tive if measurement made after 2/1/56; negative if before), and $t_{1/2}$ is the half-life of tritium, 12.46×365 days.[33]

Absence of Diphenyl and Phenyl Benzoate in Benzoyl-*p*-*t* Peroxide.—To show that the 2% of phenyl benzoate and 0.15% of biphenyl in the decomposition products were not present as radioactive impurities in the original peroxide, a non-radioactive sample of each of these was added to benzoyl peroxide-*p*-*t*, reisolated, and analyzed for tritium.

Biphenyl (1.0284 g., 6.669 millimoles) and benzoyl peroxide-*p*-*t* (0.5185 g. 2.141 millimoles) were dissolved in 25 ml. of acetone. Five grams of sodium iodide and 1 ml. of concd. hydrochloric acid were added. Iodine formed was reduced with aqueous sodium thiosulfate. Water and chloroform were added, the chloroform layer separated and extracted with aqueous sodium bicarbonate. Evaporation of the chloroform gave biphenyl, which was recrystallized from water–ethanol and analyzed for tritium. Activity of this biphenyl was 9.46×10^{-7} curie per mole; that of benzoyl peroxide 19.25. Therefore the amount of radioactive biphenyl in the peroxide is 0.0153%. Therefore about 10% of the biphenyl isolated from decomposition products may have been in the starting peroxide.

Phenyl benzoate (0.9574 g., 4.830 millimoles) and benzoyl peroxide-*p*-*t* (0.5068 g., 2.092 millimoles) were mixed and the phenyl benzoate reisolated as above. Reisolated phenyl benzoate had an activity of 3.01×10^{-6} curie per mole, corresponding to 0.0361% radioactive phenyl benzoate in the starting peroxide. Therefore only 2% of the phenyl benzoate isolated from the decomposition products could have been in the peroxide used.

These two experiments also show that the method of removing undecomposed peroxide in the run stopped at 50% reaction did not form biphenyl or phenyl benzoate.

Stability of Phenyl Benzoate to Base.—To show that phenyl benzoate is not hydrolyzed by the sodium bicarbonate used to extract benzoic acid, approximately 1 g. of phenyl benzoate was dissolved in 1000 ml. of cyclohexane and extracted with two 50-ml. portions of aqueous sodium hydroxide (1 g. of sodium hydroxide in 50 ml. of solution). The water layers were combined, acidified with hydrochloric acid, and extracted with ethyl ether. Titration of the ether layer with $0.0155\ M$ sodium hydroxide showed that not more than 0.2% of the ester had been hydrolyzed.

Stability of Benzoyl Peroxide to Base.—Treatment of 0.596 g. of benzoyl peroxide in the same way with aqueous sodium bicarbonate showed that not more than 0.15% hydrolyzed. It was necessary to show this to know that the sodium bicarbonate used to extract benzoic acid in the run stopped at 50% reaction did not hydrolyze unreacted benzoyl peroxide.

Stability of Benzyl Benzoate to Base.—Approximately 1 g. of benzyl benzoate was dissolved in cyclohexane and extracted with aqueous sodium bicarbonate solution. The water layer was separated, acidified with hydrochloric acid and extracted with ether. Evaporation of the ether gave no visible precipitate of benzoic acid.

Acknowledgment.—We are indebted to Dr. Frederick D. Greene for helpful suggestions and discussion.

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[33] G. H. Jenks, F. H. Sweeton and J. A. Ghormley, *Phys. Rev.*, **80**, 990 (1950).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC CO.]

Nucleophilic Displacement Reactions in Aromatic Systems. III. The Rates of Reaction of 2,4-Dinitrochlorobenzene with *n*-Butylamine and with Hydroxide Ion in 50% Dioxane–50% Water

BY SIDNEY D. ROSS

RECEIVED MAY 10, 1958

The rates of reaction of 2,4-dinitrochlorobenzene with *n*-butylamine and sodium hydroxide, both separately and together, in 50% dioxane–50% water at 24.8 ± 0.1° have been measured. The results suggest but do not prove that the reaction with the amine is subject to catalysis by both *n*-butylamine and hydroxide ion.

