[CONTRIBUTION FROM THE EDGAR C. BRITTON RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Ammonolysis of 2,5-Dichlorovaleric Acid and Some Related Chloro Acids

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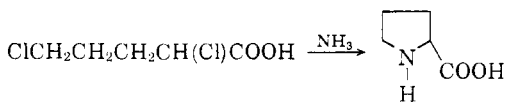
Received October 16, 1961

The reaction of 2,5-dichlorovaleric acid with ammonia yields 2-tetrahydrofuramide in addition to proline. 5-Hydroxyvaleramide was isolated in 74% yield from the ammonolysis of 5-chlorovaleric acid. The relative rates of chloride release from 2,5-dichlorovaleric acid, 5-chlorovaleric acid, 2-chlorovaleric acid, and 9-chlorononanoic acid in aqueous ammonia at 29.2° are 8.1 to 28.6 to 1 to 6.5. The terminal chloro group in 2,5-dichlorovaleric acid is about six times more reactive toward displacement by ammonia than is the α-chloro group.

The cyclization of 1,4-dihalo compounds to five-membered nitrogen heterocycles on reaction with amines is a well documented reaction.[1] Treatment of 2,5-dihalovaleric acids with ammonia and amines falls in this category and there have appeared in the literature numerous examples in which pyrrolidine carboxylic acids have been prepared in this manner.[2] Although this method provides a convenient route to proline (pyrrolidine-2-carboxylic acid), the yields reported have been in the range 10–55%. No evidence of 2,5-diaminovaleric acid has been obtained in these reactions.



This indicates that the amino group formed by displacement of the first halo group competes successfully with ammonia in displacement of the second halo group. Reasonably, intramolecular five-membered ring closure occurs faster than intermolecular displacement. Two points of interest arise concerning the ammonolysis of 2,5-dihalovaleric acids: (1) the moderate yields of proline imply that perhaps substantial yields of by-products are formed in the reaction, and (2) it may be possible to determine the difference in reactivity between the two halo groups toward ammonia. Our study of the reaction with ammonia of 2,5-dichlorovaleric acid and the model compounds 2-chlorovaleric acid, 5-chlorovaleric acid, and 9-chlorononanoic acid was undertaken with the objective of elucidating these two points.

EXPERIMENTAL

1,1,5-Trichloropentene. 1,1,1,5-Tetrachloropentane (b.p. 106–110°/20 mm.) was dehydrohalogenated with ferric chloride according to the directions given by Nesmejanov, Friedlina, and Zakharin.[3] An 82% yield of 1,1,5-trichloropentene, $n^{20}D$ 1.4888, was obtained and shown to be one component by vapor phase chromatography.

2,5-Dichlorovaleric acid. 1,1,5-Trichloropentene was chlorinated and hydrolyzed concurrently according to the directions given by Nesmejanov, Kose, and Friedlina.[4] The fraction boiling at 98–115°/4 mm., $n^{22.5}D$ 1.4806, neut. equiv. 176 (theory: 171), was used for the kinetic runs.

Anal. Calcd. for $C_5H_8O_2Cl_2$: C, 35.11; H, 4.72; Cl, 41.46. Found: C, 34.80; H, 4.52; Cl, 41.3.

Reaction of 2,5-dichlorovaleric acid with ammonia. 2,5-Dichlorovaleric acid reacted with concd. aqueous ammonia under the conditions listed in Table I. Usually 100 ml. of ammonia solution was used per 0.05 mole of 2,5-dichlorovaleric acid and the reactions were run in a stainless steel bomb. At the end of the reaction, an aliquot was titrated with silver nitrate for the amount of inorganic chloride liberated. The solution was evaporated to dryness under reduced pressure and extracted with chloroform. Evaporation of the chloroform extracts left a white, water-soluble solid (9–23% yield) which had a *p*H of 3.7 in deionized water, gave a negative ninhydrin test and contained no organic or inorganic chloride. Sublimation at 80–85°/0.5 mm gave white platelets, m.p. 78.5–81.5°. Infrared absorption indicated that it was a primary amide and possessed a C—O—C stretch of the same frequency as tetrahydrofuran. It was

TABLE I

AMMONOLYSIS OF 2,5-DICHLOROVALERIC ACID[a]

