

Advances in Heterocyclic Chemistry

By A. R. KATRITZKY

Volume 3

Advances in
HETEROCYCLIC
CHEMISTRY

Edited by

A. R. KATRITZKY

*School of Chemistry
University of East Anglia
Norwich, England*

Assistant Editors

A. J. BOULTON

*University of East Anglia
Norwich, England*

J. M. LAGOWSKI

*The University of Texas
Austin, Texas*



Volume 3

Academic Press • New York and London • 1964

COPYRIGHT © 1964, BY ACADEMIC PRESS INC.

ALL RIGHTS RESERVED.

NO PART OF THIS BOOK MAY BE REPRODUCED IN ANY FORM,
BY PHOTOSTAT, MICROFILM, OR ANY OTHER MEANS, WITHOUT
WRITTEN PERMISSION FROM THE PUBLISHERS.

ACADEMIC PRESS INC.

111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

PRINTED IN THE UNITED STATES OF AMERICA

Contributors

Numbers in parentheses indicate the pages on which the author's contribution begins.

- R. A. ABRAMOVITCH, *University of Saskatchewan, Saskatoon, Saskatchewan, Canada* (79)
- G. F. DUFFIN, *Minnesota 3M Research Limited, Pinnacles, Harlow, Essex, England* (1)
- GABRIELLO ILLUMINATI, *Department of Chemistry, University of Rome, Rome, Italy* (285)
- H. H. JAFFÉ, *Department of Chemistry, University of Cincinnati, Cincinnati, Ohio* (209)
- K. A. JENSEN, *Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen, Copenhagen, Denmark* (263)
- H. LLOYD JONES, *Department of Chemistry, University of Cincinnati, Cincinnati, Ohio* (209)
- C. PEDERSEN, *Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen, Copenhagen, Denmark* (263)
- C. W. REES, *King's College, Strand, London, England* (57)
- C. E. SMITHEN, *Research Department, Roche Products Limited, Welwyn Garden City, Herts, England* (57)
- IAN D. SPENSER, *Department of Chemistry, McMaster University, Hamilton, Ontario, Canada* (79)
- IVAR UGI, *Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer, A.G., Leverkusen, Germany* (373)

Preface

The third volume of this series covers three specific groups of compounds: the carbolines (reviewed by R. A. Abramovitch and I. D. Spenser), the thiatriazoles (K. A. Jensen and C. Pedersen), and the pentazoles (I. Ugi). The remaining four chapters deal with topics of general chemical interest from the heterocyclic viewpoint: the quaternization of heterocyclics (G. F. Duffin), carbene reactions (C. W. Rees and C. E. Smithen), applications of the Hammett equation (H. H. Jaffé and H. Lloyd Jones), and some aspects of the nucleophilic substitution of heterocyclic azines (G. Illuminati).

Suggestions for contributions to subsequent volumes of the series are welcomed; they should be submitted in the form of a short synopsis.

Thanks are due to the authors for their cooperation, the members of the Editorial Board, and the publishers. I am especially grateful to the assistant editors, Dr. A. J. Boulton and Dr. J. M. Lagowski, for all their help.

A. R. KATRITZKY

Norwich, England
April, 1964

Contents of Volume 1

Recent Advances in the Chemistry of Thiophenes

SALO GRONOWITZ

Reactions of Acetylenecarboxylic Acids and Their Esters with
Nitrogen-Containing Heterocyclic Compounds

R. M. ACHESON

Heterocyclic Pseudo Bases

DÉNES BEKE

Aza Analogs of Pyrimidine and Purine Bases of Nucleic Acids

J. GUT

Quinazolines

W. L. F. ARMAREGO

Prototropic Tautomerism of Heteroaromatic Compounds: I. General
Discussion and Methods of Study

A. R. KATRITZKY AND J. M. LAGOWSKI

Prototropic Tautomerism of Heteroaromatic Compounds: II. Six-
Membered Rings

A. R. KATRITZKY AND J. M. LAGOWSKI

Contents of Volume 2

Prototropic Tautomerism of Heteroaromatic Compounds: III. Five-Membered Rings and One Hetero Atom

A. R. KATRITZKY AND J. M. LAGOWSKI

Prototropic Tautomerism of Heteroaromatic Compounds: IV. Five-Membered Rings with Two or More Hetero Atoms

