

Advances in
HETEROCYCLIC
CHEMISTRY

A. R. KATRITZKY

A. J. BOULTON

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HETEROCYCLIC CHEMISTRY

Edited by

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Volume 7

Academic Press · New York and London · 1966

HETEROCYCLIC CHEMISTRY

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Editorial Advisory Board

Edited by

A. H. KATZ

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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



Preface

The seventh volume of *Advances in Heterocyclic Chemistry* includes surveys of four groups of heterocyclic compounds: furans (P. Bosshard and C. H. Eugster), dithiolium salts (H. Prinzbach and E. Futterer), 1,3,4-oxadiazoles (A. Hetzheim and K. Möckel), and diquinolylmethanes (G. Scheibe and E. Daltrozso). Further chapters deal with applications of mass spectrometry to heterocycles (G. Spiteller), an area which has expanded very rapidly of late, and the halogenation of heterocycles (J. J. Eisch). Finally, a summary is given of reviews in the heterocyclic field, classified by subject (A. R. Katritzky and S. M. Weeds), which it is hoped may be of assistance in literature surveys.

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

Thanks are due to the Editorial Board, the publishers, and the authors for their cooperation.

A. R. KATRITZKY
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Norwich, England

November, 1966

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Halogenation of Heterocyclic Compounds

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I. General Considerations

A. SIGNIFICANCE OF HALOGENATION IN HETEROCYCLIC CHEMISTRY

1. *Synthetic Scope*

The introduction of a halogen atom into the nucleus of an unsaturated heterocycle serves at once as a valuable synthetic route to heterocyclic derivatives and as a revealing probe of substitution processes at unsaturated carbon.¹ From a synthetic standpoint, aromatic and heterocyclic halides have become more attractive starting materials in recent years. Traditionally considered to be rather unreactive, these vinylic halides had been found suitable only in certain reactions

¹ For an excellent treatment of the preparative and mechanistic aspects of aromatic halogenation, cf. P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation." Butterworth, London and Washington, D.C., 1959.

such as: (a) the formation of the Grignard or organolithium reagent; (b) displacement processes at elevated temperatures, usually conducted in the presence of copper salts; or (c) displacements occurring under mild conditions when an electron-withdrawing substituent was situated *ortho* or *para* (alpha or gamma in heterocycles) to the carbon-halogen bond. The introduction of superior reaction solvents for organometallic processes (tetrahydrofuran and the glycol ethers) and displacement reactions (dimethyl sulfoxide and dimethylformamide), as well as an appreciation of the role of benzyne and aryne intermediates in aromatic substitution, promises a far greater importance to these unsaturated halides.

2. Mechanistic Importance

A similar situation seems to obtain in our understanding of the mechanisms of heterocyclic halogenation. Although copious research has provided accurate insight into the electrophilic substitution reactions of benzene derivatives, a correspondingly precise knowledge of heterocyclic substitution still is lacking. Admittedly formidable complexities, as the interplay of changing orientation with experimental conditions, the significance of n - or π -species in the pre-equilibria to reaction, the uncertain role of intermediate covalent addition compounds, and the possibility of rearrangements, remain unresolved. To this already bristling thicket of difficulties may be added the greater number of substitution isomers possible with many heterocyclic systems. It would appear, however, that this latter point may be viewed as an advantage for the researcher hoping to test his grasp of substitution processes at unsaturated carbon. This gradation of electronic environment within the same heterocyclic system permits the distribution of substitution isomers to be viewed as the result of a competition experiment. Hence the many complications mentioned previously can be largely canceled. More recent examination of heterocyclic substitution has demonstrated two valuable points in this connection: first, that the severe conditions of nitration, halogenation, and other substitutions traditionally used with many heterocycles are not necessary for successful reaction; and second, that the orientation displayed by heterocycles is highly dependent upon the polarity of the reagent and the medium.

Counterpoised to these experimental difficulties are certain distinct advantages to studies of heterocyclic halogenation. In the first place, the halogen family comprises a rationally related series of electrophilic

reagents of gradated reactivity and selectivity, running the gamut from the rather inert molecular iodine to the violently reactive fluorine.² A second advantage to halogenation as a mechanistic probe is the wide range of solvent polarity and acidity which can be feasibly employed. Pyridinoid heterocycles, for example, can be studied either as the protonated amine (in concentrated sulfuric acid) or as the free base (in carbon tetrachloride) with marked consequences on the rate and orientation of substitution. Third, the resulting orientation and reactivity data obtained from such adaptable halogenation studies can serve as an index of electronic character at different reacting sites in unsaturated heterocycles.