Temp.	Presence of Solvent or Cupric Ion in Addition 30% Ammonia	% Yield: Ammonium chloride	% Yield: Tetrahydrofuramide isolated	% Yield: Proline
100	Benzene	71[c]	26	47[e]
100	Benzene	98[d]	23	70[d]
100	Methanol, Cu^{++}	95[d]	13	—
60	Benzene, Cu^{++}	98[d]	13	53[e]
100	—	99.5[d]	13	—
60	Liq. NH_3 only	51[c]	9.2	—
25	—	101[c]	10	53[d], 30[c]

[a] One hundred milliliters of aqueous ammonia per 0.05 mole of 2,5-dichlorovaleric acid was used. In those runs in which benzene or methanol was a component, 100 ml. of these solvents was added. [b] The cupric salt was made by the reaction of 2,5-dichlorovaleric acid with an equivalent of cupric hydroxide. [c] By isolation. [d] By titration. [e] By isolation as copper complex.[2f]

(1) C. Hollins, "The Synthesis of Nitrogen Ring Compounds," Ernest Benn Ltd., London, 1924, p. 65.

(2) (a) R. Willstatter, *Ber.*, **33**, 1160 (1900). (b) E. Fischer, *Ber.*, **34**, 454 (1901). (c) E. Fischer and V. Suzuki, *Ber.*, **37**, 2843 (1904). (d) M. Frankel and S. Kuk, *Biochem. Z.*, **226**, 221 (1930). (e) R. Willstatter and F. Ettlinger, *Ann.*, **326**, 91 (1903). (f) R. Gaudry and L. Berlinguet, *Can. J. Research*, **27B**, 282 (1949). (g) R. Paul, *Compt. rend.*, **212**, 398 (1941). (h) A. Nesmejanov, R. Friedlina, and R. Petrova, *Acad. Sci. USSR, Bull.*, 459 (1957). English translation. (i) A. Nesmejanov *et al.*, *Chemische Technik*, **9**, 139 (1957).

(3) A. Nesmejanov, R. Friedlina, and L. Zakharin, *Doklady Akad. Nauk, SSSR*, **96**, 87 (1954).

(4) A. Nesmejanov, V. Kose, and R. Friedlina, *Doklady Akad. Nauk, SSSR*, **103**, 109 (1955).

demonstrated by infrared absorption that this compound was not 5-hydroxyvaleramide which could have arisen if 5-chlorovaleric acid had been a contaminant in 2,5-dichlorovaleric acid. These data, together with the elemental analysis, indicate the structure of the chloroform-soluble compound to be 2-tetrahydrofuramide, a known compound, m.p. 80.°[5]

Anal. Calcd. for $C_5H_9O_2N$: C, 52.17; H, 7.88; N, 12.17. Found: C, 52.33; H, 7.61; N, 12.05.

The chloroform-insoluble portion of the reaction mixture presumably contained ammonium chloride and proline. In some instances the amount of proline was determined as follows: Initially the amount of ammonium chloride was determined by titration with 0.1000 *N* silver nitrate. Another sample was used to run a formol titration. The difference between these two values gave the amount of proline in the mixture. In one case, proline was isolated as the copper chelate according to the directions of Gaudry and Berlinguet.[2f] Proline was most conveniently isolated after ion exchange chromatography on Dowex-50W-H^+ in about 30% yield. Recrystallization from ethanol–ether yielded white, crystalline proline.

2-Chlorovaleric acid. 2-Chlorovaleric acid was redistilled through a Vigreux column to give material, b.p. 105°/8 mm., neutralization equivalent 140 (theory: 138).

Anal. Calcd. for $C_5H_9O_2Cl$: C, 44.0; H, 6.65; Cl, 26.0. Found: C, 44.37; H, 6.52; Cl, 25.5.

5-Chlorovaleric acid. 5-Chlorovaleric acid for the kinetic measurements was prepared by hydrolysis of ethyl 5-chlorovalerate. Distillation gave 5-chlorovaleric acid with neutralization equivalent 141 (theory: 138).

Anal. Calcd. for $C_5H_9O_2Cl$: C, 44.0; H, 6.65; Cl, 26.0. Found: C, 43.99; H, 6.47; Cl, 25.9.

