Since $\Delta^{9,11}$-estrone 3-methyl ether is available by a highly practical and efficient four-step total synthesis from simple bicyclic precursors,[17] the transformations here described afford a totally synthetic entry to 11β-hydroxyandrostanes which in turn have been converted by well-established methods of side-chain synthesis to cortisone and the therapeutically important 16-substituted corticoids.[18]

[17] G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963). For recent reviews *cf.* I. V. Torgov, *Pure Appl. Chem.*, **6**, 525 (1963); T. B. Windholz and M. Windholz, *Angew. Chem. Intern. Ed. Engl.*, **3**, 353 (1964).

[18] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1959; L. Velluz, G. Nominé and J. Mathieu, *Angew. Chem.*, **72**, 725 (1960).

[19] Syntex Postdoctoral Fellow, 1964–1965.

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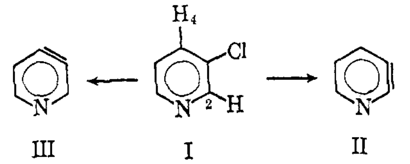
Hydrogen–Deuterium Exchange in Some Halopyridines and the Mechanism of Pyridyne Formation

Sir:

Halopyridines may undergo dehydrohalogenation in the presence of strong base to form pyridyne,[1] a heterocyclic counterpart of benzyne. With 3-chloropyridine (I) this elimination may in principle proceed by the formation of 2,3-pyridyne (II) and 3,4-pyridyne (III). Although there is solid evidence for III, no proof exists for the formation of II from I.



Dehydrochlorination of I by lithium piperidide in ether–piperidine is said to proceed by a two-step mechanism involving the formation of a lithiopyridine by removal of hydrogen adjacent to the halogen. 2-Lithio-3-chloropyridine is expected to be more stable than 4-lithio-3-chloropyridine.[1a,2] Competition experiments indicate pyridyne III is more selective and hence more stable than benzyne,[1a] and molecular orbital calculations suggest II should be more stable than III because of the added electron delocalization involving the nitrogen electron pair.[3] In light of these suggestions why does II not form from I?

In this communication we demonstrate that the rate of hydrogen exchange at the 2 position of I is immeasurably slow relative to the exchange rate at the 4 position. Two different solvent systems were employed, methanol and ammonia.

In methanol, methoxide ion brings about deprotonation of I and also of 3,5-dichloropyridine (IV) under relatively mild conditions. Both incorporation of deuterium from CH_3OD into unlabeled chloropyridine and removal of deuterium from substrate into CH_3OH were examined in each of the following experiments. Samples under nitrogen were sealed in nmr tubes and incubated in a thermostated bath. The cooled mixture was examined periodically for hydrogen content in substrate. Nonexchanging sites of substrate served as internal standards in calculating per cent deprotonation from nmr peak areas. From reactions on a larger scale, chloropyridine was recovered and the neat material was analyzed directly. The data in Table I indicate, the surprising results. With both I and IV it is H-4 which exchanges most rapidly.[4,5] There is no evidence for deprotonation at the 2 position of I.[6] Only traces of chloride ion were detected under conditions of hydrogen exchange. To further demonstrate the authenticity of 3-chloropyridine-4-*d* (V), obtained by exchange in CH_3OD, 3-chloropyridine-2-*d* (VI) was prepared for comparison by the following method. Deuteriodechlorination of 2,3-dichloropyridine (VII)[7] by refluxing with constant-boiling DI[8] for 18 hr gave 53% VI having 61% D.[9,10] That the nmr spectra of deuterated V and VI were significantly different substantiated the assignment of the position of the label.

Table I. Equilibrium Deuteration of Chloropyridines in CH_3OD at 74°

Pyridine	Position of exchange[a]	CH_3ONa, M	Time, hr[b]
3-Chloro	4	3.2	21
3,5-Dichloro	4	1.6	24[c]
3,5-Dichloro	2,6	2.6	48[d]

[a] Retention time by glpc analysis for deuterium product is identical with that for hydrogen reactant. [b] To achieve equilibrium deuteration which is no less than 75% D at the position indicated. [c] At 23°. [d] Only 39% D under these conditions.

VII VI

In ammonia, amide ion brings about both hydrogen exchange and dehydrochlorination. Deuterated chloropyridines V and VI were examined separately.[11] Reactions were interrupted before complete chloride ion loss, and recovered substrate was analyzed for deuterium content. The data in Table II indicate a large reduction

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[1] For review articles see (a) T. Kauffmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 543 (1965); (b) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocyclic Chem.*, **4**, (1965).

[2] T. Kauffmann and F. P. Boettcher, *Chem. Ber.*, **95**, 1528 (1962).

[3] H. L. Jones and D. L. Beveridge, *Tetrahedron Letters*, 1577 (1964).

[4] 3-Substituted pyridines exhibit in ABCD nmr spectrum. For a thorough analysis see (a) V. J. Kowaleski and D. G. de Kowaleski, *J. Chem. Phys.*, **36**, 266 (1962); (b) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 112.

[5] Deuteration of I leads to a large diminution in the intensity of the H-4 multiplet and simplification of the over-all coupling pattern. The most dramatic spin decoupling occurs with H-5 which changes from a quartet to a doublet with the introduction of D-4.

[6] A similar observation was made on 3-bromopyridine.

[7] H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. Trav. Chim.*, **69**, 673 (1950).

[8] Prepared by repeated exchange of constant boiling HI with >99.5% D_2O.

