculate concerning the mechanism of this hydrolysis. It is most probable that to some extent the nitrone is involved as an intermediate in this reaction.



XIV

Thus the unstable intermediate XIV may be partitioned and by loss of a proton may be converted to the nitrone or by reaction with water go to benzaldehyde and the hydroxylamine. The nitrone itself, is, of course, also hydrolyzed rapidly under these conditions to give the same products. In support of this hypothesis it was observed that when 2-*t*-butyl-3-phenyloxazirane was treated with an equivalent of methanesulfonic acid, a very hygroscopic salt crystallized out. This salt was not characterized, but it did not contain active oxygen and, since it gave nitrone, *t*-butylhydroxylamine and benzaldehyde when added to water, it was concluded that it was the methanesulfonic acid salt of the nitrone.

The behavior of 2-*t*-butyl-3-phenyloxazirane with boron fluoride etherate in benzene solution was even more illuminating, however. When equivalent amounts of these two materials were allowed



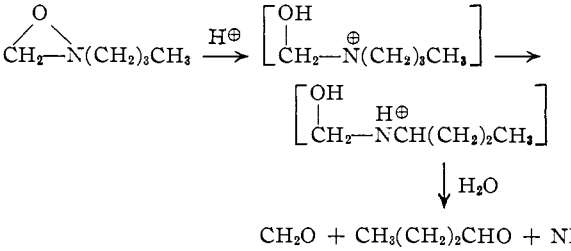
XV XVII XVI XVIII

(8) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).

to react, a crystalline salt slowly separated which did not contain active oxygen. This salt could be recrystallized from methylene chloride at low temperature and melted at 65–68°. It was difficult to obtain a reproducible melting point, however. The analysis of this compound was in agreement with that calculated for the boron fluoride salt of the nitrone XV. However, it was observed that this material on recrystallization from dry ethyl acetate was converted in high yield to another salt, m.p. 135–137°, having the same analysis and which proved to be identical with the product obtained by treatment of N-*t*-butylbenzaldoxime with boron fluoride in ether solution. The infrared spectra of these two salts were quite different in the fingerprint region, although otherwise they were very similar. Since the unstable isomer was not an active oxygen compound, the assumption was made that it was not a salt of the oxazirane. In agreement with this is the observation that the salt was not precipitated immediately from the benzene solution in which it was formed. Accordingly it was assumed that the two salts were derived from *cis* and *trans* isomers of N-*t*-butylbenzaldoxime (XVII and XVIII, respectively). In order to confirm this hypothesis, the ultraviolet spectra of these two compounds in methylene chloride were examined. When XVI was dissolved in methylene chloride at concentrations around 10^{-5} *M* a spectrum identical to that of N-*t*-butylbenzaldoxime in the same solvent was observed, λ_{max} 300 mμ, ϵ_{max} 19,300. At these low concentrations the salt was apparently completely dissociated, and the spectrum observed is that of the parent nitrone XVIII. Similarly the unstable salt showed absorption at 294 mμ, ϵ_{max} 8600. After standing 24 hr., however, the unstable salt had completely isomerized and its spectrum was identical to that of the stable isomer. The spectrum of the unstable salt observed under these conditions is almost certainly also that of the parent nitrone (presumably *cis*, XVII). In order to obtain additional evidence on this point, the spectra of the two salts were determined again in methylene chloride 10^{-2} *M* in boron fluoride etherate. Under these conditions the stable salt showed a peak at 280 mμ, ϵ 28,000, and the unstable salt at peak at 280 mμ, ϵ 10,300. Again the spectrum of the unstable salt was time dependent and after 24 hr. at room temperature was identical with that of the stable isomer. These spectra are almost certainly those of the undissociated nitrone–boron fluoride complexes XV and XVI. Accordingly the most reasonable explanation of these observations is that the two boron fluoride salts are derived from *cis*- and *trans*-nitrone isomers. Efforts to regenerate the parent nitrones from the boron fluoride salts were not very successful, chiefly because of the competing hydrolysis reaction. The unstable nitrone (presumably *cis*) also may well be a liquid but in any event it was not possible to obtain a pure product which could be characterized from its boron fluoride salt. It is interesting to note in this connection that the separation of *cis* and *trans* isomers of the N-ethers of aldoximes has never been accomplished with any degree of certainty. The formation of the unstable nitrone isomer from the oxazirane as the only product is not surprising since oxaziranes are very high energy species and the transition state for this reaction is almost certainly very close in its geometry to the oxazirane itself.[9]

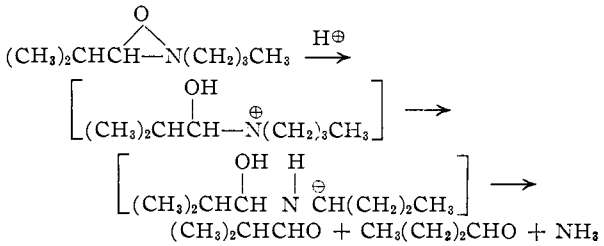
The reactions of 2-*t*-octyloxazirane with aqueous methanolic sulfuric acid and with boron fluoride etherate in benzene also were examined. In the former case the only identifiable product was *t*-nitroöctane obtained in 7% yield. In the latter case a viscous oil separated from the benzene solution and this oil, after being dissolved in water, gave again trace amounts of *t*-nitroöctane. Both of these experiments obviously involved complex reactions. Furthermore, efforts to obtain identifiable products from dialkyl- and trialkyloxaziranes after reaction with aqueous methanolic sulfuric acid were unsuccessful. The reasons for this appear to be dependent on the fact that aldehydes and ketones are the major product of these hydrolytic reactions and, once formed, these products undergo a variety of condensation reactions leading to intractable products.

In order to simplify this problem, it was decided to conduct the acid-catalyzed hydrolysis of oxaziranes in the presence of 2,4-dinitrophenylhydrazine in an effort to trap any carbonyl compounds as rapidly as they were formed. This proved to be very successful and it was possible to gain considerable insight into the acid hydrolysis of the oxaziranes. A freshly prepared sample of 2-*n*-butyloxazirane when treated in this manner gave essentially quantitative yields of 2,4-dinitrophenylhydrazones of formaldehyde and *n*-butyraldehyde. These products were separated and identified by paper chromatography. In addition, there was obtained a 79% yield of ammonia which was identified and isolated as N-phenylthiourea. The precise nature of this acidic hydrolysis is uncertain. However, a reasonable mechanism involving the formation of an electron deficient nitrogen atom may be considered and explains the products in a satisfactory fashion. In a similar manner 2-*n*-butyl-3-isopropyloxazirane gave a 67% yield of ammonia and a quantitative yield of the 2,4-dinitrophenylhydra-

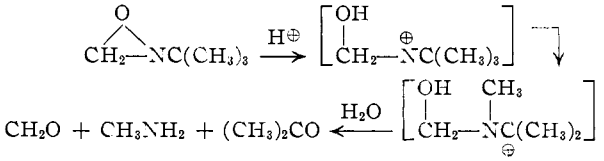


zones of isobutyraldehyde and *n*-butyraldehyde. Unfortunately, however, the characterization of this 2,4-dinitrophenylhydrazone mixture by paper chromatography was not too satisfactory since the separation of the two products was not very good. However, the paper chromatogram of an equimolar synthetic mixture of the 2,4-DNPH's of isobutyraldehyde and *n*-butyraldehyde was identical to that obtained from the experiment so the composition of the mixture is reasonably certain.

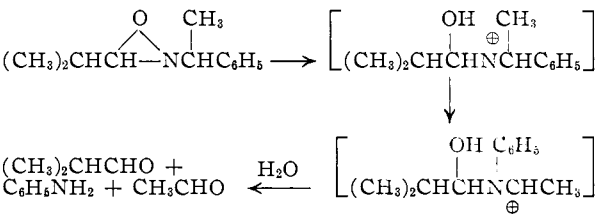
(9) G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).



The investigation of 2-*t*-butyloxazirane in this reaction was next undertaken, and it was found that the reaction took a very similar course with methyl migrating to nitrogen in this case. A mixture of the 2,4-dinitrophenylhydrazones of acetone and

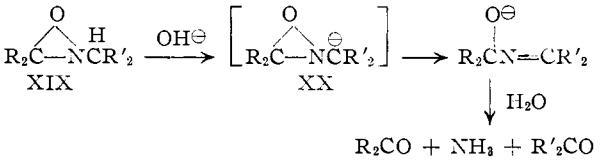


formaldehyde was obtained in quantitative yield and identified by paper chromatography. In this case the acetone 2,4-DNPH was also isolated by column chromatography using alumina with benzene as eluant. Methylamine was obtained in 67% yield and was characterized as its thiourea. Finally the behavior of 2-(α-phenylethyl)-3-isopropyloxazirane in this reaction was examined. Here the products obtained in quantitative yield were the 2,4-DNPH's of acetaldehyde and isobutyraldehyde. These products were separated by column chromatography using benzene and alumina, and the mixture was also characterized by paper chromatography. The other product obtained in 86% yield was aniline so the phenyl radical was the only detectable group which migrated.



On the basis of the four compounds examined in this reaction the migratory aptitudes to nitrogen would appear to be in the following order: C_6H_5 > H > alkyl. It is also interesting to note that there is a striking difference in the acidic hydrolysis of the 3-phenyloxaziranes and the 3-alkyloxaziranes. In the former case the ring opens in a different manner presumably due to the relatively stable carbonium ion, XIV, which can be formed. In the latter case an electron-deficient nitrogen atom is formed which can fill its octet by migration of one of the available groups. The precise nature of the latter reaction, *i.e.*, whether it is concerted, etc., is of course unknown, but the experimental observations are readily explained by the mechanism proposed above.

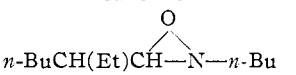
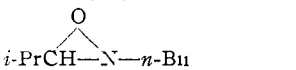
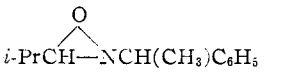
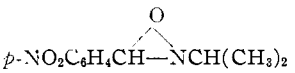
The Reaction of Basic Reagents with Oxaziranes.—The oxazirane ring itself does not appear to be very reactive toward basic reagents. Thus 2-*t*-butyl-3-phenyloxazirane did not react with sodium methoxide in methanol after 12 hr. at room temperature. In similar fashion 2-*t*-octyl-3-isopropyloxazirane did not react with either solid potassium hydroxide or with potassium hydroxide in methanol at room temperature. In contrast to those observations, however, oxaziranes with a 2-methylene or 2-methinyl substituent such as XIX



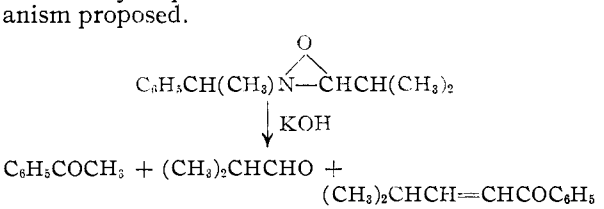
react vigorously with aqueous alcoholic alkali solutions giving ammonia as a major product. Indeed this reaction is suitable as an analytical procedure for assay of the oxazirane, since the yield of ammonia is in most cases quantitative. The results of this assay in the four cases examined are summarized in Table III. Only in the case of the *p*-nitrophenyloxazirane was the reaction not quantitative. This reaction presumably involves the abstraction of a proton forming a carbanion XX which is then degraded to carbonyl compounds as indicated above. Actually this step is probably a concerted termolecular reaction involving both an acid and a base, but in the absence of detailed information further speculation concerning its mechanism is pointless.