A. R. KATRITZKY AND J. M. LAGOWSKI

Three-Membered Rings with Two Hetero Atoms

ERNST SCHMITZ

Free-Radical Substitutions of Heteroaromatic Compounds

R. O. C. NORMAN AND G. K. RADDA

The Action of Metal Catalysts on Pyridines

G. M. BADGER AND W. H. F. SASSE

Recent Advances in Quinoxaline Chemistry

G. W. H. CHEESEMAN

The Reactions of Diazomethane with Heterocyclic Compounds

RUDOLF GOMPPER

The Acid-Catalyzed Polymerization of Pyrroles and Indoles

G. F. SMITH

1,3-Oxazine Derivatives

Z. ECKSTEIN AND T. URBĄSKI

The Present State of Selenazole Chemistry

E. BULKA

Recent Developments in Isoxazole Chemistry

N. K. KOCHETKOV AND S. D. SOKOLOV

ERRATA

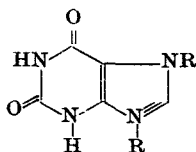
In Volume 1, in the chapter on Prototropic Tautomerism by A. R. Katritzky and J. M. Lagowski,
p. 326, the equation should read

$$K_T = \frac{K_1}{K_{(\text{HXM}^+)}} - 1 = \frac{K_{(\text{MeXH}^+)}}{K_1 - K_{(\text{MeXH}^+)}}$$

In Volume 2, in the chapter on Prototropic Tautomerism by A. R. Katritzky and J. M. Lagowski,

p. 7, line 9, vitamin A (**34**) should read vitamin C (**34**); index entry on p. 458, Vitamin A, tautomerism, 7 should read Vitamin C, tautomerism, 7

p. 59, formula [138] should be



In Volume 2, in the chapter on Free-Radical Substitutions of Heteroaromatic Compounds by R. O. C. Norman and G. K. Radda,

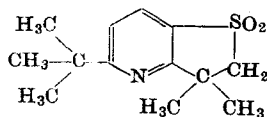
p. 156, Table VI, 5-R-Acridine should read 9-R-Acridine

p. 157, lines 17 and 18, 5-phenylacridine should read 9-phenylacridine

p. 157, lines 19 and 20, 5,10-dibenzylacridan should read 9,10-dibenzylacridan

p. 157, line 26 and p. 158, line 1, 5-phenylacridine should read 9-phenylacridine

p. 175, formula (**43**) should be



p. 176, line 30, pheny radical should read phenyl radical

Contents

CONTRIBUTORS	v
PREFACE	vii
CONTENTS OF VOLUME 1	xi
CONTENTS OF VOLUME 2	xii
ERRATA	xiii

The Quaternization of Heterocyclic Compounds

G. F. DUFFIN

I. Introduction	2
II. Reagents for Quaternization	2
III. The Influence of Substituents in Mono- <i>N</i> -Heterocyclyls	11
IV. The Position of Quaternization in Monocyclic Compounds	16
V. The Position of Quaternization in Compounds with Two or More Nitrogen-Containing Rings	38
VI. Reaction at Atoms Other Than Nitrogen	51
VII. The Mechanism of Quaternization	53

The Reactions of Heterocyclic Compounds with Carbenes

C. W. REES AND C. E. SMITHEN

I. Introduction	57
II. Reactions with Five-Membered Heterocyclic Rings	63
III. Reactions with Six-Membered Heterocyclic Rings	73

The Carbolines

R. A. ABRAMOVITCH AND IAN D. SPENSER

I. Introduction	79
II. Nomenclature	80
III. Synthesis	83
IV. Reactions of the Carbolines	142
V. Ring Extension	176
VI. Properties and Structure of the Anhydro-Bases	183
VII. Biogenesis and Biosynthesis of Naturally Occurring Carbolines	195
VIII. Spectra	202

Applications of the Hammett Equation to Heterocyclic Compounds

H. H. JAFFÉ AND H. LLOYD JONES

I. Introduction	209
II. Substituent Constants for Heteroatoms	215
III. Reactions at the Heteroatom and at Side-Chains Attached Thereon	223
IV. Transmission of Substituent Effects through Heterocyclic Systems	236
V. Polycyclic Compounds	243
VI. Tautomeric Equilibria	256
VII. Appendix: Analysis of Variance	261