B. IMPORTANT HALOGENATING AGENTS

1. Neutral Reagents

Among the customary halogenating agents, the most widely acceptable are molecular chlorine and bromine. Unfortunately, no widely applicable and easily regulated method for limited substitution by elemental fluorine is available.² In contrast, the unaided attack of molecular iodine is too slow in many cases. In the latter instance both kinetic and thermodynamic factors (reversal by the hydrogen iodide by-product) conspire against a fruitful iodination. Table 1 lists certain properties of particular interest for some halogen and interhalogen molecules. The relatively weak bonds in molecular fluorine and iodine predispose these halogens to homolytic processes. In addition, the oxidizing action of the elemental halogen also comes to the fore with these same members: with fluorine, because of its high oxidizing power; with iodine, because its lower halogenating action permits the competing oxidation to become prominent. Finally, the relative acidities of the halogens, as exhibited toward the chloride ion, give some indication of their tendency to form n - or π -adducts with heterocyclic bases.

Although nonsolvating media of low polarity are sometimes suitable for reactive heterocycles, more often polar or basic solvents such as

² Although controlled substitution with molecular fluorine is difficult to attain, noteworthy is the recent success in perfluorinating both saturated and unsaturated heterocycles by electrolysis in anhydrous hydrogen fluoride. Cf. T. C. Simmons and F. W. Hoffmann, *J. Am. Chem. Soc.* **79**, 3429 (1957), for the preparation of undecafluoropiperidine (from piperidine). The latter compound can be converted into pentafluoropyridine by passing it over an iron contact at 600° [R. E. Banks, A. E. Ginsberg, and R. N. Haszeldine, *J. Chem. Soc. p.* 1740 (1961)].

TABLE I
PROPERTIES OF CERTAIN HALOGEN MOLECULES

Property	F ₂	Cl ₂	Br ₂	I ₂	ICl
Molecular weight	38.0	70.9	160	254	162
Boiling point (°C)	-187	-35	59	184	97
Bond energy (kcal/mole)	38	58	46	36	50
Bond length (Å)	1.44	1.98	2.28	2.66	—
Electronegativity of X	3.90	3.15	2.95	2.65	—
Electron affinity of X (kcal/gm-atom)	83.5	87	82	75	—
Acid strength toward aqueous Cl ⁻ ($-\Delta F^\circ$) ^a	—	4.4	0.04	-1.14	-5.7
Oxidation potential of X ⁰ (H ₂ O)	-2.85	1.36	1.09	0.54	—

^a R. L. Scott, *J. Am. Chem. Soc.* **75**, 1550 (1953).

ethyl ether, 1,4-dioxane, ethanol, acetic anhydride, glacial acetic acid, chloroform, and water are desirable. For media of low polarity small added amounts of ethers and amines appear to catalyze the halogenation process.³ That 1:1 halogen adducts of ethers (dioxane·Br₂) and of amines (pyridine·I₂) have been characterized tends to implicate halogen complexes as the catalytically significant species in these cases.⁴

2. Sources of Positive Halogen

To catalyze the attack on certain heterocycles, the halogen may be supplemented by a Lewis acid. Granted that the mechanistic details of these so-called "positive" halogenations are supported only by circumstantial evidence, the generation of a complexed X⁺ or the radical X· seems to be involved. Aluminum and ferric halides, silver salts, and possibly solutions of halogen in concentrated or fuming sulfuric acid appear to be cases in point. Other potential sources of "positive" halogen are the interhalogen compounds (BrCl, BrI, ICl) and CF₃CO₂X, *tert*-C₄H₉OCl, SOCl₂, and SO₂Cl₂, but little is known about their detailed behavior. Recent studies on the halogenation of

³ R. Pajeau, *Bull. Soc. Chim. France* p. 621 (1961); cf. A. P. Terent'ev, L. I. Belen'kii, and L. A. Yanovskaya, *Zh. Obshch. Khim.* **24**, 1265 (1954); see *Chem. Abstr.* **49**, 12327 (1955) for brominations effected by dioxane dibromide.