Bunnett and his co-workers have claimed that the reaction of piperidine with 2,4-dinitrochlorobenzene in 95% ethanol is first-order and not a higher order in piperidine[1] and that added sodium hydroxide does not accelerate this same reaction in 50% dioxane–50% water.[2] It was further argued that these observations rigorously exclude the possibility of base-catalysis in this and similar systems.

Results from this Laboratory have shown that a complete description of the reaction of 2,4-dinitrochlorobenzene with both primary and secondary amines in chloroform and in ethanol requires two kinetic terms, one first-order in amine and the other second-order in amine.[3] In a more detailed study of the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine in chloroform it was further found that added triethylamine, which does not itself react with 2,4-dinitrochlorobenzene at an appreciable rate, nevertheless accelerates the rate of the reaction of the chloride with *n*-butylamine.[4] This latter result is in accord with a comparable, earlier observation made by Brady and Cropper[5] for the reaction of 2,4-dinitrochlorobenzene with methylamine in ethanol.

The pertinent measurements made by Bunnett, *et al.*, with 2,4-dinitrochlorobenzene and piperidine[1,2] were all with relatively low initial concentrations of both the amine (maximum concentration, $0.04\ M$) and sodium hydroxide (maximum concentration, $0.04\ M$). More important, neither the amine nor the hydroxide ion concentrations were varied appreciably. It has been our experience that for such experimental conditions third-order kinetic terms may very easily escape detection. This has raised doubts in our minds with respect to Bunnett's conclusions and led us to investigate the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine and with hydroxide ion, both separately and together, in 50% dioxane–50% water. *n*-Butylamine was used in preference to piperidine because it reacts with the chloride at a more conveniently measurable rate.

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[1] J. F. Bunnett and H. D. Crockford, *J. Chem. Ed.*, **33**, 552 (1956).

[2] J. F. Bunnett and K. M. Pruitt, *Elisha Mitchell Sci. Soc.*, **73**, 297 (1957).

[3] S. D. Ross and M. Finkelstein, THIS JOURNAL, **79**, 6547 (1957).

[4] S. D. Ross and R. C. Petersen, *ibid.*, **80**, 2447 (1958).

[5] O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

Experimental

The solvent, 50% dioxane–50% water, was made up by volume. The dioxane used was purified by the method of Eigenberger[6]; b.p. 101–102°. 2,4-Dinitrochlorobenzene and *n*-butylamine were purified as before.[3]

The procedure for the rate measurements also has been described.[3] Where both *n*-butylamine and sodium hydroxide were present simultaneously, the amine and sodium hydroxide were made up in one determinate solution and the chloride in another. The two solutions were then mixed at zero time.

Results and Discussions

In a reaction system containing 2,4-dinitrochlorobenzene, *n*-butylamine and sodium hydroxide there are four possible reactions that must be considered. These are: (a) the reaction between the chloride and the amine to form N-*n*-butyl-2,4-dinitroaniline, (b) this same reaction promoted by *n*-butylamine, (c) this same reaction promoted by hydroxide ion, (d) the reaction between 2,4-dinitrochlorobenzene and hydroxide ion to form 2,4-dinitrophenol.

If all four reactions were occurring simultaneously, the over-all rate expression would be given by

$$-\mathrm{d(A)}/\mathrm{d}t = \mathrm{d(Cl^-)}/\mathrm{d}t = k_1\mathrm{(A)(B)} + k_3\mathrm{(A)(B)}^2 + k_4\mathrm{(A)(B)(C)} + k_5\mathrm{(A)(C)} \quad (1)$$

where A is the chloride, B the amine and C hydroxide ion.

By previously described methods[3,4] the rate constants k_1 and k_3 may be determined from experiments with the chloride and the amine in the absence of hydroxide ion. The rate constant k_5 can be measured independently in experiments with 2,4-dinitrochlorobenzene and hydroxide ion alone. With these three constants available it is possible to measure the over-all rate of appearance of chloride ion, when both *n*-butylamine and hydroxide ion are present simultaneously, and calculate k_4.