1,2,3,4-Thiatriazoles

K. A. JENSEN AND C. PEDERSEN

I. Introduction	263
II. Synthesis and Chemical Properties of 1,2,3,4-Thiatriazoles	265
III. 1,2,3,4-Thiatriazoles Substituted with C-Radicals	267
IV. 1,2,3,4-Thiatriazole-5-thiol and Its Derivatives	269
V. 5-Alkoxy-1,2,3,4-thiatriazoles	277
VI. 5-Substituted-amino-1,2,3,4-thiatriazoles	277

Nucleophilic Heteroaromatic Substitution

G. ILLUMINATI

I. Introduction	285
II. Course and Kinetic Form of the Reactions	290
III. Reagent and Solvent Effects	301
IV. The Reactivity of the Heterocyclic Substrate	316
V. A General Comment on Mechanism	352
VI. Inorganic Heteroaromatic Substitution Reactions	357
VII. Appendix: Kinetic Data for Nucleophilic Heteroaromatic Substitution	359

Pentazoles

IVAR UGI

I. Introduction	373
II. The Characterization of Arylpentazoles	374
III. The Formation and Decomposition of Arylpentazoles	378

AUTHOR INDEX	385
------------------------	-----

SUBJECT INDEX	407
-------------------------	-----

The Quaternization of Heterocyclic Compounds

G. F. DUFFIN

Minnesota 3M Research Ltd.

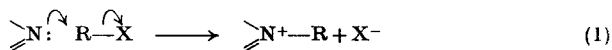
Pinnacles, Harlow, Essex, England

I. Introduction	2
II. Reagents for Quaternization	2
A. Alkyl Halides and Related Compounds	2
B. Aryl and Heterocyclyl Halides	7
C. Other Quaternizing Reagents	9
D. Solvents	10
III. The Influence of Substituents in Mono- <i>N</i> -Heterocyclyls	11
A. Aromatic Compounds	11
B. Saturated Rings	13
IV. The Position of Quaternization in Monocyclic Compounds	16
A. Pyrazole	16
B. Imidazole	17
C. Pyridazine	19
D. Pyrimidine	21
E. Pyrazine	24
F. Cinnoline	25
G. Phthalazine	28
H. Quinazoline	29
I. Quinoxaline	31
J. Thiadiazoles	33
K. Triazoles	34
L. Tetrazoles	37
V. The Position of Quaternization in Compounds with Two or More Nitrogen-Containing Rings	38
A. Diazaindenes and Related Compounds	38
B. Tetrazaindenes	42
C. Naphthyridines	46
D. Phenanthrolines	47
E. Triazaphenanthrenes	49
F. Pteridines	50
VI. Reaction at Atoms Other Than Nitrogen	51
A. Sulfur	51
B. Oxygen	52
C. Carbon	53
VII. The Mechanism of Quaternization	53

I. Introduction

If a nitrogen atom in a heterocyclic ring possesses a pair of electrons not already involved in the formation of σ or π bonding orbitals, those electrons may form a bond between that nitrogen atom and a carbon atom of suitable polarizability, the nitrogen atom becoming quaternary. The attacking molecule must be one which can split off an anion during the quaternization and alkyl halides are therefore the most usual reagents. This reaction of heterocyclic compounds is therefore one type of Menshutkin reaction.

This reaction may be regarded in two ways. The first is to see the reaction as a nucleophilic replacement of the halogen or similar group by attack of the electron pair of the base as in Eq. (1),



and, as will be seen, the reaction is bimolecular. This view shows the parallel between quaternary salt formation and the hydrolysis of an alkyl halide. Alternatively, the quaternization process may be regarded as a special type of electrophilic attack on the ring which normally takes place only at a nitrogen atom, although in certain cases reaction at carbon may also occur. It will be seen that a consideration of the reaction in this second sense helps in the correlation of the effect of substituents on the quaternization process with those of substituents on the reactivity of substituted benzenes.

It would therefore be deduced that the availability of the electron pair, as influenced by the ring containing the nitrogen atom, the substituents present in that ring, and the steric environment, should affect the rate of quaternization. Furthermore, the solvent for the reactants and the nature of the group R in Eq. (1) would be expected to be important factors in determining the course of the reaction. In the following sections the importance of each of these factors is considered.

In addition to direct attack on the nitrogen atom which finally becomes the quaternary center, it is possible for the electrophile to attack elsewhere in the heterocyclic molecule and for a mesomeric shift to proceed to completion to give a salt.