TABLE III

AMMONIA ASSAYS OF OXAZIRANES

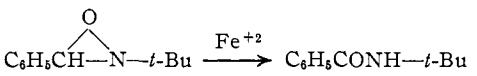
Oxaziranes	Purity by ammonia assay, %
	96
	93
	92
	59

The imine which is formed is then rapidly hydrolyzed to the parent carbonyl compound and ammonia. The aldehydes and ketones formed in this reaction are subject to secondary condensation reactions, and so the isolation of products proved very difficult. However, the reaction of potassium hydroxide in moist ethylene glycol with 2-(α-phenylethyl)-3-isopropyloxazirane gave a 57% yield of isobutyraldehyde, a 9% yield of isobutylideneacetophenone and a 25% yield of acetophenone. While the material balance of this experiment was not very satisfactory, all of the products are readily explicable on the basis of the mechanism proposed.

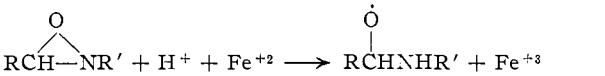


The Reactions of Oxaziranes with Ferrous Ions.—In common with the organic peroxides,

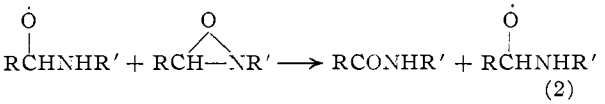
oxaziranes show some rather interesting one-electron transfer reactions with ferrous ion. 2-*t*-Butyl-3-phenyloxazirane when treated with an equivalent amount of ferrous ammonium sulfate in water at room temperature rapidly was converted to N-*t*-butylbenzamide in 98% yield. When the reaction was repeated with ten mole per cent. of ferrous ion, the amide was isolated in 68% yield



and the remaining material was accounted for as recovered oxazirane. When 2-*t*-octyloxazirane was allowed to react with ten mole per cent. of aqueous ferrous ammonium sulfate, there was obtained an 87% yield of N-*t*-octylformamide. These products may be accounted for readily on the basis of the following chain reactions where (1) represents initiation and (2) propagation. Alternative mechanisms can also be considered, but the one described



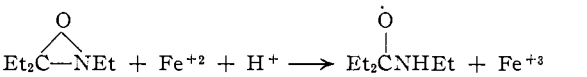
(1)



(2)

above would appear to be the least complex and in the absence of more detailed information appears quite reasonable.[10]

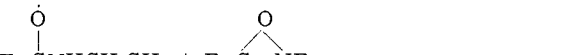
The reaction of triethyloxazirane with ferrous ion was somewhat more complex. This material when treated with twenty mole per cent. of aqueous ferrous ammonium sulfate gave diethyl ketone (50%), N-ethylpropionamide (32%), ammonia (55%) and a mixture of gases. Examination of the gases by infrared and mass spectroscopic techniques indicated that the major components were butane, ethane and ethylene. The ethane–ethylene ratio was approximately 3:1. Again these products are accounted for readily on the basis of the following equations. The chain-carrying species, XXI, can either fragment to give an ethyl radical and the amide (equation 4) or can react with more oxazirane by expelling a hydrogen atom from its 2-(α-methylene) substituent (equation 6). In the latter case diethyl ketone and acetaldehyde imine are formed along with the regeneration of the chain-propagating species. The ethyl radical once formed can be partitioned in a number of ways. Dimerization and disproportionation are probably important, but numerous other reactions such as those represented by equations 5 and 7 are also possibilities. Equation 7 would lead to the formation of another chain-propagating species XXII and to a chain reaction yielding diethyl ketone and acetaldehyde imine. The acetaldehyde imine would of course be hydrolyzed rapidly to acetaldehyde and ammonia.



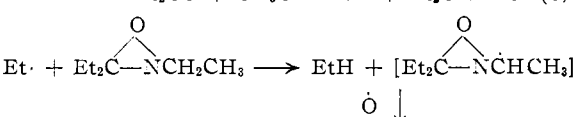
(3)

(4)

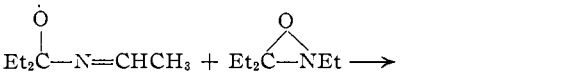
(5)



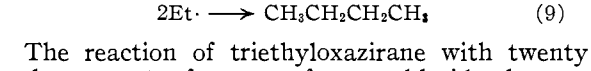
(6)



(7)

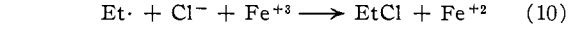


(8)



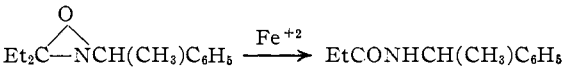
(9)

The reaction of triethyloxazirane with twenty mole per cent. of aqueous ferrous chloride also was examined briefly. In this case a very similar product distribution was obtained except that a considerable amount of ethyl chloride resulted at the expense of some of the ethane and ethylene. The origin of this product is obscure but presumably it comes from some sort of one-electron transfer reaction such as



(10)

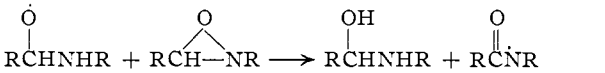
The reaction of 2-(α-phenylethyl)-3,3-diethyloxazirane also was investigated. In this case the products isolated were N-(α-phenylethyl)-propionamide (81%), butane, ethane and ethylene in a 2:1 ratio, ammonia (2%) and a trace of acetophenone. When the reaction was carried out with ferrous chloride, a considerable amount of ethyl chloride



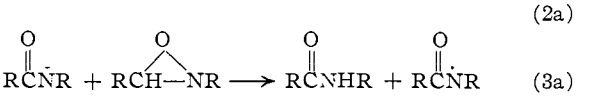
also was obtained. These results may again be explained by chain reactions similar to those represented by equations 3 to 9. In this case, however, the yield of N-alkylamide is much higher than was obtained from triethyloxazirane. Also no diethyl

(10) One such possibility is

(1a)



(2a)

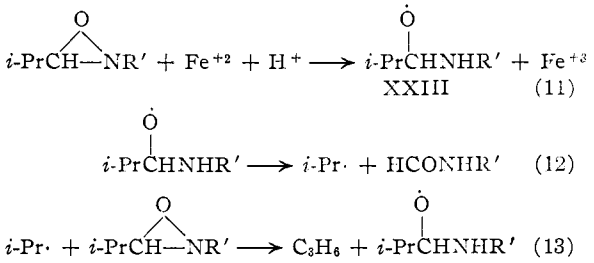


(3a)

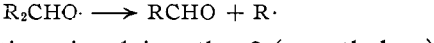
This type of hydrogen transfer is well established in radical solution reactions. However, neither benzaldehyde nor N-benzylidene-*t*-butylamine which would be products of the initiation step (equations 1a and 2a) were detected in the reaction mixtures. Accordingly we have some preference for the mechanism described above.

ketone and very little acetophenone were obtained. Presumably a small amount of diethyl ketone was formed, however, since the postulated reactions predict that the ammonia and ketone yields should be equivalent. In any event these results suggest that attack of the ethyl radical on the 2-(α-methylene) substituent (equation 7) does not take place to any major extent with this oxazirane. Furthermore fragmentation of the chain propagator with hydrogen atom transfer (equation 6) is also not important. These results are of some interest since *a priori* one might expect that the benzylic hydrogen involved in this case would be very active in chain transfer reactions. Actually, however, the transition state for this chain transfer reaction is probably fairly close to reactants, and the reactions themselves may well be governed by steric factors.[9] Under these circumstances the resonance stabilization available to a benzyl-type radical is not of great importance in determining the reaction path, and indeed in the case described here very little if any attack on this hydrogen atom is observed.

Finally the reactions of 2-isobutyl-3-isopropyloxazirane and 2-*t*-butyl-3-isopropyloxazirane with ferrous ammonium sulfate were examined. In the former case N-isobutylformamide (83%) and propane and propylene in approximately equal amounts were obtained. In the latter case the products were N-*t*-butylformamide (82%), propylene and propane. The propylene–propane ratio was essentially 3:1. These results can also be interpreted by chain reactions of the type previously described. It is also conceivable that some ammonia was formed in the former case but the complexity

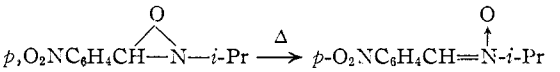


of the experimental system prevented its determination by a reliable method. It is interesting to note that the chain-carrying species XXIII reacts by fragmentation to give an isopropyl radical in which case a carbon–carbon bond is ruptured. This process occurs to the complete exclusion of carbon–hydrogen bond breaking, since the latter reaction would give as a product N-isobutylisobutyramide and none of this was found. This observation is in agreement with the behavior of alkoxyl radicals in which case a carbon–carbon bond normally is broken before a carbon–hydrogen bond.[11] It is also interesting to note that chain

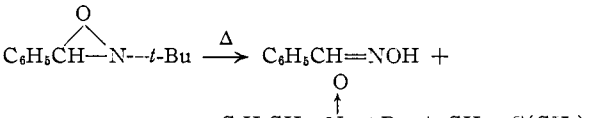


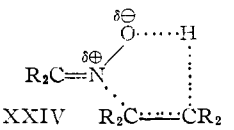
transfer reactions involving the 2-(α-methylene) hydrogen atoms of 2-isobutyl-3-isopropyloxazirane are not very important since very little if any ammonia was formed from the reaction of this oxazirane and ferrous ion. Again this may well be due to steric factors. It should be emphasized that all the reactions discussed in this section are extremely complex, and detailed studies well beyond the scope of this investigation would be required to elucidate their mechanism. The hypotheses presented here are simply intended to correlate the various experimental observations. It should be pointed out, however, that these reactions do have considerable analogy with one-electron transfer reactions of organic peroxides and have been discussed partly in terms of this analogy.[12]

Pyrolysis and Thermal Decomposition Reactions of Oxaziranes.—One of the more interesting facets of oxazirane chemistry is the behavior of these compounds at elevated temperatures. The thermal isomerization of 3-phenyloxaziranes to nitrones already has been discussed and appears to be a general reaction. The thermal isomerization of 2-isopropyl-3-*p*-nitrophenyloxazirane in boiling toluene also was carried out. In this case the reaction product was a mixture of compounds. However, by chromatography a 54% yield of N-isopropyl-*p*-nitrobenzaldoxime was isolated along with a trace of *p*-nitrobenzaldehyde. The nature of the other products formed in this reaction is unknown, but at least a moderate amount of nitrone was produced.