The second-order rate constants for the reaction of *n*-butylamine with 2,4-dinitrochlorobenzene in 50% dioxane–50% water at 24.8 ± 0.1° are given in Table I. All of the runs were followed to at least 60% reaction and, as before,[3,4] individual runs gave satisfactory second-order plots. The rate constants, however, increase with increasing initial amine concentrations, with an almost 15-fold increase in the amine concentration resulting in a more than 28% increase in the rate constant. As shown in Fig. 1 a plot of the rate constants *vs.* the initial amine concentrations is linear. The least squares values for the intercept k_1 and the slope k_3 are 2.10 × 10^{-3} l.mole^{-1}sec.$^{-1}$ and 0.83 × 10^{-3} l.^{2} mole^{-2}sec.$^{-1}$, respectively.

TABLE I

RATES OF REACTION OF 2,4-DINITROCHLOROBENZENE AND *n*-BUTYLAMINE IN 50% DIOXANE–50% WATER AT 24.8 ± 0.1°

2,4-Dinitrochlorobenzene, mole/l.	*n*-Butylamine, mole/l.	$k \times 10^3$, l. mole^{-1} sec.$^{-1}$
0.01334	0.05042	2.12
.01291	.1004	2.18
.01280	.2008	2.31
.01310	.2490	2.31
.01267	.5011	2.50
.01298	.7470	2.72
.02512	.2970	2.32

Thus, in 50% dioxane–50% water, as well as in chloroform and in ethanol, both a second-order and a third-order term are required to fit the experimental data over any extensive range of amine concentrations. The rate expression is

$$\mathrm{d(Cl^-)}/\mathrm{d}t = k_1\mathrm{(A)(B)} + k_3\mathrm{(A)(B)}^2 \quad (2)$$

More reliable values for the two constants may be obtained by using this rate expression in its integrated form (3).

$$\frac{1}{t(B_0 - 2A_0)} \ln \frac{A_0B}{AB_0} - \frac{1}{t}\frac{k_3}{k_1}\left[\ln \frac{B_0}{B} - \ln \frac{B_0 + (k_1/k_3)}{B + (k_1/k_3)}\right] = k_1 + k_3[B_0 - 2A_0] \quad (3)$$

In applying equation 3 to the present data we first plotted (Cl$^-$) *vs.* *t* for each of the runs in Table I. Values of (Cl$^-$) for three different times in each run were then taken from the plots and used to calculate values of A and B for those times. In this way times ranging from 8 minutes to 120 minutes and reaction percentages ranging from less than 40% to more than 85% were included. The remaining procedure was as previously described,[4] except that in this case we used all twenty-one points rather than one point from each run at a single fixed time. The values that finally resulted were 2.21 × 10^{-3} l.mole^{-1} sec.$^{-1}$ for k_1 and 0.63 × 10^{-3} l.^{2} mole^{-2} sec.$^{-1}$ for k_3.

The need for this third-order rate constant, k_3, to describe fully the reactions of 2,4-dinitrochlorobenzene with primary and secondary amines is now certain. It has been demonstrated in three solvents and for four different amines. Nevertheless, its significance for the mechanism of the reaction is not clear. We have previously discussed this phase of the total reaction as a possible base-catalysis in which the second amine molecule facilitates the over-all reaction by assisting in the removal of a proton. However, neither the simple stoichiometry which we have demonstrated nor the rate studies which we have reported prove this hypothesis. It has been suggested that a general medium effect, linear with the amine concentration, might be a more likely interpretation,[7] particularly in more polar solvents such as ethanol, and in actual fact the rate measurements reported to date in no sense distinguish between these two possibilities. Except for the studies in chloroform, the proposed medium effect is the converse of what we would have anticipated. *n*-Butylamine has a dielectric constant of 5.3 at 21°[8] whereas chloroform has a dielectric constant of 4.806 at 20°.[9] High concentrations of the amine might, therefore, increase the polarity of this medium and accelerate the reaction, although it does seem improbable that this small increase in dielectric constant would account for the large rate effects that were observed. Ethanol, on the other hand, has a dielectric constant of 24.3 at 25°,[10] and 50% diox-

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[6] E. Eigenberger, *J. prakt. Chem.*, [2] **130**, 75 (1931).

[7] Private communication from J. F. Bunnett and J. J. Randall. We thank Dr. Bunnett for sending us copies of pertinent articles in advance of publication.

[8] H. S. Schlundt, *J. Phys. Chem.*, **5**, 503 (1901).

[9] A. O. Ball, *J. Chem. Soc.*, 570 (1930); H. O. Jenkins, *ibid.*, 480 (1934); R. M. Davies, *Phil. Mag.*, **21**, 1 (1936).