⁴ O. Hassel, *Dansk Tidsskr. Farm.* **36**, 41 (1962); see *Chem. Abstr.* **57**, 9228 (1963).

methyl pyrrole-2-carboxylate suggest that the selective chlorination at C-5 with *tert*-butyl hypochlorite is due to a radical process. The indiscriminate attack at C-4 and C-5 by molecular chlorine and by sulfuryl chloride in the presence of peroxides indicates the importance of both polar and radical processes.^{4a} On the other hand, halogenations

TABLE II
HETEROCYCLIC HALOGENATION PROCEDURES

Neutral
X_2 (Cl_2 , Br_2 , I_2 , ICl) in $CHCl_3$, CCl_4 , CS_2 , C_6H_6 , ROR , or ROH with HX scavenger: MCO_3 , HgO , R_2SO , $MOAc$ $\begin{array}{c} O \\ \\ X-N(C-R)_nH_{2-n} \end{array}$ in CCl_4 SOX_2 , SO_2X_2 , PCl_5 , <i>tert</i> - C_4H_9OCl
Acidic
X_2 (Cl_2 , Br_2 , I_2) in HOH , ROH , $RCOOH$, $(RCO)_2O$ X_2 in conc. H_2SO_4 or $H_2S_2O_7$ with or without Ag_2SO_4 X_2 with Al_2X_6 , $AgOAc$ X_2 with acidic oxidant: HXO_3 , HNO_3 $\begin{array}{c} O \\ \\ X-N(C-R)_nH_{2-n} \end{array}$ with Al_2X_6 , Fe_2X_6 HX with oxidizing conditions: H_2O_2 , R_2SO , anodic electrolysis HOX or PCl_5
Basic
X_2 (Cl_2 , Br_2 , I_2) in aqueous solution with R_3N , $NaOH$, $NaOAc$, Na_2CO_3 X_2 added to preformed metallic salt, $M-R$, prepared from $R-H + MR'$, MH , MOH , or MOR

by solutions of hypohalous acids have been shown by kinetic studies to involve "positive" halogen species (X^+ in its solvated forms, $X-OH_2^+$, $X-OHR^+$, or $X-NR_3^+$). By and large, then, similar

^{4a} P. Hodge and R. W. Rickards, *J. Chem. Soc.* p. 459 (1965).

moieties seem important in the halogenating action of *N*-haloamides (*N*-bromosuccinimide) and acyl hypohalites ($\text{CH}_3\text{CO}_2\text{X}$) in aqueous solution.

Less explored halogenation methods of promise involve the use of *N*-haloamides in nonaqueous media and the combination of an alkyl or hydrogen halide with an oxidizing agent. Despite their wide acceptance as reagents for allylic bromination, the *N*-haloamides (*N*-bromosuccinimide, *N*-haloacetamides, and *N*-halohydantoins) have not been utilized to their full in aromatic nuclear substitution.⁵ The controlled halogenation by the use of sulfoxides or peroxides with hydrogen halides⁶ or alkyl halides⁷ generates the actual halogenating agent *in situ* (solvated X^+ or X_2). This permits the substitution of sensitive, reactive nuclei under mild conditions without a large excess of reagent. In Table II are compiled some of the most important halogenating agents for heterocyclic systems and their appropriate experimental conditions.

3. Individuating Character of the Heterocycle

In closing this brief survey of halogenating agents, comment is in place on the role which the specific heterocycle plays in the choice of halogenating agent. The hydrogen halide liberated in the halogenation may interfere in two ways. Either it may protonate some of the unreacted heterocycle, thereby depressing or changing the nuclear reactivity, or it may cause reversal of the halogenation process. Consequently, the inclusion of hydrogen halide scavengers is desirable; these may be bases (NaHCO_3 , $\text{NaC}_2\text{H}_3\text{O}_2$, CaCO_3 , or R_3N) or oxidizing agents (HNO_3 , HXO_3 , or SO_3). Occasionally, the change in the heterocycle's orientation upon protonation may be turned to preparative advantage. Witness the following reactions in which substitution occurs exclusively in the pyridinoid⁸ or benzenoid⁹ ring, depending upon the acidity of the medium [Eqs. (1) and (2)]:

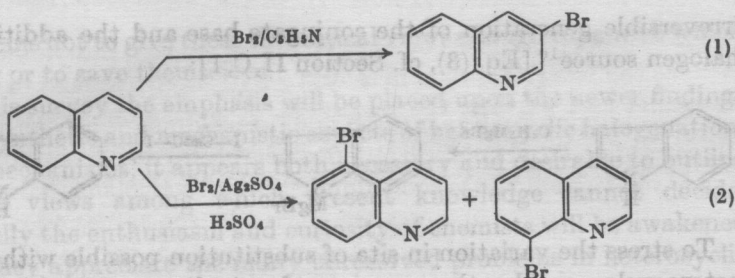
⁵ See, e.g., Ng. Ph. Buu-Hoi and J. Lecocq, *Compt. Rend.* **222**, 1441 (1946); **226**, 87 (1948); H. Schmid, *Helv. Chim. Acta* **29**, 573 (1946).

⁶ H. Gilman and J. Eisch, *J. Am. Chem. Soc.* **77**, 3862 (1955).

⁷ B. C. Saunders and B. P. Stark, *Tetrahedron* **4**, 169 (1958); T. L. Patterson and H. L. Pan, *J. Am. Chem. Soc.* **78**, 4812 (1956); *Chem. Ind. (London)* p. 660 (1957).

⁸ J. J. Eisch, *Chem. Ind. (London)* p. 1449 (1959); *J. Org. Chem.* **27**, 1318 (1962).

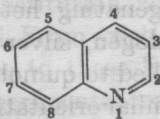
⁹ P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *Chem. Ind. (London)* p. 361 (1958); *J. Chem. Soc.* p. 561 (1960).



With heterocycles possessing fairly acidic hydrogens (e.g., pyrroles, indoles, and imidazoles), highly basic conditions may lead to halogenation via the conjugate base of the heterocycle. An appealing modification for preparative halogenation then would seem to be the

TABLE III

THE VARIEGATED BROMINATION OF QUINOLINE



Product (yield, %)	Conditions
1-Dibromide (ca 100)	Br ₂ in cold CCl ₄ ^a
2-Bromo (50-60)	Br ₂ in vapor phase at 500° ^b
3-Bromo (51)	Br ₂ in hot CCl ₄ with C ₆ H ₅ N ^c
4-Bromo ^d	3-Bromoquinoline·HBr at 300° ^e
5-Bromo (28)	Br ₂ and Ag ₂ SO ₄ in H ₂ SO ₄ ^f
6-Bromo (ca 2) ^g	Br ₂ in hot CCl ₄ with C ₆ H ₅ N ^c
8-Bromo (29)	Br ₂ and Ag ₂ SO ₄ in H ₂ SO ₄ ^f
3,6-Dibromo (35)	Br ₂ in glacial HOAc ^c
5,8-Dibromo (43)	2Br ₂ and Ag ₂ SO ₄ in H ₂ SO ₄ ^f
3,6,8-Tribromo	Br ₂ in glacial HOAc ^c
5,6,8-Tribromo	3Br ₂ and Ag ₂ SO ₄ in H ₂ SO ₄ ^f

^a J. J. Eisch, *Chem. Ind. (London)* p. 1449 (1959).

^b H. E. Jansen and J. P. Wibaut, *Rec. Trav. Chim.* **56**, 699 (1937).

^c J. J. Eisch, *J. Org. Chem.* **27**, 1318 (1962).

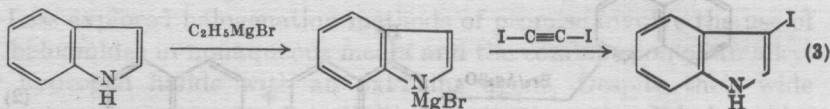
^d A 38% yield of quinoline was realized.

^e J. J. Eisch, *J. Org. Chem.* **27**, 4682 (1962).

^f P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.* p. 561 (1960).

^g Presumed precursor of 3,6-dibromoquinoline.

irreversible generation of the conjugate base and the addition of a halogen source¹⁰ [Eq. (3), cf. Section II, C, 1]:



To stress the variation in site of substitution possible with a given heterocycle consider the response of quinoline under the different conditions shown in Table III. The results also exemplify other intriguing aspects of halogenation, such as reversibility, temperature coefficient, and metal salt catalysis. These will be discussed in Sections II, C, 3 and III, C.