The behavior of 2-*t*-butyl-3-phenyloxazirane in a pyrolysis tube at 250° also was investigated. At this temperature isobutylene (60%), benzaldoxime (36%) and nitrone (12%) were obtained. The oxime and nitrone were separated by chromatography, and since there was a large intermediate fraction, the yields are understated. The formation of olefin and oxime from the nitrone is a reaction which deserves additional study. While the thermal isomerization of certain nitrones to oxime O-ethers has been reported,[13] a reaction involving β-elimination has not been described previously. The reaction probably involves a cyclic transition state such as XXIV and amounts to *cis* elimination. This reaction is in some respects analogous to the thermal decomposition of amine oxides.[14]





XXIV

The behavior of various alkyloxaziranes in a pyrolysis tube also was investigated and proved particularly interesting. 2-*t*-Octyloxazirane was converted to N-*t*-octylformamide in 66% yield at 200°, and no oxazirane was recovered. Similarly, when this oxazirane was heated under reflux in di-

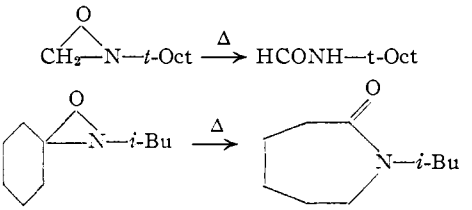
(11) M. S. Kharasch, A. Fono and W. Nudenberg, *J. Org. Chem.*, **15**, 763 (1950).

(12) A. V. Tobolsky and R. B. Mesrobian, "Organic Peroxides," Interscience Publishers, Inc., New York, N. Y., 1954.

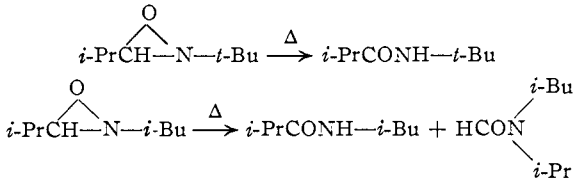
(13) A. C. Cope and A. C. Haven, THIS JOURNAL, **72**, 4896 (1950)

(14) A. C. Cope, T. T. Foster and P. H. Towle, *ibid.*, **71**, 3929 (1949).

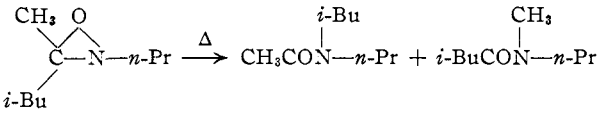
methylformamide solution, the same product was obtained in 75% yield. The behavior of 2-isobutyl-3,3-pentamethyleneoxazirane in this reaction



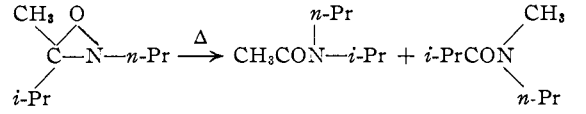
was also examined, and at 300° it was converted to N-isobutyl caprolactam in 83% yield. When 2-*t*-butyl-3-isopropyloxazirane was pyrolyzed at 250°, there was isolated N-*t*-butylisobutyramide (63%) and some unreacted oxazirane (13%). There was no evidence that any amide other than N-*t*-butylisobutyramide was formed in this reaction. In contrast to this experiment the pyrolysis of 2-isobutyl-3-isopropyloxazirane gave N-isobutylisobutyramide (25%) and N-isobutyl-N-isopropylformamide (49%) at a temperature of 300°.



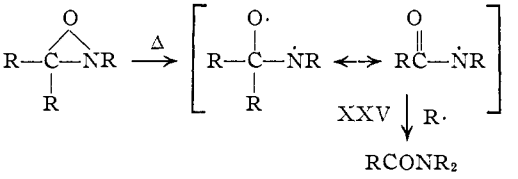
The examination of two trialkyloxaziranes in this reaction was then undertaken. At 300°, 2-*n*-propyl-3-methyl-3-isobutyloxazirane gave a 67% yield of mixed amides. This mixture consisted entirely of N-isobutyl-N-*n*-propylacetamide and N-methyl-N-*n*-propylisovaleramide. These two compounds were independently synthesized and the composition of the pyrolysis mixture determined by quantitative infrared analysis. It was found that the mixture consisted of 64% of the isovaleramide



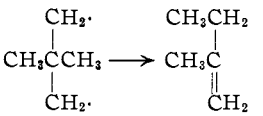
and 36% of the acetamide. Similarly the pyrolysis of 2-*n*-propyl-3-methyl-3-isopropyloxazirane at 300° gave a mixture of the two possible isomeric amides. Again the two amides were independently synthesized and the mixture was assayed by infrared techniques. It was thus established that the pyrolysis mixture consisted of N-*n*-propyl-N-isopropylacetamide (39%) and N-methyl-N-propylisobutyramide (61%). In no case was any other product identified from any of these pyrolysis reactions, although some carbonaceous residue was generally found in the pyrolysis tube after completion of an experiment. The tube employed was packed with glass helices and invariably was burned out between runs.



An explanation of the above results is necessarily limited to speculation in view of the rather limited amount of experimental data available at present. However, these reactions most probably occur in the gaseous phase. The temperatures employed were invariably well above the boiling point of the oxaziranes, and furthermore pyrolysis of oxaziranes in the liquid phase yields in some cases quite different products from those obtained in the vapor phase. In any event the hot tube reactions presumably involve free radicals generated in the gaseous phase. Under these conditions a chain reaction is unlikely, and it is rather tempting to consider the formation of a species which may be best described as a biradical XXV. The conversion of oxaziranes to amides may well be a concerted reaction initiated by the homolytic cleavage of the



relatively weak oxygen–nitrogen bond. The migration of an alkyl group is also of considerable interest. While there is no recorded instance of migration of a simple alkyl group in a free radical reaction,[15] there is one reported rearrangement of the trimethylene diradical generated in the electrolysis of potassium β,β-dimethylglutarate.[16] In this case 2-methyl-1-butene was formed, and this rearrangement is quite similar to that observed in oxazirane pyrolysis. The question of migratory

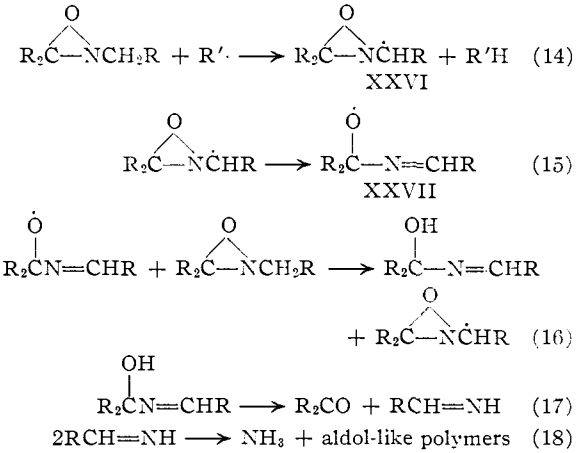


aptitudes in this rearrangement is also of some interest, but at present very little can be said about it. Thus in the pyrolysis of 2-*t*-butyl-3-isopropyloxazirane, hydrogen migrated exclusively at 250°. At 300° in the case of 2-isobutyl-3-isopropyl oxazirane both groups migrated and the ratio of hydrogen to isopropyl migration was 0.5. While these experiments were not comparable in that different pyrolysis temperatures were employed, they probably do represent a significant difference in the behavior of the two compounds. Since nothing is known currently about the transition state for this reaction, an explanation of these results is not possible at present. However, it is most likely that the differences in behavior of these two compounds is a result of steric factors. The migratory aptitudes determined from pyrolysis of the two trialkyloxaziranes were also of some interest. The ratio of methyl to isobutyl migration was 1.8 and methyl to isopropyl, 1.6. At the temperatures employed for the pyrolysis reactions, the relative lack of discrimination in terms of which alkyl group migrates is again not surprising. It is nevertheless interesting that the methyl group has a significantly greater migratory aptitude than either isopropyl or isobutyl groups. Whether this

(15) J. A. Berson and W. M. Jones, THIS JOURNAL, **78**, 6045 (1956).
(16) J. Walker and J. K. Wood, *J. Chem. Soc.*, **89**, 598 (1906).

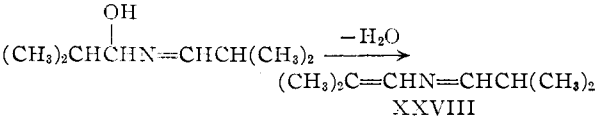
is a consequence of polar or steric factors or both is, of course, impossible to say at present.[17]

In order to contrast the vapor phase pyrolysis with that observed in the liquid phase, the decomposition of 2-*n*-propyl-3-methyl-3-isobutyloxazirane under reflux was investigated. This oxazirane is relatively stable, but when heated under nitrogen it began to boil at 168°. The temperature steadily dropped and after 2 hr. it had reached 128°. The products obtained were methyl isobutyl ketone (92%), ammonia (32%), recovered oxazirane (2%), an acid-soluble black tar and a mixture of amides (4%) very similar in composition to that obtained from the vapor phase pyrolysis of the same compound. These results are readily explained by a chain reaction possibly initiated by the biradical XXV. This suggestion is in agreement with the isolation of a small amount of the same mixed amides obtained from the vapor phase pyrolysis of the oxazirane.[18] In any event the chain reaction, regardless of the exact species of initiator, readily can be pictured as

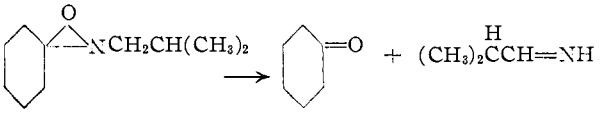


Reaction 16 is, of course, the chain-carrying step, and the formation of the chain-propagating radical XXVII may well be concerted. At the relatively high temperatures employed here the imine once formed would be expected to undergo rapid aldol condensations, and this is apparently what is observed. On the basis of the stoichiometry of reaction 18 the yield of ammonia obtained was actually 65%, and the acid-soluble tar was very probably the polymeric imine derived from the condensation reaction.

The liquid phase decomposition of 2-isobutyl-3-isopropyloxazirane also was examined. This material when heated to reflux (165°) underwent fairly rapid decomposition giving as one product water. Fractionation of the mixture gave a 32% yield of the olefinic imine XXVIII. This compound is presumably formed by the chain reaction represented by equations 14 to 16 and a subsequent dehydration. Its structure was proved by independent synthesis of the same material from isobutyraldehyde and ammonia.[19] Other products were obtained in this reaction, but it was not possible to separate and characterize them. Nevertheless the isolation of XXVIII does substantiate the postulated mode of liquid phase decomposition.