5-Chlorovaleric acid had also been prepared by us in 70–80% yield according to directions given in the literature.[6,2i]

9-Chlorononanoic acid. 9-Chlorononanoic acid was prepared from 1,1,1,9-tetrachlorononane.[2i,6] The fraction boiling at 108–112°/0.10 mm. (neut. equiv., 196.2; theory, 192.7; $n^{25}D$ 1.4570) was used in the kinetic studies.

Anal. Calcd. for $C_9H_{17}O_2Cl$: C, 56.10; H, 8.89; Cl, 18.40. Found: C, 56.09; H, 8.71; Cl, 18.41.

Preparation of rate solutions. Concd. aqueous ammonia was used as solvent and displacing agent. Somewhat more than 200 ml. of aqueous ammonia was placed in a 200 ml. volumetric rubber-stoppered flask, and the flask was placed in a constant temperature water bath held at 29.2 ± 0.1° and allowed to come to temperature. Titration of the ammonia at this point showed it to be 13.3 *N*. Approximately 25 ml. of the solution was poured out of the volumetric flask, a weighed amount of chloroacid was added, and a sufficient amount of the aqueous ammonia was used to rinse and bring the solution up to the 200 ml. mark.

Amounts of chloroacids used:

5-Chlorovaleric acid	6.8276 g. (5.006×10^{-2} mole)
2-Chlorovaleric acid	6.8290 g. (5.000×10^{-2} mole)
2,5-Dichlorovaleric acid	8.4640 g. (4.914×10^{-2} mole)

Kinetic measurement. At appropriate time intervals, a 5-ml. sample of the solution was pipetted from the reaction flask and added directly to a mixture of 15 ml. of 5 *N* nitric acid and ice to quench the reaction. The time recorded was that of half addition to the acid–ice mixture. Titration for chloride ion with 0.1000 *N* silver nitrate was made using a MacBeth titration-*p*H meter and the results are given in Table II.

5-Hydroxyvaleramide from 5-valerolactone and ammonia. 5-Hydroxyvaleramide, m.p. 103.5–106.5°, (lit., m.p. 107–107.5[7]) was obtained from 5-valerolactone and aqueous ammonia and used as a known compound for comparison with the product obtained from 5-chlorovaleric acid and ammonia.

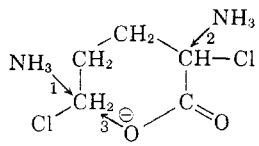
Pyrolysis of 5-hydroxyvaleramide. In a semimicro distillation apparatus was heated with a small flame 5.00 g. (4.27×10^{-2} mole) of 5-hydroxyvaleramide. After melting, a colorless liquid distilled accompanied by a strong ammonia odor. The product (4.00 g.) contained a small amount (0.50 g.) of white solid which was starting material that was carried over during distillation and removed by filtration. An infrared spectrum of the liquid (3.50 g., 93%) suggested it to be valerolactone.

Anal. Calcd. for $C_5H_8O_2$: C, 60.00; H, 8.06; N, 0. Found: C, 58.50; H, 8.11; N, 0.49.

Isolation of 5-hydroxyvaleramide from the reaction of 5-chlorovaleric acid and ammonia. From the reaction between 5-chlorovaleric acid (6.8376 g., 5×10^{-2} mole) and aqueous ammonia (total volume of solution: 200 ml.) for which kinetic measurements were made, there was left 58 ml. of solution. After allowing it to remain at 29.2° for 2 days, the solution was evaporated under reduced pressure to leave 2.68 g. (theory: 2.48 g.) of white crystalline material which was repeatedly extracted with chloroform. Evaporation of the chloroform extracts yielded 1.24 g. (74%) of white solid, m.p. 95–100°, mixed m.p. with 5-hydroxyvaleramide (m.p. 103.5–106.5,° made from valerolactone and ammonia) was 98–105°. Comparison of the infrared absorption curves of 5-hydroxyvaleramide from the two sources showed them to be essentially identical. The chloroform-insoluble portion (1.130 g.) was titrated for inorganic chloride ion and found to contain 90% of the theoretical amount of chloride ion expected in 58 ml. of solution; hence the original residue was 70% ammonium chloride. Infrared absorption suggested that the remainder consisted of a very small amount of amino acid and some amide whose spectrum was not identical with 5-hydroxyvaleramide.