C. CURRENT RESEARCH EMPHASIS AND THE SCOPE OF THIS REVIEW

Appreciable recent effort has been devoted to developing highly selective methods for halogenating heterocycles. The method of Derbyshire and Waters (halogen, silver sulfate, and concentrated sulfuric acid)¹¹ has been applied to quinoline⁹ giving results in agreement with nitration. Quite similar orientation patterns in halogenation have been obtained with quinoline and isoquinoline by use of stoichiometric amounts of aluminum chloride.¹² The reductive halogenation of sulfoxides with hydrohalic acids has special appeal for the substitution of cyclic sulfides.⁶ The vapor phase halogenation of heterocycles under improved contact catalysis appears to be an attractive approach to desired isomers, if decomposition and rearrangements are minimized.

The complexity of individual halogenation mechanisms has become clear in more recent years from the diverse isomer distributions observed under different reaction conditions. Quantitative product studies are beginning to make a welcome appearance, but kinetic studies are almost wholly lacking. The recent kinetic work on the iodination of imidazole may signal the onset of improvement in this aspect. On the theoretical side, much attention has been given to the several possible quantum mechanical approximations applicable to heterocyclic substitution. Here again the lack of ample quantitative

¹⁰ V. Franzen, *Ber.* **87**, 1148 (1954).

¹¹ D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.* pp. 564 and 574 (1950).

¹² M. Gordon and D. E. Pearson, *J. Org. Chem.* **29**, 329 (1964).

data seems not to give these theoretical views enough rope with which to hang or to save themselves.

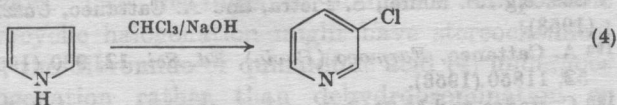
In this survey the emphasis will be placed upon the newer findings in the synthetic and mechanistic aspects of heterocyclic halogenation. As to mechanisms, it appears both necessary and desirable to outline possible views among which present knowledge cannot decide. Hopefully the enthusiasm and curiosity of chemists will be awakened when they appreciate the many unresolved problems in heterocyclic halogenation.

II. Preparation of Halogen Derivatives

A. GROSS TRANSFORMATIONS

The classical ambiguity between direct substitution on an aromatic system and substitution via an addition-elimination pathway [Eq. (16), Section III, A] persists for the halogenation of heterocycles under conditions of low polarity. Indeed, with suitable heterocyclic nuclei the three possibilities of substitution, addition, and addition-elimination have all been observed. From existing evidence one cannot assign as yet relative importance to these limiting cases in halogenation mechanisms. However, experimental conditions often can be regulated to favor one or other process for preparative success. These three processes will receive our attention in this review.

Of lesser relevance to this discussion are halogenation methods involving the modification of the carbon skeleton (synthesis and degradation). The Hunsdiecker reaction, as applied to certain heterocyclic acids, has had limited application for the synthesis of halogen derivatives. The preparation of 3-bromo-4,6-dimethyl-2-pyridone from the silver salt of the respective 3-carboxylic acid by treatment with bromine in carbon tetrachloride is a rare example of success.¹³ The interaction of carbenes with heterocycles also has been employed infrequently, but recent advances in carbene generation may reactivate this approach.¹⁴ The Ciamician-Dennstedt ring expansion of pyrrole to β -halopyridines is a case in point¹⁵ [Eq. (4)]:



¹³ R. G. Johnson and R. K. Ingham, *Chem. Rev.* **56**, 247 (1956).

¹⁴ J. Hine, "Divalent Carbon." Ronald Press, New York, 1964.

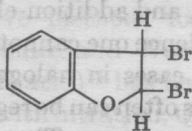
¹⁵ Cf. G. L. Closs and G. M. Schwartz, *J. Org. Chem.* **26**, 2609 (1961).

These and other methods of introducing halogen into heterocycles, such as the transformation of α - and γ -hydroxypyridinoid bases with inorganic acid halides, the treatment of pyridinoid *N*-oxides with sulfur or phosphorus halides, and the decomposition of diazonium compounds, are treated adequately in existing references.