II. Reagents for Quaternization

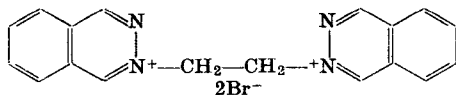
A. ALKYL HALIDES AND RELATED COMPOUNDS

By far the commonest reagents for the formation of heterocyclic quaternary salts are the alkyl halides, and, indeed, methiodides out-

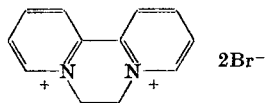
number all the other salts reported. The order of reactivity of the alkyl derivatives is $I > Br \gg Cl^1$; no alkyl fluorides have been reported to take part in the reaction.

Primary halides are more reactive than secondary compounds²⁻⁴; quaternary salt formation does not occur with tertiary halides, elimination always occurring to give the hydride and an olefin.⁵ Also, the larger the alkyl group the slower is the reaction⁶; this is shown by the very slow reaction of dodecyl bromide with quinoline,⁷ and even butyl iodide is much slower to react than methyl iodide.^{8, 9} The longer chain primary halides commonly undergo elimination rather than cause quaternization; for example, *n*-octyl and cetyl iodides give only the hydrides when heated with 9-aminoacridine.¹⁰

There has been much interest recently in the reaction of α , ω -dihalogenoalkanes. 1,2-Dibromoethane reacts with phthalazine to give ethane 1,2-bis-phthalazinium dibromide (1),¹¹ none of the mono salt being formed directly, but the same dibromo compound¹² and α , α' -dipyridyl give the cyclic compound 2.¹²



[1]



[2]

¹ R. P. Larsen and C. A. Kraus, *Proc. Natl. Acad. Sci. U.S.* **40**, 70 (1954); *Chem. Abstr.* **48**, 7996 (1954).

² H. C. Brown and A. Cahn, *J. Am. Chem. Soc.* **77**, 1715 (1955).

³ C. A. Bunton, C. H. Greenstreet, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.* 647 (1954).

⁴ W. Cuisa and L. Lipparini, *Gazz. Chim. Ital.* **90**, 147 (1960); *Chem. Abstr.* **52**, 2850 (1958).

⁵ H. C. Brown and N. Nakagawa, *J. Am. Chem. Soc.* **78**, 2197 (1956).

⁶ S. K. Mukherjee and S. R. Palit, *J. Indian Chem. Soc.* **27**, 175 (1950); *Chem. Abstr.* **45**, 425 (1951).

⁷ A. V. Few, A. R. Gilby, R. H. Ottewill, and H. C. Parriera, *J. Chem. Soc.* 1489 (1958).

⁸ J. Druey and H. U. Daeniker, U.S. Patent 2,945,037 (1956).

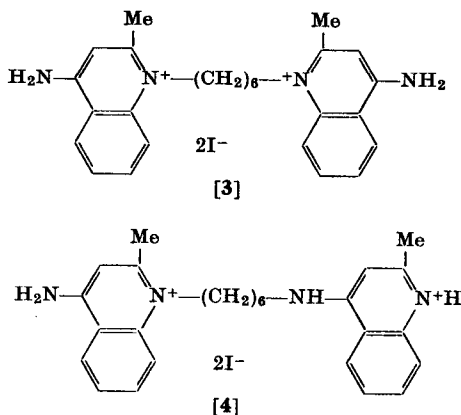
⁹ R. M. Fuoss, M. Watanabe, and B. D. Coleman, *Mezhdunar. Simpozium po Makromolekul. Khim., Dok., Moscow* **3**, 134 (1960); *Chem. Abstr.* **55**, 7411 (1961).

¹⁰ I. S. Joffe and N. A. Selezneva, *Zh. Obshch. Khim.* **31**, 50 (1961); *Chem. Abstr.* **55**, 24751 (1961).

¹¹ J. Druey and H. U. Daeniker, U.S. Patent 2,945,036 (1956).

¹² R. F. Homer and T. E. Tomlinson, *J. Chem. Soc.* 2498 (1960).

A range of bis-quaternary salts from various bases and α - ω compounds is described by Libman *et al.*,¹³ while the reactions of 4-aminoquinaldine and similar dihalogen compounds have been studied by Austin *et al.*¹⁴ These workers discovered that the crude product obtained from the reaction of dihexamethylene diiodide with 4-aminoquinaldine was very active against *Trypanosoma congolense* whereas the purified product was very low in activity. The main product was the expected 1,1'-bis salt **3**, and the active impurity (about 10% of the total yield) was the unsymmetrical derivative **4**.