[10] J. Wyman, THIS JOURNAL, **53**, 3292 (1931); G. Akerlof, *ibid.*, **54**, 4125 (1932); R. J. W. Lefevre, *Trans. Faraday Soc.*, **34**, 1127 (1938).

ane–50% water has a dielectric constant of 53.43 at 20°.[11] In both these solvents the addition of *n*-butylamine would lower the dielectric constant of the medium, and the rate of the reaction might be expected to decrease rather than increase with increasing amine concentration. In this discussion the dielectric constants have been used as a qualitative guide to possible medium effects. It is, of course, recognized that the dielectric constant is neither a unique nor a completely reliable criterion for solvent effects.

In principle, equation 3 permits a choice between a third-order kinetic term and a medium effect. This requires a series of experiments with B_0 large and constant and A_0 small and varying. By selecting a time from each of several runs such that B is the same for all runs, k_1 and k_3 can be evaluated by equation 3. If k_3 results from a medium effect, its value, as determined in this manner, will be zero, since the media are all essentially the same. In practice, $(B_0 - 2A_0)$ should vary over a wide range, and, furthermore, a high order of precision of measurement and a k_3 much larger than k_1 are desirable. Thus far, we have been able to approach suitable conditions, but we have not yet had sufficient success to reach a definite conclusion.

The reaction between 2,4-dinitrochlorobenzene and *n*-butylamine is subject to a small, positive salt effect as shown in Table II. In the last column of Table II the experimental second-order rate constants have been expressed as first-order rate constants, since these will be used in the subsequent discussion. A plot of the rate constants *vs.* the sodium nitrate concentrations is linear and may be used to estimate rate constants at other salt concentrations.

TABLE II

SALT EFFECTS IN THE REACTION OF 2,4-DINITROCHLOROBENZENE AND *n*-BUTYLAMINE IN 50% DIOXANE–50% WATER AT 24.8 ± 0.1°

2,4-Dinitrochlorobenzene, mole/l.	*n*-Butylamine, mole/l.	Sodium nitrate, mole/l.	$k_2 \times 10^{-3}$, l. mole^{-1} sec.$^{-1}$	$k \times 10^4$, sec.$^{-1}$
0.01291	0.1004	0	2.18	2.19
.01342	.0992	.0786	2.24	2.22
.01285	.0998	.1572	2.27	2.27
.01261	.0991	.2363	2.33	2.31

Since reliable values for the rate of the reaction of 2,4-dinitrochlorobenzene with hydroxide ion at 24.8° in 50% dioxane–50% water were not available in the literature,[12] the measurements shown in Table III were made. The average value obtained for k_5 from the five measurements was 6.4×10^{-4} l.mole^{-1} sec.$^{-1}$. The maximum deviation from this average value was 6.3% and the average deviation was 2.2%. This reaction is, therefore, bimolecular. In these experiments the hydroxide ion concentration was varied almost fivefold, yet there is no indication that the rate constants either increase or decrease with increasing hydroxide ion concentrations. We conclude, therefore, that this reaction is not subject to an appreciable salt effect.

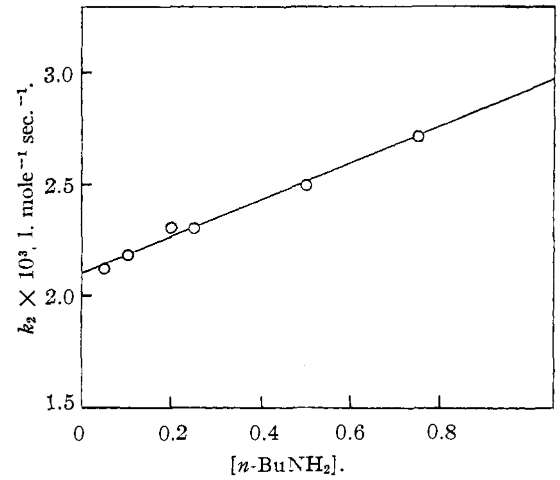

Fig. 1.—A plot of the second-order rate constants *vs.* the *n*-butylamine concentrations for the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine in 50% dioxane–50% water at 24.8 ± 0.1°.

