Advances in Heterocyclic Chemistry

By A. R. KATRITZKY

Volume 3

Advances in HETEROCYCLIC CHEMISTRY

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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

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ERRATA

In Volume 1, in the chapter on Prototropic Tautomerism by A. R. Katritzky and J. M. Lagowski,

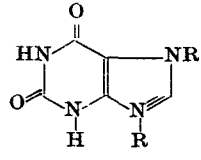
p. 326, the equation should read

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

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,

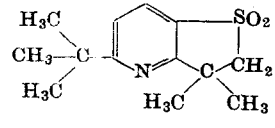
p. 156, Table VI, 5-R-Acridine should read 9-R-Acridine

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

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IVAR UGI

The Quaternization of Heterocyclic Compounds

G. F. DUFFIN

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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),

$$\geqslant\!\ddot{N}\!: \; R\!-\!\ddot{X} \longrightarrow \geqslant\!N^{+}\!-\!R + X^{-} \tag{1}$$

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

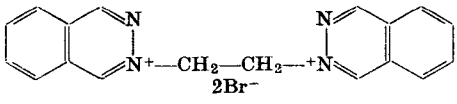
A. Alkyl Halides and Related Compounds

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

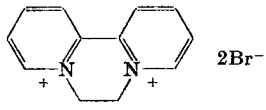
number all the other salts reported. The order of reactivity of the alkyl derivatives is I > Br ≫ Cl[1]; no alkyl fluorides have been reported to take part in the reaction.

Primary halides are more reactive than secondary compounds[2–4]; quaternary salt formation does not occur with tertiary halides, elimination always occurring to give the hydriodide and an olefin.[5] Also, the larger the alkyl group the slower is the reaction[6]; 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 hydriodides 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 compound[12] 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).

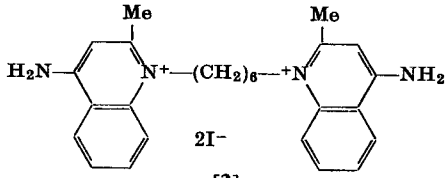
[9] R. M. Fuoss, M. Watanabe, and B. D. Coleman, *Mezhdunar. Simpozium po Makromolekul. Khim., Dok., Moscow* **3**, 134 (1960); *Chem. Abstr.* **55**, 7411 (1961).

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

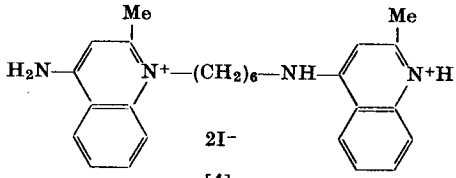
[11] J. Druey and H. U. Daeniker, U.S. Patent 2,945,036 (1956).

[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**.



[3]



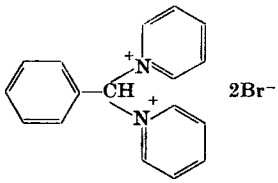
[4]

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



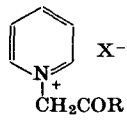
[5]

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.

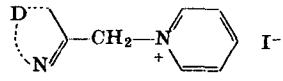
The reaction between phenacyl bromide and pyridine to give salts of type **6** (R = Ph) was first described by Kröhnke,[17] and more recently there has been widespread interest in this type of salt.[18–20] The phenacyl halide, or similar halogen compound, may be prepared *in situ* by the reaction of 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]

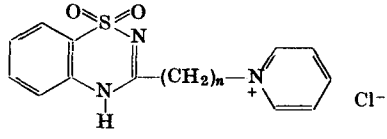


[6]



[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}
n-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}
p-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 later[32] 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).