In spite of the fact that the vast majority of quaternizations of amino-heterocyclic compounds are reported as occurring on the ring nitrogen atom only, it seems quite likely that salt formation may also take place on the exocyclic nitrogen in other cases but that it has been overlooked in the absence of a test such as was available for **4**.

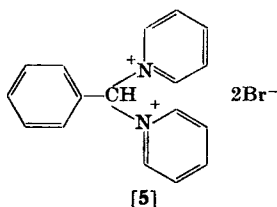
The formation of quaternary salts from benzyl halides and related compounds occurs readily and has been known for many years. More recently, Kröhnke and co-workers, who have studied the reactions of many heterocyclic quaternary salts, reported the formation of **5** from pyridine and benzylidene dibromide on heating the reactants together for 1 hr at 100°. ¹⁵ The salt is sufficiently stable to be recrystallized from methanol containing a trace of hydrogen bromide. Isoquinoline gives a similar salt.

¹³ D. D. Libman, D. L. Pain, and R. Slack, *J. Chem. Soc.* 2305 (1952).

¹⁴ W. C. Austin, M. D. Potter, and E. P. Taylor, *J. Chem. Soc.* 1489 (1958).

¹⁵ F. Kröhnke and H. Leister, *Chem. Ber.* **91**, 1295 (1958).

Pyridine and chloroacetic acid react normally to give the stable betaine derivative, but 2,5-dimethylpyrazine is quite different in its behavior. Chloroacetic acid is without action while both bromo- and iodo-acetic acid react smoothly, more rapidly in nitrobenzene than in



benzene, to give 1,2,5-trimethylpyrazinium salts with the loss of carbon dioxide.¹⁶ It has been suggested that the decarboxylation is facilitated by the participation of the second nitrogen atom. Quinoxaline and bromoacetic acid yielded a small amount of carbon dioxide, but no quaternary salt could be isolated from the reaction mixture.

The reaction between phenacyl bromide and pyridine to give salts of type 6 (R = Ph) was first described by Kröhnke,¹⁷ and more recently there has been widespread interest in this type of salt.¹⁸⁻²⁰ The phenacyl halide, or similar halogen compound, may be prepared *in situ* by the reaction of iodine or bromine with the appropriate methyl ketone, and this method has been applied to the preparation of pyridinium salts, in particular where R is a phenyl,²⁰ *p*-fluorophenyl,²¹ 2-, 3- or 4-pyridyl,²² 3-indolyl,²³ or 2-thienyl group.²⁴ This method is not always satisfactory and fails with acetophenone, iodine, and quinoline, while the corresponding salt from 4-picoline is difficult to purify; in these two cases it is only Kröhnke's original method which gives good yields.²⁰ The hetero ring in this class of compounds has been pyridine or a substituted pyridine,¹⁹ quinoline,

¹⁶ E. V. Hart and P. E. Spoerri, *J. Am. Chem. Soc.* **77**, 5898 (1955).

¹⁷ F. Kröhnke, *Ber.* **68**, 1177 (1935).

¹⁸ L. C. King, *J. Am. Chem. Soc.* **66**, 894 (1944).

¹⁹ L. C. King and M. McWhirter, *J. Am. Chem. Soc.* **68**, 717 (1946).

²⁰ J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.* **68**, 868, 1131 (1946).

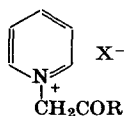
²¹ C. T. Bahner, W. T. Easley, B. G. Walden, H. D. Lyons, and G. E. Biggerstaff, *J. Am. Chem. Soc.* **74**, 3960 (1952).

²² F. Kröhnke and K. F. Gross, *Chem. Ber.* **92**, 22 (1959).

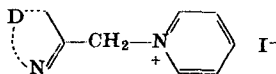
²³ G. Hart and K. T. Potts, *J. Org. Chem.* **27**, 2940 (1962).