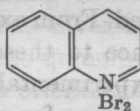
B. ADDITION PROCESSES

1. Types of Adduction

A posteriori, the addition of halogen to heterocycles can ensue in at least three distinct fashions, exemplified by the following adduct types: (a) covalent bonding of halogen to carbon with the partial or complete saturation of the ring¹⁶ (1); (b) *n*-complexation of the halogen at the hetero atom^{4,17} (2); and (c) π -complexation of the molecular halogen¹⁸ (3). Whereas *n* and π types of adduction occur



(1)



(2)



(3)

with extreme ease, the covalent fixation of halogen may require photochemical or radical source promotion. Molecular chlorine dissolved in carbon tetrachloride, in conjunction with illumination and iodine promoter, constitutes a successful set of conditions for many cases.^{19,19a,b} More polar solvents and elevated temperatures often cause the decomposition of intermediate adducts, either by hydrogen halide elimination²⁰ [Eq. (5)] or by solvolytic substitution²¹ [Eq. (6)]:

¹⁶ R. Stoermer and B. Kahlert, *Ber.* **35**, 1633 (1902).

¹⁷ J. J. Eisch and B. Jaselskis, *J. Org. Chem.* **28**, 2865 (1963).

¹⁸ R. P. Lang, *J. Am. Chem. Soc.* **84**, 4439 (1962).

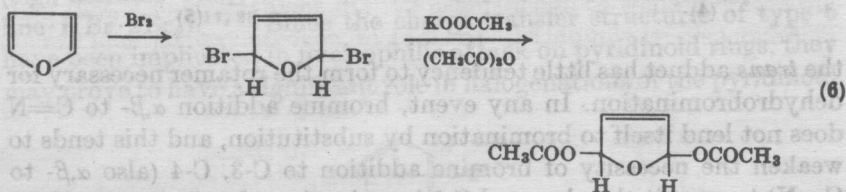
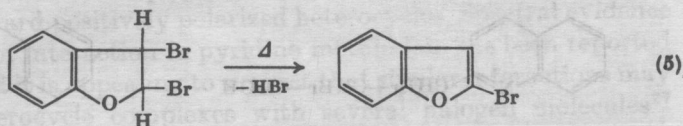
¹⁹ See, e.g., S. Maffei, S. Pietra, and A. Cattaneo, *Gazz. Chim. Ital.* **83**, 812 (1953).

^{19a} A. Cattaneo, *Farmaco (Pavia), Ed. Sci.* **12**, 930 (1957); see *Chem. Abstr.* **52**, 11850 (1958).

^{19b} C. Bodea and M. Raileanu, *Ann.* **631**, 194 (1960).

²⁰ H. L. Coonradt and H. D. Hartough, *J. Am. Chem. Soc.* **70**, 1158 (1948); R. Pieck and J. C. Jungers, *Bull. Soc. Chim. Belges* **60**, 357 (1951).

²¹ N. Clauson-Kaas, S.-O. Li, and N. Elming, *Acta Chem. Scand.* **4**, 1233 (1950).



The kinetic significance of these adducts in the ultimate substitution is at present uncertain. Indeed, the isolation of covalent halogen adducts and substitution products from the same system is no compelling proof for a sequential connection. Price's investigation of the bromination of phenanthrene has revealed the importance of this distinction in kinetic studies.²² The same caveat applies with even greater force to the detectable n - and π -halogen adducts of heterocycles. Since such adducts are readily dissociable into their components, the establishment of their role in halogenation substitution processes requires far more convincing evidence than a mere proof of their existence in the reacting medium.

2. Covalent Adducts

With the foregoing reservations in mind about the relation of such adducts to heterocyclic substitution, it is of interest to inquire about the structure and behavior of these halogen adducts. As to the covalent halogen adducts of heterocycles, the site of attachment, but not the stereochemistry of addition, is known for a number of ring systems (e.g., the dibromide of benzofuran¹⁶ and the tetradecachloride of acridine^{19b}). The *cis* or *trans* location of vicinal halogens would be of importance in any future studies of substitution via addition-elimination pathways. Two instances of adduction of possible relevance to heterocyclic halogenation might have stereochemical implications. First, the dibromide of quinaldinic acid (4) undergoes principally dehalogenation rather than dehydrobromination or decarboxylative debromination when treated with base.²³ Possibly

²² C. C. Price, *Chem. Rev.* **29**, 37 (1941).

²³ A. A. Alberts and G. B. Bachman, *J. Am. Chem. Soc.* **57**, 1284 (1935).