The mode of decomposition described above is in all probability that responsible for the relative instability of many oxaziranes previously discussed. The radical-initiating chain decomposition is unknown, but oxygen may possibly function as an initiator in this system. In any event the products of decomposition are quite similar to those obtained in the high temperature liquid-phase pyrolyses. Thus a sample of 2-isobutyl-3,3-pentamethyleneoxazirane which had decomposed at room temperature contained large amounts of cyclohexanone and a small amount of a product of unknown structure, $C_{14}H_{28}N_2$, presumably derived from condensation of one mole of cyclohexanone and two moles of isobutyraldehyde imine. In most cases



where decomposition of an oxazirane was observed, separation of a lower aqueous layer took place. In general very complex mixtures were formed from such decompositions, and it was not possible to separate and characterize the products obtained. However, this is not surprising since mixtures of ketones and reactive imines would be expected to give a variety of different products. Finally the existence of this decomposition reaction provides a satisfactory explanation of the remarkable stability of the 2-*t*-alkyloxaziranes which are not subject to the type of chain reaction outlined here. It is also probably worth pointing out that reaction 16, the chain-propagating step of this decomposition, appears to be subject to a pronounced steric effect. In general oxaziranes with a number of bulky substituents are much more stable than those without such substituents. A notable example of this is 2-*n*-butyloxazirane, which was extremely unstable.

Acknowledgment.—We are greatly indebted to M. F. Hawthorne, G. S. Hammond, R. W. Walker and W. D. Niederhauser for their many helpful suggestions during the course of this work. The infrared analyses were carried out by K. S. McCallum, the mass spectra work by Al Kennedy and the ultraviolet spectra were determined by R. D. Strahm. Finally we wish to express our appreciation for the invaluable technical assistance of Mrs. I. G. Shepard.

Experimental

Preparation of Imines.—The imines employed as starting materials were all prepared by condensation of the appro-

(17) Interesting polar mechanisms involving surface catalysis can also be written to account for these observations and our prejudices in favor of the biradical hypothesis, although real, are not strong.

(18) This fraction was not sufficiently pure for quantitative determination of its composition. Infrared did show, however, that it was composed almost entirely of N-methyl-N-*n*-propylisovaleramide and N-isobutyl-N-*n*-propylacetamide.

(19) H. J. Hagemeyer and G. C. DeCroes, "The Chemistry of Isobutyraldehyde," Tennessee Eastman Co., Kingsport, Tenn., 1953, p. 57; see also J. W. Clark and A. L. Wilson, U. S. Patent 2,319,848, May 25, 1943.

TABLE IV

PHYSICAL PROPERTIES OF IMINES, RR'C=NR"

R	R'	R"	B.p. °C.	B.p. Mm.	$n^{20}D$	Infrared stretching frequency (C=N), cm.$^{-1}$
H	H	*t*-Bu[a]	65	740	1.4151	1652[m]
H	H	*t*-Oct[a]	50–52	13	1.4381	1642
C_6H_5	H	*t*-Bu[a]	90–92	11	1.5211	1638
p-$O_2NC_6H_4$	H	*t*-Bu[b]	73–75	(M.p.)[c]		1638
p-$O_2NC_6H_4$	H	*t*-Oct[d]			1.5430	1644
p-$O_2NC_6H_4$	H	*i*-Pr[e]	54–55	(M.p.)		1644
p-$O_2NC_6H_4$	H	Et[f]	75–76	(M.p.)		1646
i-Pr	H	*t*-Bu[g]	51–53	83	1.4078	1670
i-Pr	H	*n*-Bu[h]	67	68	1.4151	1668
i-Pr	H	$CH_3CHC_6H_5$[j]	68	0.8	1.4975	1660
i-Bu	Me	*n*-Pr	65	22	1.4272	1656
$C_{10}H_{20}N_2$[a,n]			52–53	(M.p.)		1628
n-BuCH(Et)	H	*n*-Bu[k]	87	8	1.4338	1666
2-Pyridyl	H	*t*-Bu[l]	56–58	0.2	1.5335	1643
C_6H_5	H	*t*-Oct[a]	100	0.4	1.5162	1639
i-Pr	Me	*n*-Pr	48	26	1.4230	1660
Et	Me	Allyl	94	100		1658
Et	Et	Et[o]	52–54	54	1.4230	1660
Me	Me	*n*-Hex[p]	53–55	5.0	1.4319	1668
i-Pr	H	*i*-Bu[q]	57	64	1.4097	1676
Et	Et	$C_6H_5CH(CH_3)$[r]	64	0.2	1.5050	1660

[a] M. D. Hurwitz, U. S. Patent 2,582,128; January 8, 1952. [b] Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.31; H, 6.98; N, 13.35. [c] Recrystallized from petroleum ether. [d] Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 69.13; H, 8.62; N, 9.89. An oil which could not be crystallized. [e] Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.45; H, 6.45; N, 14.13. [f] F. G. Baddar, *J. Chem. Soc.*,136 (1950). [g] Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.00. Found: C, 76.29; H, 13.78; N, 10.52. [h] G. E. Coates and L. E. Sutton, *J. Chem. Soc.*, 1187 (1948). [i] Calcd. for $C_{12}H_{17}N$: C, 82.33; H, 9.78; N, 7.99. Found: C, 82.30; H, 9.91; N, 7.30. [k] D. G. Norton, V. E. Haury, F. C. Davis, L. J. Mitchell and S. A. Ballard, *J. Org. Chem.*, 19, 1054 (1954). Calcd. for $C_{12}H_{25}N$: C, 78.61; H, 13.75; N, 7.64. Found: C, 78.37; H, 13.53; N, 7.91. [l] Calcd. for $C_{10}H_{14}N_2$: C, 74.04; H, 8.70; N, 17.26. Found: C, 74.34; H, 9.24; N, 16.54. [m] A very weak broad band. [n] This compound was *t*-BuN=CHCH=N-*t*-Bu and was recrystallized from ethyl acetate. [o] Calcd. for $C_{17}H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.18; H, 13.50; N, 12.08. [p] Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.91. Found: C, 76.41; H, 13.45; N, 9.93. [q] Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.14; N, 11.00. Found: C, 74.80; H, 13.41; N, 9.84. [r] Calcd. for $C_{13}H_{19}N$: C, 82.49; H, 10.12; N, 7.40. Found: C, 82.30; H, 10.00; N, 7.23.

priate amine and ketone or aldehyde.[20] The physical properties of these compounds along with the pertinent analytical data for those which have not been previously described in the literature are summarized in Table IV. Most of the imines were purified shortly before use by distillation in a spinning band column.

Preparation of Oxaziranes.—The procedures for preparations of these compounds were generally very similar so only a few examples are described in detail.

2-*t*-Butyloxazirane.—To 100 ml. of methylene chloride with vigorous stirring and cooling in an ice-bath was added 30.0 ml. (1.1 moles) of 90% hydrogen peroxide and two drops of sulfuric acid.[21] Acetic anhydride (135 g., 1.32 moles) was then added dropwise to the cooled solution over a 30-minute period. The mixture subsequently was stirred 15 minutes in the ice-bath and 30 minutes at room temperature. The clear solution of peracetic acid so obtained was then added dropwise over a 30-minute period to a solution of 85 g. (1.0 mole) of *t*-butylazomethine in 100 ml. of methylene chloride stirred in an ice-bath. After the initial third of the reagent had been added, a blue color (presumably *t*-nitrosobutane) developed. After addition, the ice was allowed to melt and the mixture to stand overnight at room temperature. It was then washed with 500 ml. of water, two 200-ml. portions of cold 15% aqueous ammonia and finally with 100 ml. of 10% sulfuric acid.[22] The organic extract was dried over magnesium sulfate, and most of the solvent was distilled off at atmospheric pressure through a short column packed with glass helices. During this distillation the pot temperature was not allowed above 60°. The residue still containing a little solvent was then fractionated in a spinning band column.[23] There was obtained 46.4 g. (46%) of 2-*t*-butyloxazirane, b.p. 52–54° (75 mm.). Active oxygen assays on this compound as well as on the others described in Table I were determined using potassium iodide and acetic acid.[24]

2-*t*-Butyl-3-phenyloxazirane.—A peracetic acid solution was prepared as described above from 15 ml. (0.55 mole) of 90% hydrogen peroxide, 50 ml. of methylene chloride, one drop of sulfuric acid and 67.2 g. (0.66 mole) of acetic anhydride. This solution was then added dropwise with stirring to a mixture of 80.5 g. (0.5 mole) of N-benzylidene-*t*-butylamine in 100 ml. of methylene chloride cooled in an ice-bath. The ice was allowed to melt overnight and the solution worked up as described above. Evaporation of the methylene chloride at reduced pressure yielded 79.5 g. (90%) of the crude oxazirane. This product, although it was contaminated by a little benzaldehyde, was sufficiently pure for most purposes. Distillation of the oxazirane in a spinning band column yielded 63.1 g. (71%) of 2-*t*-butyl-3-phenyloxazirane, b.p. 61–63° (0.3 mm.). It was necessary to carry out this distillation fairly rapidly since some thermal isomerization of the oxazirane to nitrone took place. The molecular weight of this compound determined ebullioscopically in acetone was 166 (calcd. 177).

Bis-(2-*t*-butyloxazirane).—A peracetic acid solution was prepared in the usual manner from 25.3 ml. (0.93 mole) of 90% hydrogen peroxide, 100 ml. of methylene chloride, two drops of sulfuric acid and 114 g. (1.12 moles) of acetic

(20) For typical procedures see footnotes *a* and *j* (Table IV) and K. N. Campbell, A. H. Sommers and B. K. Campbell, THIS JOURNAL, **66**, 82 (1944).

(21) Preparations of peracetic acid were routinely carried out behind a safety screen. For information concerning possible hazards of 90% hydrogen peroxide see E. S. Shanley and F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 1536 (1947).

(22) The ammonia wash was found to be an extremely effective method for removal of trace amounts of acetic anhydride.

(23) All distillations of oxaziranes were routinely carried out behind a safety screen.