TABLE III

RATES OF REACTION OF 2,4-DINITROCHLOROBENZENE WITH SODIUM HYDROXIDE IN 50% DIOXANE–50% WATER AT 24.8 ± 0.1°

2,4-Dinitrochlorobenzene, mole/l.	Sodium hydroxide, mole/l.	$k_5 \times 10^4$, l. mole^{-1} sec.$^{-1}$
0.02068	0.06175	6.4
.02164	.1544	6.3
.02055	.2413	6.4
.01935	.3017	6.2
.02044	.3088	6.8

In a system where 2,4-dinitrochlorobenzene is reacting simultaneously with both *n*-butylamine and hydroxide ion, the rate of chloride ion production is given by (1), and, at zero time, the specific rate k is given by

$$k = k_1(B_0) + k_3(B_0)^2 + k_4(B_0)(C_0) + k_5(C_0) \quad (4)$$

where k is the initial, first-order rate of chloride ion production, and k_1, k_3 and k_5 are the rate constants which have been determined. The term involving k_4 has been included intentionally, since it is our present purpose to determine whether or not this term is significant. The pertinent data are given in Table IV, and the experimental values for k are given in the fourth column. In determining these rate constants, the chloride ion concentrations produced were measured at various times until at least 60% reaction was attained in each run, and the initial rates were obtained by extrapolation to zero time. These extrapolations were straightforward, since the first-order plots were all linear to beyond 30% reaction and showed only minor deviations at higher reaction percentages. With k available, the only remaining unknown quantity in equation 4 is k_4, and this rate constant may now be calculated. The resultant values are given in the fifth column of Table IV. In making these calculations the values used were 2.21×10^{-3} l. mole^{-1} sec.$^{-1}$, 0.63×10^{-3} l.^{2} mole^{-2} sec.$^{-1}$ and

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(11) G. Akerlof and O. A. Short, THIS JOURNAL, **58**, 1241 (1936). The solvent composition in these measurements was by weight rather than by volume.

(12) The rate in 60% aqueous dioxane at 25.2° has been reported by J. F. Bunnett and G. T. Davis (*ibid.*, **76**, 3011 (1954)), and some estimates for the rate in 50% aqueous dioxane at 0° and at 45.95° have been made by Bunnett and Pruitt.[3]

TABLE IV

RATES OF REACTION OF 2,4-DINITROCHLOROBENZENE WITH *n*-BUTYLAMINE AND SODIUM HYDROXIDE IN 50% DIOXANE–50% WATER AT 24.8 ± 0.1°

2,4-Dinitrochlorobenzene, mole/l.	*n*-Butylamine, mole/l.	Sodium hydroxide, mole/l.	$k \times 10^4$, sec.$^{-1}$	$k_4 \times 10^4$, l.^{2} mole^{-2} sec.$^{-1}$	$k_4^* \times 10^4$ l.^{2} mole^{-2} sec.$^{-1}$
0.01326	0.09816	0.0603	2.62	0	1.7
.01312	.09909	.0741	2.67	Neg.	Neg.
.01293	.09903	.1207	3.21	15.9	12.0
.01312	.09856	.1481	3.32	8.9	7.5
.01278	.09915	.1810	3.63	12.3	10.6
.01317	.09867	.2222	3.85	8.7	5.9
.01333	.09932	.2413	4.00	8.8	7.5
.01248	.04955	.2500	2.85	10.5	

6.4×10^{-4} l. mole^{-1} sec.$^{-1}$ for k_1, k_3 and k_5, respectively.

Except for the two measurements at the lowest sodium hydroxide concentrations, where one k_4 is negative and the other zero, the values obtained are appreciable and of the same order of magnitude as k_3. However, even in those cases where the k_4's are positive, the contribution of the $k_4(B_0)(C_0)$ term to the total rate, k, is small and varies from 3.9 to 6.1%. This makes the zero and negative values at the lowest sodium hydroxide concentrations understandable, since in these experiments the contribution from the k_4 term probably is less than the experimental uncertainties involved.