²⁴ L. C. King, M. McWhirter, and R. L. Rowland, *J. Am. Chem. Soc.* **70**, 240 (1948).

isoquinoline,^{19, 20} pyrazine,²¹ and quinoxaline.²⁵ The halogenoacetones behave similarly to give salts (cf. 6; R = Me), although in the case of the sterically hindered 2-phenylpyridine only iodoacetone gives a quaternary salt.²⁶

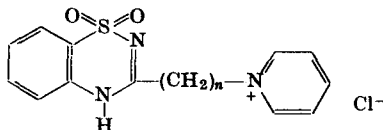


[6]



[7]

In a similar manner to a methyl ketone, heterocyclic compounds with a reactive methyl group may be condensed with iodine and pyridine to give a quaternary salt of type 7; for example, 2-methylbenzothiazole gives a high yield of the salt after 6 hr at 100°. Reid and Bender found that D in such salts (cf. 7) could also be derived from 2-methylquinazoline, 2-methylbenzoxazole, and 2-methylbenzothiazole.²⁷ The reactive methyl compound may also be 2-picoline N-oxide, though the latter compound is surprisingly slow to react.²⁸



[8]

3-Chloromethylbenzo-1,2,4-thiadiazine 1,1-dioxide forms quaternary salts, e.g. 8 ($n = 1$), with pyridine, 2- and 3-picolines, and isoquinoline, but the 3-(2'-chloroethyl) compound gives a lower yield of the salt, e.g. 8 ($n = 2$), because some of the halogen derivative is converted into the 3-vinyl compound.²⁹

Pearson *et al.*³⁰ have presented a useful compilation of the reactivity

²⁵ W. T. Easley and C. T. Bahner, *J. Chem. Soc.* 710 (1942).

²⁶ C. K. Bradsher and L. F. Beavers, *J. Am. Chem. Soc.* **77**, 453 (1955).

²⁷ W. Reid and H. Bender, *Chem. Ber.* **89**, 1893 (1956).

²⁸ M. Hamana, B. Umezama, Y. Goto, and K. Noda, *Chem. Pharm. Bull. (Tokyo)* **8**, 692 (1960); *Chem. Abstr.* **55**, 18723 (1961).

²⁹ L. Raffa, R. Cameroni, and M. T. Bernabei, *Farmaco (Pavia), Ed. Sci.* **15**, 842 (1960); *Chem. Abstr.* **55**, 19944 (1961).

³⁰ R. G. Pearson, S. H. Sanger, F. V. Williams, and W. J. MacGuire, *J. Am. Chem. Soc.* **74**, 5130 (1952).

of a number of alkyl bromides with pyridine in methanol. Their results are given in Table I.

TABLE I
SECOND ORDER REACTION RATES FOR PYRIDINE AND
ALKYL BROMIDES IN METHANOL AT 35°³⁰

Alkyl compound	K (l/mole min)
Ethylene bromohydrin	1.7×10^{-5}
2-Phenoxyethyl bromide	2.0×10^{-5}
<i>n</i> -Propyl bromide	1.0×10^{-4}
Ethyl bromide	2.3×10^{-4}
2,4,6-Trimethylphenacyl bromide	2.5×10^{-4}
Alkyl bromide	8.3×10^{-3}
Benzyl bromide	3.1×10^{-2}
Ethyl bromoacetate	8.5×10^{-3}
Phenacyl bromide	4.5×10^{-2}
<i>p</i> -Bromophenacyl bromide	7.2×10^{-2}

B. ARYL AND HETEROCYCLYL HALIDES

Heterocyclic bases which readily form quaternary salts with the more usual reagents will also react with suitably activated aryl and heterocyclyl halogen compounds, the classic case being the salt formed from pyridine and 1-chloro-2,4-dinitrobenzene. Reactions of this type have been studied by Chapman *et al.*^{31, 32} Salt formation between pyridine and 3- and 4-picolines on the one hand, and between 1-chloro-2,4-dinitrobenzene and 2- and 4-chloro-3-nitropyridine and 2-chloro-5-nitropyridine on the other, was investigated. The expected higher activity of the two picolines was attributed to the increase in electron density produced by induction and hyperconjugation, but the overall lower reactivity of the pyridine compounds in comparison to that of aniline derivatives of similar basicity was believed to be due to the interaction of the *o*-nitro group in the transition state, which could assist the latter but not the former. Further suggestions were made later³² and are discussed in Section VI. As would be expected, picryl chloride is a very reactive quaternizing reagent and reacts easily with pyridine, the picolines (including the 2-isomer), quinoline, and iso-

³¹ E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.* 3392 (1953).

³² R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.* 437 (1952).