(24) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 100.

anhydride. This solution was then added dropwise to an ice-cooled solution of 71 g. (0.423 mole) of the bifunctional imine derived from condensation of glyoxal and *t*-butylamine in 75 ml. of methylene chloride. After the mixture had stood overnight, it was washed with 200 ml. of water, two 100-ml. portions of cold aqueous ammonia and 100 ml. of 10% sulfuric acid. The organic extract was dried over magnesium sulfate, and the volatile solvent was evaporated at reduced pressure. There was obtained a mushy solid which was recrystallized from petroleum ether at −78° to yield 40 g. (51%) of crystalline solid, m.p. 53–56°. The infrared spectrum of this crude sample showed that it contained none of the parent imine. A portion of this material was chromatographed over silica gel using methylene chloride as eluent. The first fraction off the column melted at 82–84° (presumably *meso*) and was followed by a second fraction melting at 42–43° (probably *dl*). Both samples were recrystallized from petroleum ether, and the infrared spectra of the two isomers were very similar. Active oxygen assay on the higher melting product showed 93.7% purity and on the lower, 92.6%.

Anal. Calcd. for $C_{10}H_{22}N_2O_2$: C, 60.05; H, 10.08; N, 14.01. Found (m.p. 43°): C, 60.05; H, 10.26; N, 13.80. Found (m.p. 84°): C, 60.57; H, 10.34; N, 13.81.

2-Isobutyl-3,3-pentamethyleneoxazirane.—A peracetic acid solution was prepared from 50 ml. of methylene chloride, 9.8 ml. (0.36 mole) of 90% hydrogen peroxide, one drop of sulfuric acid and 44.1 g. (0.432 mole) of acetic anhydride. The clear solution so obtained was added dropwise to 45.9 g. (0.3 mole) of N-cyclohexylideneisobutylamine in 50 ml. of the same solvent stirred in an ice-bath. The product was allowed to stand overnight, worked up in the usual way and distilled in a spinning band column. There was obtained 41.1 g. (81%) of the oxazirane, b.p. 59–62° (1.5 mm.), $n^{20}D$ 1.4569. The purity of this sample by iodimetric assay was 97.2%.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.69; H, 11.49; N, 7.71.

After standing one month at room temperature the active oxygen assay of this compound had dropped to 32% and a lower aqueous layer separated. The organic layer was removed, dried over magnesium sulfate and distilled at reduced pressure in a spinning band column. From 21 g. of organic product there was obtained 7.5 g. of cyclohexanone, 5.1 g. of recovered oxazirane and 5.0 g. of pot residue. From the pot residue there was isolated 3.5 g. of faintly yellow liquid, b.p. 68–70° (0.01 mm.). This material had a strong band in the infrared at 1665 cm.$^{-1}$ and appeared to be a condensation product of cyclohexanone with two moles of isobutyraldehyde imine.

Anal. Calcd. for $C_{14}H_{28}N_2$: C, 74.94; H, 12.58; N, 12.49. Found: C, 75.45; H, 11.74; N, 12.25.

Acid-catalyzed Hydrolysis of 2-*t*-Butyl-3-phenyloxazirane.—A mixture of 100 ml. of water, one liter of methanol and 60 ml. of sulfuric acid was stirred in an ice-bath while 177 g. (1.0 mole) of 2-*t*-butyl-3-phenyloxazirane was added dropwise. After addition the ice was allowed to melt and the mixture was stirred at room temperature 20 hr. It was then poured into one liter of water and extracted with five 200-ml. portions of ether. The ether extract was dried over magnesium sulfate and evaporated to yield 98.8 g. (93%) of benzaldehyde, b.p. 75° (16 mm.). The infrared spectrum of this compound was identical with that of an authentic sample of benzaldehyde. The pot residue from this distillation crystallized and after recrystallization from petroleum ether amounted to 1.2 g., m.p. 75°. It was later identified by mixed melting point as N-*t*-butylbenzaldoxime (see below). The acidic aqueous layer from the ether extraction was made strongly alkaline by the slow addition of a solution of 150 g. of sodium hydroxide in 300 ml. of water. The resulting solution was continuously extracted with ether for three days. The ether was dried over magnesium sulfate and the solvent was evaporated at reduced pressure. There was obtained 73 g. (8%) of fairly pure crystalline β-*t*-butylhydroxylamine, m.p. 60–61°. After recrystallization from petroleum ether it melted at 64–65°. This compound was kept under nitrogen in the refrigerator since on exposure to air it was oxidized to the blue *t*-nitrosobutane.

Anal. Calcd. for $C_4H_{11}ON$: C, 53.98; H, 12.44; N, 15.70. Found: C, 53.69; H, 12.64; N, 15.47.

Acid-catalysed Hydrolysis of 2-*t*-Octyl-3-phenyloxazirane.—This hydrolysis was carried out as described above with 233 g. (1.0 mole) of the oxazirane. The hydrolysis mixture was, however, stirred three days at room temperature, and it was unnecessary to employ continuous extraction to isolate the hydroxylamine from the alkaline solution. There was obtained 86 g. (81%) of benzaldehyde and 120 g. (83%) of the crude β-*t*-octylhydroxylamine. The latter compound was purified by distillation, b.p. 50–53° (0.02 mm.), and finally by vacuum sublimation. The sample so obtained melted at 40–42° and also was subject to air oxidation to the nitrosoalkane.

Anal. Calcd. for $C_8H_{19}ON$: C, 66.16; H, 13.19; N, 9.64. Found: C, 66.42; H, 13.24; N, 9.86.

N-*t*-Butylbenzaldoxime.—A mixture of 4.5 g. (0.05 mole) of β-*t*-butylhydroxylamine and 5.3 g. (0.05 mole) of benzaldehyde was heated to 45°. At this point an exothermic reaction was noted. After the reaction had subsided, the mixture was kept at 50–60° for 1 hr. and then separation of an aqueous phase was observed. The product was taken up in 50 ml. of methylene chloride and the aqueous layer was removed. The solvent was dried and evaporated yielding after recrystallization from petroleum ether 5.5 g. (62%) of the nitrone, m.p. 75–76°. This product did not give an active oxygen test with potassium iodide in aqueous acetic acid. It was independently prepared by heating 8.8 g. of 2-*t*-butyl-3-phenyloxazirane in 100 ml. of dry acetonitrile under reflux for three days. Evaporation of the solvent gave a quantitative yield of the same nitrone. This nitrone when hydrolyzed by the same procedure employed with 2-*t*-butyl-3-phenyloxazirane gave essentially quantitative yields of benzaldehyde and β-*t*-butylhydroxylamine.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 75.54; H, 8.53; N, 7.90. Found: C, 74.60; H, 8.55; N, 7.62.

N-*t*-Octylbenzaldoxime.—A mixture of 14.5 g. (0.1 mole) of β-*t*-octylhydroxylamine and 10.6 g. (0.1 mole) of benzaldehyde was heated 30 minutes on a steam-bath. The crystalline product was taken up in 50 ml. of methylene chloride. The solution was dried over magnesium sulfate and the volatile solvent evaporated. There was obtained after recrystallization from ligroin 15.8 g. (68%) of the crystalline nitrone, m.p. 103–104°. This compound on hydrolysis with aqueous methanol and sulfuric acid gave quantitative yields of benzaldehyde and *t*-octylhydroxylamine.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.56; H, 9.98; N, 5.58.

N,N′-Di-*t*-butylglyoxime.—A mixture of 8.9 g. (0.1 mole) of β-*t*-butylhydroxylamine and 4.2 g. (0.022 mole) of 30% aqueous glyoxal solution was shaken vigorously at room temperature for 15 minutes. A crystalline solid separated and was extracted with 100 ml. of methylene chloride. The organic extract was washed with 50 ml. of water and the wash water was back extracted with 125 ml. of solvent. The combined organic extracts were dried and evaporated at reduced pressure. There was obtained 4.7 g. of crude product which was recrystallized from ligroin. The nitrone was a cream-colored solid, m.p. 193–195°, yield 3.6 g. (82%), and was fairly soluble in water.

Anal. Calcd. for $C_{10}H_{22}N_2O_2$: C, 59.96; H, 10.07; N, 13.99. Found: C, 59.95; H, 10.06; N, 13.74.

N-*t*-Butyl-*p*-nitrobenzaldoxime.—A solution of 9.1 g. (0.06 mole) of *p*-nitrobenzaldehyde, 8.9 g. (0.1 mole) of *t*-butylhydroxylamine and 100 ml. of benzene was heated under reflux for 10 hr., and the water was removed azeotropically with a Dean–Stark trap. The solvent was then evaporated under reduced pressure, and the product was recrystallized from a 3:1 ethyl ether–petroleum ether mixture. There was obtained 10.0 g. (74%) of yellow nitrone, m.p. 134–135°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 59.44; H, 6.35; N, 12.60. Found: C, 59.60; H, 6.52; N, 12.21.

N-*t*-Octyl-*p*-nitrobenzaldoxime.—A mixture of 14.5 g. (0.1 mole) of *t*-octylhydroxylamine, 15.1 g. (0.1 mole) of *p*-nitrobenzaldehyde and 125 ml. of benzene was heated under reflux for 20 hr. during which time the water was removed by a Dean–Stark trap. The benzene was then evaporated at reduced pressure, and the residue was recrystallized from petroleum ether, yield 12.8 g. (49%), m.p. 119–121°.

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 64.72; H, 7.97; N, 10.07. Found: C, 64.58; H, 7.71; N, 10.14.

N-Isopropyl-*p*-nitrobenzaldoxime.—A solution of 2-isopropyl-3-*p*-nitrophenyloxazirane was heated under reflux in 25 ml. of toluene for 14 hr. The dark solution was evaporated under reduced pressure and the residue chromatographed over silica gel. Elution with methylene chloride gave a mixture of *p*-nitrobenzaldehyde and an unknown material. Subsequent elution with 10% ethyl acetate in methylene chloride gave 2.7 g. (54%) of the nitrone which was recrystallized from petroleum ether, m.p. 98–100°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 58.02; H, 6.04; N, 14.12.

Reduction of 2-*t*-Butyl-3-phenyloxazirane with Lithium Aluminum Hydride.—To a solution of 3.8 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of ether was added 17.7 g. (0.1 mole) of the oxazirane in 50 ml. of ether. After addition was complete, the mixture was heated under reflux for 2 hr. It was then decomposed by cautious addition of 200 ml. of 20% hydrochloric acid. The aqueous extract was immediately made alkaline and extracted with three 100-ml. portions of ether. The ether was evaporated to give an oil. This oil on distillation yielded 14.6 g. (91%) of N-benzylidene-*t*-butylamine, b.p. 48° (0.1 mm.). The infrared spectrum of this product was identical with that of an authentic specimen.

Reduction of 2-*t*-Butyl-3-phenyloxazirane with Potassium Iodide.—To a solution of 25 g. of potassium iodide, 100 ml. of water, 200 ml. of ethanol and 40 ml. of acetic acid was added dropwise with stirring 8.9 g. (0.05 mole) of the oxazirane. After 15 minutes the iodine was destroyed by addition of sodium bisulfite. The mixture was made alkaline and extracted with three 100-ml. portions of methylene chloride. The extract was dried with magnesium sulfate and the volatile solvent evaporated. There was obtained 6.5 g. (80%) of N-benzylidene-*t*-butylamine, b.p. 48° (0.1 mm.), which was contaminated by a trace of benzaldehyde. The infrared spectrum of this sample was identical with that of an authentic specimen.