RESULTS AND DISCUSSION

Product analysis. In the presence of ammonia, the first chloro group can be displaced from 2,5-dichlorovaleric acid by three major reaction paths: (1) attack by ammonia on the terminal carbon, (2) attack by ammonia on the α-carbon, and (3) intramolecular attack by carboxylate anion on the terminal carbon. 9-Chlorononanoic acid, 2-chloro-



valeric acid and 5-chlorovaleric acid were chosen as model compounds to separate these three modes of reaction.[8] From 9-chlorononanoic acid and ammonia, 9-aminononanoic acid has been isolated in 80% yield.[2i] This suggests a relatively clean attack by ammonia at the terminal position. The likelihood of intramolecular carboxylate attack with ten-membered lactone formation seems remote and hence 9-chlorononanoic acid provides a model for attack by ammonia on a primary alkyl chloride.

(5) H. Wienhans and H. Sorge, *Ber.*, **46**, 1930 (1927).

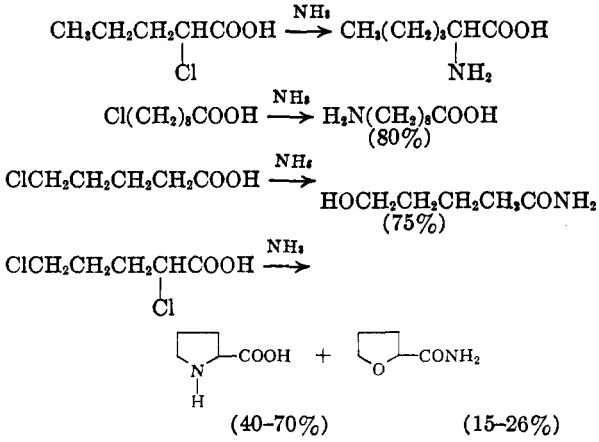
(6) R. Joyce, W. Hanford, and J. Harmon, *J. Am. Chem. Soc.*, **70**, 2529 (1948).

(7) E. Goodings and C. Wilson, *J. Am. Chem. Soc.*, **73**, 4794 (1951).

(8) The formation of noncyclic secondary amines has been omitted in this discussion on the ground that it should be approximately the same for any given position on 2,5-dichlorovaleric acid and the corresponding model compound and hence should not detract from the validity of comparison.

CHART I

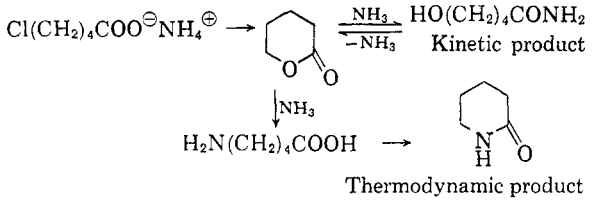
AMMONOLYSIS OF CHLORO ACIDS



Although no product was isolated in this work from the ammonolysis of 2-chlorovaleric acid, alanine has been formed in about 80% analyzed yield from the ammonolysis of 2-chloropropionic acid.[9] A model for the third mode of attack is the reaction of 5-chlorovaleric acid and ammonia from which we have isolated 5-hydroxyvaleramide in 74% yield. Intramolecular carboxylate attack on the terminal chloro group forms valerolactone which reacts at the carbonyl group with ammonia to give 5-hydroxyvaleramide.[10]

(9) N. D. Cheronis and K. H. Spitzmueller, *J. Org. Chem.*, 6, 349 (1941).

(10) 5-Hydroxyvaleramide, identical with the product obtained from the reaction of valerolactone and ammonia, has not been previously isolated from the reaction of 5-chlorovaleric acid and ammonia. Ammonolysis at room temperature yields only a small amount of 5-aminovaleric acid, *cf.*, Nesmejanov *et al.*[21] At 250° in the course of 8–10 hours, a 93% yield of α-piperidone is formed from 5-chlorovaleric acid and ammonia.[21] We have found that 5-hydroxyvaleramide reverts to valerolactone and ammonia on heating. These facts suggest the reaction path is that shown below:



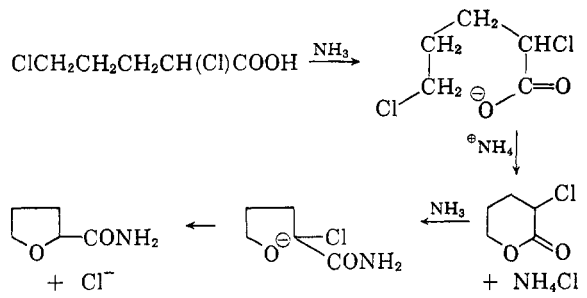
Thermodynamic product

Attack at the carbonyl group is kinetically favored. However, the product usually isolated in the reaction of five- and six-membered lactones with nucleophiles such as $HS^{\ominus}$, $PhS^{\ominus}$, $CN^{\ominus}$ is that in which attack has occurred at the terminal aliphatic carbon. The initial product, *e.g.*, $HO(CH_2)_4COSPh$ possibly is too unstable relative to lactone and $PhS(CH_2)_4COOH$ to allow easy isolation.[11] Ammonia differs from the above nucleophiles in that the product arising from attack on the carbonyl group is sufficiently stable to permit its isolation in good yield.

(11) A. Nesmejanov and L. Zekharkin, *Isvest. Akad. Nauk. USSR, Otdel. Khim. Nauk*, 224 (1955); *Bull. Acad. Sci., USSR Div. Chem. Sci.*, 199 (1955), (English translation).

CHART II

A PATH FOR THE FORMATION OF 2-TETRAHYDROFURAMIDE



From the reaction of 2,5-dichlorovaleric acid and ammonia there were isolated two products, proline (III) (40–70% yield) and 2-tetrahydrofuramide (IV) (10–26% yield). Reaction conditions are listed in Table I. A reaction sequence for the production of 2-tetrahydrofuramide is shown in Chart II and is patterned after the behavior of 5-chlorovaleric acid.

It should be noted that ammonia in solution is not only a poor competitor in displacing the second chloro group from x-chloro-y-aminovaleric acid but also ineffective in displacing directly the chloro group from α-chlorovalerolactone. No 5-hydroxy-2-aminovaleramide, the product from such a displacement, was found.

Rate analysis. Comparison of the rates of chloride ion appearance from the four acids is made in Table II. If in 2,5-dichlorovaleric acid, the three reaction paths are treated as independent, concurrent, pseudo first-order reactions,[12] then the rate of chloride ion appearance can be thought of as being the sum of the rates of chloride ion displacement by ammonia at the 2- and 5-positions and carboxylate displacement at the 5- position. The following breakdown may be made:

TABLE II

RELATIVE RATES OF CHLORIDE ION RELEASE AT 29.2 ± 0.1°

	$k_1 \times$ min.	Relative Rate
$Cl(CH_2)_4COOH$	$2.67 \pm 0.4 \times 10^{-3}$	28.6
$Cl(CH_2)_5COOH$	$6.00 \pm 0.3 \times 10^{-4}$	6.5
$CH_3(CH_2)_2CH(Cl)COOH$	$9.24 \pm 0.2 \times 10^{-5}$	1
$Cl(CH_2)_3CH(Cl)COOH$	$7.46 \pm 0.14 \times 10^{-4}$ ($\times 2$)[a]	8.1 ($\times 2$)[a]

[a] To obtain first-order kinetics for 2,5-dichlorovaleric acid, the amount of chloride ion present at any time was divided by two; hence the real rate of chloride ion appearance is $2k_1$. The second chloride ion per molecule is apparently displaced more rapidly than the first.

(12) A. Frost and R. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, 1953, p. 147.

7.46×10^{-4} min.$^{-1}$	Total rate of 2,5-dichlorovaleric acid
-0.92×10^{-4} min.$^{-1}$	Rate due to displacement of 2-chloro group (rate of 2-chlorovaleric acid)
6.54×10^{-4} min.$^{-1}$	Sum of displacement of 5-chloro group by ammonia and by α-chlorocarboxylate anion
-6.0×10^{-4} min.$^{-1}$	Rate due to displacement of 5-chloro group by ammonia (rate of 9-chlorononanoic acid)
5.4×10^{-5} min.$^{-1}$	Rate due to displacement of 5-chloro group by α-chlorocarboxylate anion