[9] This reaction frequently has been used for proteodechlorinations. See H. E. Mertel, "Pyridine and Its Derivatives," Part II, E. Klingsberk, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, pp 339–344.

[10] Acid-catalyzed H-D exchange in pyridines is a slow process. See (a) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **12**, 1384 (1964); (b) A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.*, 3753 (1963).

[11] Reaction conditions and work-up are essentially those employed in ref 12 except that nmr was used to analyze for deuterium.

[12] J. A. Zoltewicz and J. F. Bunnett, *J. Am. Chem. Soc.*, **87**, 2640 (1965).

Table II. Interrupted Reactions of 3-Chloropyridine-*d* with $NaNH_2$ in Ammonia[a]

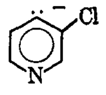
Position of D	Atom % D[b]		% Cl^- Formed
	Initial	Final	
2	61	61	30
4	75	20	46

[a] A molar excess of $NaNH_2$ was employed and the reaction was quenched after about 15 min by the addition of solid NH_4NO_3 to a solution at reflux. [b] Reproducibility of the nmr analyses is ±5%.

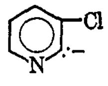
in the quantity of D-4 under conditions leading to extensive chloride ion formation.[13] In marked contrast there is no detectable change in the amount of D-2 label even after 30% chloride ion is liberated.

Our observations may be rationalized in terms of a 3-chloro-4-pyridyl anion intermediate (VIII) which reacts by two competing processes. Formation of this anion may occur by base-catalyzed proton abstraction from the 4 position of I. The anion may react by chloride ion loss to give pyridyne III or by proton capture from solvent to regenerate substrate I and base. When hydrogen isotopes are employed, the exchange process becomes observable. In methanol, proton exchange is overwhelmingly favored over chloride ion loss, but in the less acidic ammonia both reactions are observed. The extent of 3,4-pyridyne formation relative to hydrogen exchange is largely determined by solvent acidity; the latter reaction becomes increasingly important as the protonating ability of the solvent increases.

This mechanism ought to apply to the formation of II from I by a 3-chloro-2-pyridyl anion (IX). However, no evidence exists for the formation in detectable



VIII



IX

quantity of IX or even for the conversion of I to II. If II were to be formed from IX, it then is understandable why there is no evidence for this pyridyne. The shortcoming of our interpretation is that it does not account for the preferred position of exchange in I.

More needs to be known about H–D exchange in pyridines. This area of investigation presently is characterized by a paucity of data and seemingly divergent observations. An excellent illustration of the latter is H–D exchange in pyridine itself.[10a,14] We shall shortly report kinetic data on D–H exchange for some halopyridines and their N-oxides.

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[13] The extent of D–H exchange and chloride ion loss is not unlike that for chlorobenzene under similar conditions. See ref 12 and references cited therein.

[14] I. F. Tupitsyn and N. K. Semenova, *Tr. Gos. Inst. Prikl. Khim.*, **49**, 120 (1962); *Chem. Abstr.*, **60**, 6721c (1964).

Book Reviews

Methods of Quantum Chemistry. By M. G. Veselov, Leningrad State University, Leningrad, U.S.S.R. Academic Press Inc., 111 Fifth Ave., New York, N. Y. *1965.* xi + 181 pp. 15.5 × 23.5 cm. $7.50.

The book contains five review articles by Russian authors on the determination of molecular wave functions. Two of the articles are based on papers presented at the first Soviet Conference on Quantum Chemistry in 1961 and the other three were apparently written in 1962.

In the first chapter Rebane gives a brief review of the "Atoms in Molecules" and the "United Atoms" methods for diatomic molecules and a comparison of the relative merits of the two approaches.

The second chapter is a discussion by Mestechkin of the Hartree–Fock method, the Roothaan SCF–LCAO theory, and the Hückel method. This chapter contains very little material that cannot be found elsewhere, but its merit is that these various methods are combined in a logical way. In a few places the author expresses his personal opinion; of particular interest is the remark on page 65 that the LCAO method is better justified for the σ bonds than for the π electrons. It should be realized that Mestechkin wrote this in 1962 and that he predicted many recent developments in the extended Hückel LCAO theory.

The third chapter contains a study of the chemical properties of conjugated and aromatic molecules based on the Hückel LCAO method by Tupitsyn and Adamov. We found nothing in this chapter that has not already been presented in one of the many books on MO theory for organic chemists. For example, in Streitwieser's book this topic was discussed much more extensively.

In the fourth chapter Nikitin attempts to apply some of the theories for many-electron systems that were developed in solid-state physics to long conjugated molecules. The conclusions are of a very general nature and they do not indicate that these physical methods will solve many chemical problems in detail.

The last chapter, by Rebane, is entitled "Application of the Method of Finite Differences to Problems in Molecular Orbital Theory." This is a method for solving secular equations by first combining the atomic orbitals to Bloch functions or similar functions. We agree with the author that this method is but little known among quantum chemists and that it is hard to find it in the literature.

The most interesting aspect of the book is that it shows us how some Russian scientists judge the existing theories on molecular wave function determination. All five articles are well written and in many places they give us a fresh outlook on quantum chemical methods. However, the bulk of the material is not new and is beginning to be outdated. We feel that the publication of five-year old review articles is of little use to the scientific community if a large number of up-to-date reviews in the field are already available. Needless to say that the responsibility for this lies with the publisher and not with the authors.

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