Reduction of N-*t*-Butylbenzaldoxime with Lithium Aluminum Hydride.—A solution of 5.6 g. (0.03 mole) of the nitrone in 50 ml. of ether was added dropwise to a stirred mixture of 1.2 g. (0.03 mole) of lithium aluminum hydride in 200 ml. of ether. The mixture was then refluxed 2 hr. and decomposed with 200 ml. of 10% aqueous hydrochloric acid. The aqueous layer was treated with excess sodium hydroxide and extracted with five 100-ml. portions of ether. The extract was dried and evaporated at reduced pressure. The residual solid was recrystallized from ligroin to yield 4.3 g. (77%) of N-*t*-butyl-N-benzylhydroxylamine, m.p. 71–73°.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.72; H, 9.77; N, 7.60.

Reduction of N-*t*-Octylbenzaldoxime.—To a mixture of 1.2 g. (0.03 mole) of lithium aluminum hydride in 200 ml. of ether was added 7.5 g. (0.03 mole) of the nitrone dissolved in 50 ml. of the same solvent. The solution was then heated under reflux 1 hr. and decomposed with 100 ml. of 20% hydrochloric acid. At this point 4.5 g. (52%) of the hydrochloride salt of N-*t*-octyl-N-benzylhydroxylamine was filtered off. This product was not very soluble in water and gave a positive chloride test with silver nitrate. After recrystallization from ethyl acetate it melted at 172–174°.

Anal. Calcd. for $C_{16}H_{26}ONCl$: C, 66.28; H, 9.64; N, 5.15; Cl, 13.04. Found: C, 66.27; H, 9.53; N, 4.86; Cl, 12.85.

The hydrochloride salt was converted to the free hydroxylamine by sodium hydroxide in aqueous methanol. The latter compound was an oil which could not be crystallized. Its neutral equivalent of 253.9 was in fair agreement, however, with the theoretical value of 235.3. The infrared spectrum of the compound was also consistent with that expected for a hydroxylamine.

Reduction of 2-*t*-Octyloxazirane with Lithium Aluminum Hydride.—To 3.8 g. (0.1 mole) of lithium aluminum hydride in 150 ml. of ether was added 15.7 g. (0.1 mole) of 2-*t*-octyloxazirane in 50 ml. of the same solvent. The mixture was heated under reflux 1 hr. and decomposed with 150 ml. of 10% hydrochloric acid. The aqueous extract was made strongly alkaline and extracted with four 75-ml. portions of methylene chloride. The organic extract was dried and evaporated. Distillation of the residual oil yielded 10.4 g. (73%) of N-methyl-*t*-octylamine, b.p. 56–58° (19 mm.), $n^{20}D$ 1.4305.

Anal. Calcd. for $C_9H_{21}N$: C, 75.45; H, 14.78; N, 9.77. Found: C, 76.17; H, 14.99; N, 9.54.

The hydrochloride salt was prepared by dissolving the amine in a little hydrochloric acid and evaporating the solution to dryness. The salt was recrystallized from ethyl acetate and melted at 158–159°.

Anal. Calcd. for $C_9H_{22}NCl$: C, 60.14; H, 12.34; N, 7.79; Cl, 19.73. Found: C, 59.22; H, 12.55; N, 7.53; Cl, 19.83.

The same reduction was carried out on *t*-octylazomethine and gave a 74% yield of N-methyl-*t*-octylamine identical in all respects to that prepared by reduction of the oxazirane.

Resolution of 2-*n*-Propyl-3-methyl-3-isobutyloxazirane.—A solution of 30.4 g. (0.077 mole) of brucine and 27.6 g. (0.175 mole) of the oxazirane was heated under reflux with stirring in 80 ml. of methylene chloride for 16 hr. After this time 28.5 g. (90%) of the insoluble brucine-N-oxide was collected on a filter and washed with a little cold methylene chloride. The filtrate was then washed with 200 ml. of 10% sulfuric acid and 100 ml. of water. It was dried over magnesium sulfate and the volatile solvent was evaporated at reduced pressure. The residual oil was distilled to yield 8.1 g. of recovered oxazirane, b.p. 30–34° (0.8 mm.). This was then distilled through a semi-micro spinning band column and a 4.3-g. center cut of the oxazirane collected, b.p. 60° (8.0 mm.), $n^{20}D$ 1.4260. The infrared spectrum of this sample was identical in all respects to that of an authentic sample and showed no extraneous bands. The optical rotation of this sample was determined, $\alpha^{24}D$ −2.80°, l = 1, neat.[25] The brucine N-oxide melted at 194° with decomposition, and its infrared spectrum was identical in all respects with an authentic sample prepared by reaction of brucine with aqueous hydrogen peroxide.[26]

Reaction of Boron Fluoride Etherate with 2-*t*-Butyl-3-phenyloxazirane.—To a stirred solution of 35.4 g. (0.2 mole) of the oxazirane in 100 ml. of dry benzene was added dropwise with ice-bath cooling 28.4 g. (0.2 mole) of freshly distilled boron fluoride etherate in 50 ml. of benzene. After a 30-minute period a granular precipitate was observed. The mixture was allowed to stand an additional hour at room temperature and the product was then collected on a filter. It was washed with benzene and with petroleum ether and was then dried in a vacuum desiccator at a pressure of 1 mm. for 2 hr. There was obtained 40 g. (82%) of the boron fluoride salt of the unstable isomer of N-*t*-butylbenzaldoxime (presumably *cis*). A portion of this material was recrystallized from methylene chloride at −80° and melted at 65–68°. The sample before recrystallization melted at 80–88°.

Anal. Calcd. for $C_{11}H_{15}NOBF_3$: C, 53.91; H, 6.17; N, 5.71. Found: C, 53.40; H, 5.99; N, 5.75.

On recrystallization from hot ethyl acetate this material was converted to the stable isomer of the nitrone (probably *trans*) which melted at 135–137°.

Anal. Calcd. for $C_{11}H_{15}NOBF_3$: C, 53.91; H, 6.17; N, 5.71. Found: C, 53.61; H, 6.24; N, 5.44.

The latter compound also was obtained in essentially quantitative yield from reaction of boron fluoride etherate with N-*t*-butylbenzaldoxime in ether solvent at room temperature. The infrared spectra of the two isomeric salts were quite different in the fingerprint region and each isomer appeared to be spectroscopically pure. However, the unstable isomer salt after standing at room temperature for several days was observed to undergo some isomerization to the stable isomer.

Reaction of 2-*n*-Butyloxazirane with Acid.—To a solution of 5.0 g. (0.025 mole) of 2,4-dinitrophenylhydrazine, 25 ml. of concentrated sulfuric acid, 36 ml. of water and 125 ml. of ethanol was added 1.0 g. (0.01 mole) of 2-*n*-butyloxazirane. The mixture was allowed to stand overnight and the crystalline precipitate was then filtered and washed with a little cold 50% ethanol. There was obtained 4.2 g. (95%) of 2,4-dinitrophenylhydrazones. The aqueous filtrate was made strongly alkaline and distilled until all of the volatile base was collected. The aqueous alcoholic solution so obtained was shaken with 1.35 g. of phenyl isothiocyanate for 1 hr. at room temperature. The thiourea was then extracted with three 50-ml. portions of methylene chloride.

(25) A duplicate experiment with somewhat different stoichiometry gave $\alpha^{22}D$ −3.94°.

(26) A. Kogure and M. Kotake, *J. Inst. Polytech. Osaka City Univ., Ser. C*, **2**, No. 2, 49 (1951).

Evaporation of this solvent yielded 1.2 g. (79%) of N-phenylthiourea (m.p. 152–154°, mixture melting point 153–154°). The 2,4-dinitrophenylhydrazone mixture was characterized by paper chromatography.[27] Identical chromatograms were obtained from the unknown mixture and a synthetic equimolar mixture of the 2,4-dinitrophenylhydrazones of formaldehyde and *n*-butyraldehyde. The two derivatives separated cleanly, and no evidence of any other compounds in the unknown mixture was obtained.

Reaction of 2-*n*-Butyl-3-isopropyloxazirane with Acid.—This oxazirane (1.4 g., 0.01 mole) was treated with acid as described above. There was otained 4.6 g. (100%) of the 2,4-dinitrophenylhydrazone mixture and a 66% yield of ammonia isolated as N-phenylthiourea as described above. The 2,4-DNPH mixture was again characterized by paper chromatography and the chromatogram of the mixture was identical to that from an equimolar mixture of the *n*-butyraldehyde and isobutyraldehyde 2,4-dinitrophenylhydrazones. The separation of these two isomers on the chromatogram was not very satisfactory, however, so the identification of this product mixture must be accepted with reservation.

Reaction of 2-*t*-Butyloxazirane with Acid.—From 1.0 g. (0.01 mole) of this compound under the usual conditions there was obtained 4.0 g. (91%) of 2,4-dinitrophenylhydrazone mixture and a 60% yield of methylamine isolated as N-phenyl-N'-methylthiourea (1.0 g., m.p. 111–112°, mixture m.p. 111–112°). Paper chromatograms of the mixture of 2,4-DNPH's and an equimolar mixture of the 2,4-dinitrophenylhydrazones of formaldehyde and acetone were identical. Again no evidence of other compounds in the mixture was obtained. The 2,4-dinitrophenylhydrazone of acetone, m.p. 126°, also was isolated by column chromatography over alumina with benzene eluent and was identified by mixed melting point. It was not possible to isolate the formaldehyde 2,4-DNPH in this way, however.

Reaction of 2-(α-Phenylethyl)-3-isopropyloxazirane with Acid.—The oxazirane (1.9 g., 0.01 mole) when treated as described above gave 4.6 g. (100%) of mixed 2,4-dinitrophenylhydrazones. Steam distillation of the alkaline filtrate gave 0.8 g. (86%) of aniline which was identified by comparison of its infrared spectrum with that of an authentic sample and by preparation of its tribromide, m.p. 120°. Paper chromatograms of the 2,4-DNPH mixture and an equimolar mixture of isobutyraldehyde and acetaldehyde 2,4-dinitrophenylhydrazones were identical. Column chromatography with alumina and benzene eluent also separated the two compounds. The isobutyraldehyde 2,4-DNPH melted at 181° and the acetaldehyde 2,4-DNPH at 164–166°. Mixture melting points with authentic samples of these compounds showed no depression. However, since a very large intermediate fraction was obtained in the column chromatogram, the characterization of the reaction mixture necessarily was based on the paper chromatograms.