This, of course, brings into question the reliability of even those experiments for which k_4 is positive, for, even under the most favorable conditions, we are still trying to determine a small difference between relatively large quantities. There is the possibility that the positive k_4 that we have obtained is really the result of a positive salt effect on k_1 and k_3. The data of Table II can be used to eliminate this explanation. These measurements were at approximately the same chloride and amine concentrations as the first seven experiments of Table IV and, since a plot of the first-order rate constants *vs.* the sodium nitrate concentrations is linear, we can use these data to estimate $k_1(B_0) + k_3(B_0)^2$ at any particular sodium hydroxide concentration. This assumes that sodium hydroxide and sodium nitrate will have equivalent salt effects on k_1 and k_3. Actually, sodium hydroxide might be expected to be less dissociated in 50% dioxane–50% water than sodium nitrate, since the hydroxide ion is smaller, and its charge is less distributed. By using these values for $k_1(B_0) + k_3(B_0)^2$, the k_4's shown in the last column of Table IV were calculated. At the two lowest sodium hydroxide concentrations the k_4 values are in one case small and in the other negative. The remaining values are not appreciably lower than those given in the fifth column of Table IV. These positive values for k_4 cannot, therefore, be attributed to a salt effect on k_1 and k_3.

These results, taken at their face value, suggest that the $k_4(B_0)(C_0)$ term is significant and that the reaction of 2,4-dinitrochlorobenzene with *n*-butylamine is subject to catalysis by hydroxide ion. They are not, however, sufficient to constitute clear proof of these contentions. We are not prepared to claim that we have demonstrated the fact of catalysis by hydroxide ion, but we would insist that, on the basis of the available evidence, the assertion that the reaction of 2,4-dinitrochlorobenzene with primary and secondary amines is not subject to hydroxide ion catalysis is unjustified.

Acknowledgment.—I am indebted to Dr. R. C. Petersen of these laboratories for many helpful and stimulating discussions.

NORTH ADAMS, MASS.

COMMUNICATIONS TO THE EDITOR

BISMETHYLENEDIOXY STEROIDS. II. SYNTHESIS OF 9α-METHYLHYDROCORTISONE AND 9α-METHYLPREDNISOLONE[1]

Sir:

Replacement of the hydrogen atom at C-9 in adrenocortical steroids by various substituents produces a pronounced effect on biological activity.[2] We felt that knowledge of the bioactivity of 9-methyl corticoids would advance the theory of how these effects are mediated. This communication outlines a synthesis of these difficultly accessible steroids.

Jones, Meakins and Stephenson[3] have reported the preparation of a 9α-methyl-Δ^7-11-ketosteroid by alkylation of a Δ^7-11-ketone with methyl iodide–potassium *t*-butoxide.

The initial compound in our synthesis, 9,11β-oxido-4-pregnene-17α-21-diol-3,20-dione[4] (I), was combined with formaldehyde–hydrobromic acid to give 9α-bromohydrocortisone-BMD (IIa): m.p. 170–190° (dec.); found C, 57.35; H, 6.34; $\lambda_{\max}^{\text{MeOH}}$ 243 mμ, *E* 15,500; $\lambda_{\max}^{\text{Nujol}}$ 2.7, 5.98, 6.1, 8.9–9.3 (BMD)μ. Oxidation of IIa with chromic acid in tetrahydrofuran–acetic acid or pyridine gave 9α-bromocortisone-BMD (IIb): m.p. 205–210° (dec.); found C, 57.48; H, 5.97; $\lambda_{\max}^{\text{MeOH}}$ 238 mμ, *E* 15,800; $\lambda_{\max}^{\text{Nujol}}$ 5.80, 5.91, 6.1, 9.0–9.2μ. Reaction of IIb with ethylene glycol-*p*-toluenesulfonic acid yielded 9α-bromocortisone-BMD-3-dioxolane (IIIa): m.p. 190–195°, 215–220° (dec.); found C, 57.48; H, 6.04; $\lambda_{\max}^{\text{Nujol}}$ 5.87, 8.9–9.3μ.

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[1] Paper I in this series: R. E. Beyler, R. M. Moriarty, Frances Hoffman and L. H. Sarett, THIS JOURNAL, **80**, 1517 (1958).

[2] J. Fried, *Ann. N. Y. Acad. Sci.*, **61**, 573 (1955).

[3] E. R. H. Jones, G. D. Meakins and J. S. Stephenson, *J. Chem. Soc.*, 2156 (1958).

[4] J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).