From this and the rate of chloride appearance from 5-chlorovaleric acid, one may conclude that the nucleophilicity of carboxylate anion is roughly forty times greater $\left(\frac{2.07 \times 10^{-3}}{5.4 \times 10^{-5}}\right)$ than that of α-chlorocarboxylate anion in attacking the 5-position intramolecularly.[13] The lowered yield of product (2 - tetrahydrofuramide) from 2,5 - dichlorovaleric acid compared to that (5-hydroxyvaleramide) from 5-chlorovaleric acid due to carboxylate attack may be rationalized on this basis. Further, the ratio of displacement by ammonia on the 5- and 2- positions is about six to one $\left(\frac{6.0 \times 10^{-4}}{9.2 \times 10^{-5}}\right)$ and hence, six times as much proline is formed by initial ammonia attack on the terminal as on the alpha carbon atom.

Acknowledgment. We are indebted to Dr. W. Potts for infrared spectral data and interpretation and to Dr. S. Shrader and associates for microanalyses.

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(13) This conclusion is tenuous since it is based on the subtraction of two large numbers. The order of magnitude is probably correct, however, because nucleophilicity parallels basicity in most cases. The electrolytic dissociation constants for valeric acid[14] and 2-chlorobutyric acid[15] at 25° are 1.50×10^{-5} and 1.39×10^{-3}, respectively, a factor of about 90 in basicity.

(14) E. Franke, *Z. Phys. Chem.*, **16A**, 483 (1895).

(15) D. Lichty, *Ann.* **319**, 380 (1901).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF STEVENS INSTITUTE OF TECHNOLOGY]

Studies on Lactams. III.[1] Mechanism of Cyclization

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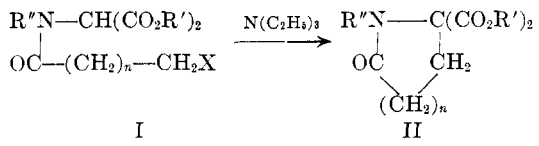
Received November 10, 1961

The cyclization of diethyl *N*-(α,β-dibromo)propionylanilinomaolonate with triethylamine led exclusively to a γ-lactam In an analogous experiment a β-lactam was formed exclusively in preference to a δ-lactam. It was found that the amides from the *N*-acylation of diethyl anilinomalonate with (substituted) acrylic acids do not cyclize in presence of a base. On the basis of this and other observations, it was possible to conclude that a β-haloacylaminomalonate cyclizes by intramolecular alkylation rather than through an internal Michael addition.

In a previous publication[1] it was shown that the cyclization of ω-haloacylaminomalonic esters (I) in presence of a base proceeds in high yield when $n = 0$ or 1, but when $n = 2$ or 3, no cyclization takes place. Since, in general, six-membered and five-membered rings are formed more easily than



I II

four-membered rings, it seemed to be of interest to further investigate this type of cyclization.

The first point to be studied was the relative ease of formation of four- and five-membered lactams under competitive conditions. Diethyl *N*-(α,β-dibromo)propionylanilinomalonate (IV) was prepared by the acylation of diethyl anilinomalonate (III) with α,β-dibromopropionic acid in the presence of phosphorus trichloride. When a benzene solution of IV was treated with triethylamine at room temperature, there was a ready separation of triethylamine hydrobromide. The product VI (83% yield) from this reaction appeared to be essentially homogeneous. A comparison of the NMR spectra of the recrystallized material and the mother liquor confirmed the absence of any other product.

The product from the cyclization of IV could be either the β-lactam VIb or the γ-lactam VIa. Both infrared and NMR spectra were compatible with the latter structure. For further confirmation VI was hydrogenated in presence of a palladium catalyst to a halogen-free liquid VII. An unequivocal decision between the alternative structures VIIa and VIIb was possible on the basis of the NMR spectrum. The absence of a split methyl

(1) (a) Presented at the 140th Meeting of the American Chemical Society, Chicago, Ill., September 1961. (b) Part I, A. K. Bose, B. N. Ghosh-Mazumdar, and B. G. Chatterjee, *J. Am. Chem. Soc.*, **82**, 2382 (1960). (c) Part II, A. K. Bose, M. S. Manhas, and B. N. Ghosh-Mazumdar, *J. Org. Chem.*, **27**, 1458 (1962).

(2) On leave of absence from the University of Saugar, India.