Reaction of 2-(α-Phenylethyl)-3-isopropyloxazirane with Potassium Hydroxide.—To an ice-cooled solution of 8.6 g. of potassium hydroxide in 100 ml. of ethylene glycol was added dropwise with stirring 19.1 g. (0.1 mole) of the oxazirane. After 1 hr. the ice-bath was removed and an exothermic reaction brought the temperature to 45°. The odor of ammonia was apparent at this point. After 1 hr. the reaction mixture was heated at 60° (5.0 mm.) and the isobutyraldehyde was collected in a cold trap. There was obtained 4.1 g. (57%) of isobutyraldehyde contaminated by trace amounts of water and ammonia. This was characterized by preparation of its 2,4-dinitrophenylhydrazone, m.p. 179–181°, and by comparison of its infrared spectrum with that of an authentic sample. The ethylene glycol solution was then poured into 300 ml. of water and extracted with two 100-ml. portions of methylene chloride. The organic extract was washed with 50 ml. of water, dried over magnesium sulfate and evaporated to yield a solid–liquid mixture. To this mixture was added 100 ml. of cold ethanol. The isobutylideneacetophenone was filtered and recrystallized from ethanol, yield 1.5 g. (8%), m.p. 139–140°. A mixture melting point with an authentic sample of isobutylideneacetophenone prepared by the base-catalyzed condensation of isobutyraldehyde and acetophenone showed no depression. The infrared spectrum of this compound was also consistent with that of an α,β-unsaturated ketone. The ethanol filtrate was then evaporated to yield 6.7 g. of oil which on distillation gave 3.1 g. (25%) of acetophenone, b.p. 83–85° (12.0 mm.). The infrared spectrum of this ketone was identical with that of an authentic specimen.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10; N, 9.18. Found: C, 82.70; H, 8.03; N, 8.96.

Reaction of 2-*t*-Butyl-3-phenyloxazirane with Ferrous Ion.—To a solution of 12.0 g. (0.03 mole) of ferrous ammonium sulfate hexahydrate in 100 ml. of distilled water was added at room temperature with vigorous stirring under nitrogen 5.3 g. (0.03 mole) of 2-*t*-butyl-3-phenyloxazirane. After 2 hr. the mixture was extracted with three 100-ml. portions of methylene chloride. The extract was dried and evaporated yielding a crystalline product which was washed with a little cold petroleum ether. There was obtained 5.2 g. (98%) of N-*t*-butylbenzamide, m.p. 134°. The mixture melting point of this sample and of an authentic specimen of this amide[28] showed no depression. When this experiment was repeated using only 1.2 g. (0.003 mole) of ferrous ammonium sulfate, the product was 5.3 g. of solid, m.p. 108–112°. After this material was washed with cold petroleum ether, there was obtained 3.7 g. (70%) of N-*t*-butylbenzamide, m.p. 134°. Evaporation of the petroleum ether filtrate gave 1.5 g. (28%) of recovered oxazirane.

Reaction of 2-*t*-Octyloxazirane with Ferrous Ion.—A solution of 1.2 g. (0.003 mole) of ferrous ammonium sulfate in 100 ml. of distilled water was stirred vigorously with 4.7 g. (0.03 mole) of 2-*t*-octyloxazirane under nitrogen at room temperature for 2 hr. Extraction of this mixture with ether yielded 4.1 g. (87%) of N-*t*-octylformamide, b.p. 84° (0.5 mm.), $n^{20}D$ 1.4555.[29] The infrared spectrum of this compound was identical with that of an authentic specimen prepared from ethyl formate and *t*-octylamine.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.90. Found: C, 68.71; H, 12.10; N, 8.74.

Reaction of Triethyloxazirane with Ferrous Ion.—To 8.0 g. (0.02 mole) of ferrous ammonium sulfate hexahydrate in 100 ml. of distilled water was added with vigorous stirring 12.9 g. (0.1 mole) of triethyloxazirane. The reaction was conducted under helium and the effluent gases were run through Drierite and then through Dry Ice–acetone and liquid nitrogen traps. After addition of the oxazirane a mildly exothermic reaction was observed. The mixture was stirred 36 hr. at room temperature and was then continuously extracted with methylene chloride for three days. A considerable amount of gas was produced in the reaction. Examination of the Dry Ice trap contents by mass spectrometer and infrared showed that it contained *n*-butane. The liquid nitrogen trap contained largely ethane and ethylene in a ratio of 3:1, respectively. The methylene chloride extract of the aqueous layer was dried, and the volatile solvent was distilled in an efficient column at atmospheric pressure. After solvent removal was complete, there was obtained 4.3 g. (50%) of diethyl ketone, b.p. 96–98°. The infrared spectrum of this sample was identical to that of an authentic specimen of this ketone. The residue of this distillation yielded 3.2 g. (32%) of N-ethylpropionamide, b.p. 65° (0.5 mm.), $n^{20}D$ 1.4369. The infrared spectrum of this amide was also identical to that of an authentic specimen prepared from ethylamine and propionyl chloride.

The yield of ammonia was determined in a duplicate experiment. The aqueous solution was extracted with 50 ml. of ether, and the aqueous phase was made strongly alkaline and distilled. Titration of the volatile base showed that 0.127 mole was obtained. When corrected for the ethylamine produced in the hydrolysis of the amide and for the ammonia added as ferrous ammonium sulfate, this amounted to an ammonia yield of 0.055 mole (55%).

Reaction of 2-(α-Phenylethyl)-3,3-diethyloxazirane with Ferrous Ion.—The reaction of 15.7 g. (0.077 mole) of the oxazirane with 16 g. (0.04 mole) of ferrous ammonium sulfate in 150 ml. of distilled water was carried out as described above. In this case, however, the reaction was slower and no exotherm was observed. After 40 hr. of vigorous stirring at room temperature all of the oxazirane was destroyed. The gaseous product in the Dry Ice trap was *n*-butane. In the liquid nitrogen trap there was a mixture of ethane and ethylene and a trace of butane. The

(27) W. S. Lynn, L. A. Steel and E. Staple, *Anal. Chem.*, **28**, 132 (1956).

(28) R. Brown and W. E. Jones, *J. Chem. Soc.*, 781 (1946).

(29) J. J. Ritter and P. P. Minieri, THIS JOURNAL, **70**, 4045 (1948).

ethane–ethylene ratio in this case was 2:1. The aqueous layer was extracted with five 100-ml. portions of methylene chloride. The organic extract was dried with magnesium sulfate and evaporated. Distillation of the residual oil yielded a trace of acetophenone, b.p. 85° (12.0 mm.). In addition there was obtained 11.2 g. (81%) of N-α-phenylethylpropionamide, b.p. 121° (0.05 mm.), $n^{20}D$ 1.5262. This sample on standing at room temperature crystallized, m.p. 58–60°. An authentic specimen of the same amide was prepared by reaction of propionyl chloride with α-phenylethylamine and pyridine in ether solvent. The infrared spectra of the two amides were identical.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 75.03; H, 8.83; N, 7.33.

The yield of ammonia was again obtained from a duplicate experiment. In this case the aqueous mixture from the reaction was extracted with three 100-ml. portions of ether. The aqueous phase was made strongly alkaline and distilled. Titration of the distillate and correction for the ferrous ammonium sulfate initially added showed that 0.0015 mole (2%) of ammonia was produced in this reaction.

Reaction of 2-Isobutyl-3-isopropyloxazirane with Ferrous Ion.—A solution of 8.0 g. (0.02 mole) of ferrous ammonium sulfate in 100 ml. of distilled water was stirred 8 hr. with 14.3 g. (0.1 mole) of the oxazirane under helium. The effluent gases were passed through Drierite and collected in a liquid nitrogen trap. Mass spectrometer examination of the contents of this trap showed that approximately equivalent amounts of propane and propylene were obtained. After the reaction was complete, the aqueous solution was extracted continuously with ether for six days. Evaporation of the ether gave 8.5 g. (83%) of N-isobutylformamide, b.p. 60° (0.1 mm.), $n^{20}D$ 1.4388. The infrared spectrum and physical properties of this amide were identical to those of an authentic sample prepared from methyl formate and isobutylamine.

Reaction of 2-*t*-Butyl-3-isopropyloxazirane with Ferrous Ion.—A mixture of 16 g. (0.04 mole) of ferrous ammonium sulfate, 150 ml. of distilled water and 14.3 g. (0.1 mole) of the oxazirane was stirred under helium for 16 hr. The liquid nitrogen trap contained propylene and propane in a ratio of 3:1. Continuous ether extraction of the aqueous solution for six days gave 8.4 g. (82%) of N-*t*-butylformamide, b.p. 48° (0.2 mm.), $n^{20}D$ 1.4326. The infrared spectrum of this material was identical with that of authentic specimen.[30]

Pyrolysis of 2-*t*-Butyl-3-phenyloxazirane.—The vapor phase pyrolysis reactions were all carried out in a vertically mounted glass tube 3 cm. in diameter. The tube was packed with glass helices and was heated by a cylindrical furnace 30 cm. in length which was thermostatically controlled. The liquid sample was dripped in at the top of the tube, and a nitrogen stream (50 ml. of gas per minute) was used as the carrier. The effluent gases were condensed in ice and Dry Ice–acetone traps. The pyrolysis of 34.4 g. (0.2 mole) of 2-*t*-butyl-3-phenyloxazirane was carried out at 200° over a 2-hr. period. There was obtained in the Dry Ice trap 7.2 g. (60%) of fairly pure isobutylene. This material was characterized by its infrared spectrum which also showed that the product was contaminated by minor amounts of nitrous oxide, carbon dioxide and *t*-nitrosobutane. The ice trap contained 27 g. of fairly viscous liquid. This was dissolved in 100 ml. of methylene chloride and chromatographed over silica gel. Elution with 10% ethyl acetate in methylene chloride gave 8.8 g. (36%) of benzaldoxime, an intermediate fraction, and finally 4.1 g. (12%) of N-*t*-butylbenzaldoxime, m.p. 76°. The infrared spectra of these two compounds were identical to those of an authentic specimen.

Pyrolysis of 2-*t*-Octyloxazirane.—A 30.0-g. sample of this oxazirane was pyrolyzed at 200° over a 2-hr. period. Distillation of the product obtained gave 19.7 g. (66%) of N-*t*-octylformamide, b.p. 82° (0.5 mm.), $n^{20}D$ 1.4552. The infrared spectrum of this sample was identical with that of an authentic specimen. This isomerization was also carried out by heating 15 g. of the oxazirane in 50 ml. of dimethylformamide overnight at reflux. The dark mixture so obtained was poured into 200 ml. of water and extracted with three 300-ml. portions of methylene chloride. Evaporation of the solvent and distillation of the residual oil yielded 11.2 g. (75%) of N-*t*-octylformamide.

(30) J. J. Ritter and J. Kalish, THIS JOURNAL, **70**, 4048 (1948)

Pyrolysis of 2-Isobutyl-3,3-pentamethyleneoxazirane.—A 20.0-g. sample of this oxazirane was dripped into the pyrolysis tube at 300° over a 1-hr. period. The column was allowed to cool and rinsed with methylene chloride. The solvent was evaporated, and the viscous liquid so obtained was fractionated in the spinning band column. The product consisted of a trace of cyclohexanone and 16.5 g. (83%) of N-isobutyl caprolactam, b.p. 75° (0.7 mm.), $n^{20}D$ 1.4750. The infrared spectrum showed an amide carbonyl at 1642 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.11; H, 11.38; N, 8.19.

Pyrolysis of 2-*t*-Butyl-3-isopropyloxazirane.—Pyrolysis of 25.3 g. of this oxazirane over a 2-hr. period at 250° gave a solid–liquid mixture. The solid was collected on a filter and was identified as N-*t*-butylisobutyramide. The liquid filtrate was distilled at reduced pressure giving 3.2 g. (13%) of recovered oxazirane and a residue of solid N-*t*-butylisobutyramide. The total yield of amide amounted to 15.9 g. (63%), m.p. 118–120°. An authentic specimen of this amide was prepared from isobutyryl chloride and *t*-butylamine and was recrystallized from ligroin, m.p. 119–120°.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.23; H, 11.90; N, 9.58.

Pyrolysis of 2-Isobutyl-3-isopropyloxazirane.—A 20.0-g. sample of this oxazirane was pyrolyzed at 300° in the usual way. At the completion of the experiment the column was cooled and rinsed with methylene chloride. The volatile solvent was evaporated and the residual oil distilled in an efficient spinning band column. There was obtained a small forerun, 9.7 g. (48%), of N-isobutyl-N-isopropylformamide, b.p. 78–80° (3.0 mm.), $n^{20}D$ 1.4409, and 4.9 g. (24%) of N-isobutylisobutyramide, b.p. 85–88° (0.2 mm.). The latter compound crystallized on standing and melted at 43–45°. The infrared spectra of these two amides were identical to those of authentic samples (see below).

N-Isobutyl-N-isopropylformamide.—An 8.0-g. sample (0.07 mole) of N-isobutylisopropylamine was stirred in an ice-bath while 10.5 g. (0.07 mole) of chloral was added.[31] The mixture was allowed to stand overnight at room temperature. The product was dissolved in 50 ml. of methylene chloride and washed with 100 ml. of water. The organic extract was dried and evaporated to give 7.5 g. (74%) of N-isobutyl-N-isopropylformamide, b.p. 65° (1.0 mm.), $n^{20}D$ 1.4411.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.00; H, 11.70; N, 9.38.

N-Isobutylisobutyramide.—To a solution of 11.2 g. (0.11 mole) of isobutyryl chloride in 100 ml. of dry ether was added 14.6 g. (0.2 mole) of isobutylamine dropwise. After addition was complete the mixture was stirred under reflux 1 hr. The solution was then washed with 100 ml. of 20% sodium carbonate and dried. Evaporation of the volatile solvent gave 13.0 g. of N-isobutylisobutyramide, b.p. 82° (0.1 mm.), m.p. 43–45°.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.03; H, 12.01; N, 9.73.

Pyrolysis of 3-*n*-Propyl-3-methyl-3-isobutyloxazirane.—The pyrolysis of 100 g. of this oxazirane was carried out at 300° over a 4-hr. period. The product was fractionated in a spinning band column. After a small unidentified forerun there was obtained 67.0 g. (67%) of mixed amides, b.p. 85–87° (4.0 mm.). This mixture was shown by quantitative infrared techniques to consist of a mixture of N-methyl-N-*n*-propylisovaleramide (64%) and N-isobutyl-N-*n*-propylacetamide (36%). N-Methyl-N-propylisovaleramide was prepared by reaction of N-methylpropylamine with isovaleryl chloride in ether solution, b.p. 93° (5.0 mm.), $n^{20}D$ 1.4437.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.90. Found: C, 69.07; H, 12.21; N, 8.63.

N-Isobutyl-N-*n*-propylacetamide was prepared by reaction of acetic anhydride and N-isobutyl-*n*-propylamine, b.p. 91° (5.0 mm.), $n^{20}D$ 1.4440.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.90. Found: C, 68.70; H, 12.24; N, 8.70.

The infrared analysis was carried out on the pure liquids by using a fixed cell 0.025 mm. thick. The acetamide was

(31) F. F. Blicke and C. J. Lu, *ibid.*, **74**, 3933 (1952).

determined using the band at 9.58 μ and the isovaleramide the band at 11.93 μ by using the base line technique.

Pyrolysis of 3-*n*-Propyl-3-methyl-3-isopropyloxazirane.—The pyrolysis of 25.0 g. of this oxazirane was carried out as described above at 300°. The column was rinsed with 100 ml. of methylene chloride. The solution so obtained was washed with 50 ml. of water and 50 ml. of 10% sulfuric acid. The organic extract was then dried over magnesium sulfate and the volatile solvent evaporated. Distillation of the residual oil in the spinning band column gave 13.9 g. (56%) of mixed amides, b.p. 63–68° (6.0 mm.). Quantitative infrared analysis showed that the mixture consisted of N-*n*-propyl-N-isopropylacetamide (39%) and N-methyl-N-*n*-propylisobutyramide (61%). The acetamide was prepared from acetic anhydride and N-isopropyl-*n*-propylamine, b.p. 68–70° (5.0 mm.), $n^{20}D$ 1.4437.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.23; H, 12.17; N, 9.64.

The isobutyramide was prepared from isobutyryl chloride and N-methylpropylamine, b.p. 67° (5.5 mm.), $n^{20}D$ 1.4409.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.97; N, 9.78. Found: C, 67.27; H, 11.65; N, 9.84.

The quantitative analysis was again carried out on the pure amides in a 0.025 mm. cell using the base line technique. The isobutyramide was assayed by its band at 8.43 μ and the acetamide by its band at 9.74 μ.

Liquid Phase Pyrolysis of 2-*n*-Propyl-3-methyl-3-isobutyloxazirane.—A 27.6-g. (0.175 mole) sample of this oxazirane was heated to reflux (168°) under nitrogen. After a 2-hr. period the temperature had dropped to 128°. The effluent gases were passed over aqueous boric acid to remove any ammonia. Titration of the boric acid showed that 0.057 mole (0.33%) of ammonia was obtained. The liquid product was then distilled at atmospheric pressure through a Holzman column[32] to give 16.1 g. (92%) of methyl isobutyl ketone, b.p. 114–116°. The infrared spectrum of this sample was identical with that of an authentic specimen. The residual oil was distilled in a semi-micro spinning band column giving 0.8 g. of unreacted oxazirane, b.p. 43° (3.0 mm.), and 1.0 g. (4%) of mixed amides, b.p. 68–70° (3.0 mm.), very similar in composition to that obtained in the vapor phase pyrolysis of this oxazirane. The identities of these two fractions were based on their infrared spectra. From this distillation a black viscous residue was also obtained which was soluble in acid.

Liquid Phase Pyrolysis of 2-Isobutyl-3-isopropyloxazirane.—A 25.0-g. sample of this oxazirane was heated to reflux (165°) under nitrogen. After 3 hr. the pot temperature had dropped to 105°. The mixture was cooled and the aqueous phase was separated. The organic layer was dried over magnesium sulfate and fractionated. There was obtained 8.0 g. (32%) of N-isobutylideneisobutenylamine, b.p. 60° (47 mm.). The infrared spectrum of this compound was identical to that of an authentic sample prepared from anhydrous ammonia and isobutyraldehyde.[18] In addition there were higher boiling products obtained from the pyrolysis reaction but these could not be conveniently separated or characterized.

(32) C. W. Gould, G. Holzman and C. Nieman, *Anal. Chem.*, **20**, 361 (1948).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Hypotensive Agents. VI. 3- and 4-(3′-Aminopropyl)-piperidine Derivatives

BY ARTHUR P. PHILLIPS

RECEIVED JUNE 7, 1957

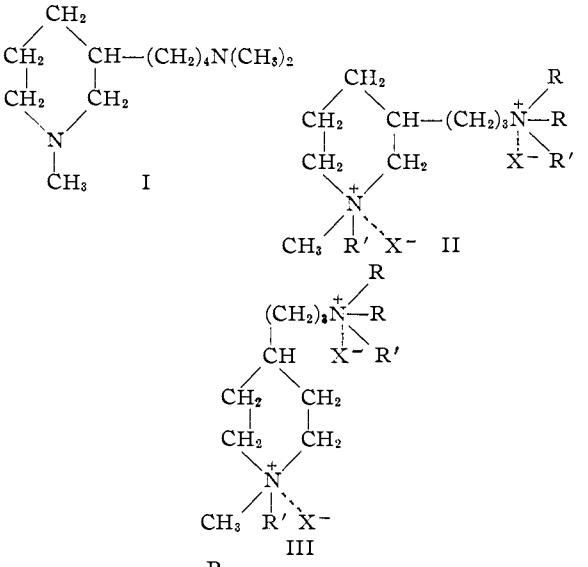
A series of 1-methyl-3(and 4)-(3′-tertiaryaminopropyl)-piperidines and their bis-quaternary ammonium salts have been made for testing as potential hypotensive ganglionic blocking drugs. Several members of this series have shown potencies equal to or greater than hexamethonium as ganglionic blockers in laboratory animals.

In continuation[1] of the investigation of compounds structurally related to 1-methyl-3-(4′-dimethylaminobutyl)-piperidine[2] (I) as potential hypotensive, ganglionic blocking agents, some 1-methyl-3(and 4)-(3′-aminopropyl)-piperidines (II and III) and their bis-quaternary salts have now been made and examined.

Quaternization of the 3-(3′-hydroxypropyl)-pyridine (IV) with methyl iodide gave the methiodide V readily. Attempts to hydrogenate the methiodide catalytically were unsatisfactory because of extremely slow and incomplete hydrogen uptake. After conversion to the chloride VI, catalytic hydrogenation over Adams catalyst proceeded rapidly and quantitatively to give VII.

Chlorination of the 1-methyl-3-(3′-hydroxypropyl)-piperidine hydrochloride (VII) using thionyl chloride gave the chloropropyl compound VIII readily and in excellent yield.

The bis-tertiary amines such as IX were obtained in good yields by heating the chloropropyl-piperidine hydrochlorides (VIII) for several hours with excess of the appropriate secondary amines. The secondary amines used were dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine. Addition of hydrogen chloride or refluxing



For II and III: $N\langle^{R}_{R}$ = $(CH_3)_2N$, $(C_2H_5)_2N$, pyrrolidino, piperidino and morpholino, etc.
R′X = HCl, CH_3I, C_2H_5I, etc.

(1) Paper V of this series: A. P. Phillips, THIS JOURNAL, **79**, 2836 (1957).

(2) A. P. Phillips, *ibid.*, **76**, 2211 (1954).