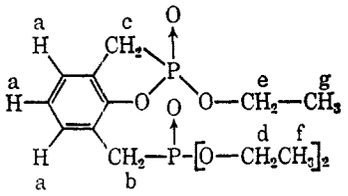
Anal. Calcd for $C_{12}H_{19}O_4P$: C, 55.85; H, 7.44; P, 12.0. Found: C, 55.46; H, 7.01; P, 12.1.

Preparation and Reactions of α,α′-Dichloro-2,6-xylenol.—The α,α′-dichloro-2,6-xylenol was prepared from α,α′-dichloro-2,6-xylyl chloroformate using the same procedure employed for α-chloro-*p*-cresol.

2-Ethoxy-2-oxo-7-diethylphosphonomethyl-1,2-benzoxaphosphole.—A solution of 0.10 mol of α,α′-dichloro-2,6-xylenol and 42 g (0.25 mol) of triethyl phosphite in 75 ml of acetonitrile was heated on a steam bath for 45 min. Following the usual procedure, distillation of the oil from solvent evaporation yielded 10.2 g (29%) of product, bp 166–200° (<1 μ). The infrared spectrum shows no hydroxyl absorption and is otherwise consonant. The nmr spectrum (δ, ppm (in $CDCl_3$)) showed a, 6.7–7.3; b, doublet, J = 21 Hz, 3.08; c, doublet, J = 17 Hz; 3.04; d, e, 3.6–4.4; f, triplet, J = 9 Hz, 1.23; g, triplet, J = 9.4 Hz, 1.34.



Anal. Calcd for $C_{14}H_{22}O_6P_2$: C, 48.25; H, 6.12; P, 17.8. Found: C, 48.46; H, 6.42; P, 17.5.

Registry No.—Dimethylformamide, 68-12-2; 2,6-xylyl chloroformate, 876-99-3; **1**, 15451-04-4; α-chloro-2,6-xylylchloroformate, 15451-05-5; α,α′-dichloro-2,6-xylyl chloroformate, 15451-06-6; 3-(4′-hydroxybenzyl)-2,4-pentanedione (keto form), 15451-07-7; 3-(4′-hydroxybenzyl)-2,4-pentanedione (enol form), 15451-10-2; 4-diethylphosphonomethylphenol, 3173-38-4; 2-methyl-6-diethylphosphonomethylphenol, 15451-11-3; 2-ethoxy-2-oxo-7-diethylphosphonomethyl-1,2-benzoxaphosphole, 15451-09-9.

Acid- and Base-Catalyzed Deuterium–Protium Exchange of Some Polyazaindenes

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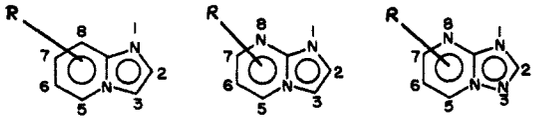
Received August 28, 1967

The acid-catalyzed deuterium–protium exchange of compounds **1**, **2**, and **3** occurs at the positions typical for electrophilic substitutions. These substitutions are shown to occur on the free bases. The base-catalyzed deuterium–protium exchange of compounds **1**, **2**, and **3** occurs at positions adjacent to nitrogen atoms which possess a partial positive charge as indicated by major resonance contributing structures. Proton transfer is shown to be involved in the rate-determining step.

We have recently[1] described some preliminary results of hydrogen–deuterium exchange studies on imidazo[1,2-*a*]pyridine (**1**), imidazo[1,2-*a*]pyrimidine (**2**), and 1,2,4-triazolo[1,5-*a*]pyrimidine (**3**). These studies have shown that electrophilic substitution by D^+ in these ring systems occurs at position 3 in the ring systems **1** and **2** and at position 6 in the ring system **3** (the



numbering of the positions in the manner shown in structure **3** is done for the sake of clarity in comparing the various structures). The positions of deuterium–protium exchange are the same as those involved in the brominations of these compounds.

It now remains to consider if these electrophilic substitutions occur on the protonated or on the free bases. We have previously shown that the methylation, with methyl iodide, of these compounds occurs at the same nitrogen atom (N-1) as protonation does in salt formation.[2–4] If electrophilic substitution occurs on the protonated bases, the deuterium–hydrogen exchange rate of the methiodides should be the same or faster than the exchange in the protonated bases. Table I shows the results of this study and clearly demonstrates that the electrophilic substitution, under the conditions of these experiments, occurs on the free base since the exchange rate on the methiodides is considerably slower than that of the free bases. In view of the fact that the brominations of these compounds are done under milder acidic conditions[2,5,6] (bromine–water) than those employed in the exchange studies, we can say that the electrophilic brominations on these ring systems also occur on the nonprotonated compounds.

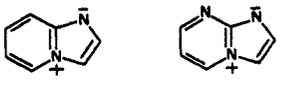
TABLE I

ACID-CATALYZED H–D EXCHANGE[a] ($t_{1/2}$ hr)

Compd	H-3	H-5
1 (R = H)	4.5	
1·CH_3I (R = H)[b]	31	
2 (R = H)	13	
2·CH_3I (R = H)[b]	>300	>300
3 (R = H)		15
3·CH_3I (R = H)[b]		165

[a] 3 *M* D_2SO_4 was used at 100°. [b] The methyl group in the methiodides is at N-1.

In view of the strong contribution of resonance structures such as **4** and **5**, causing an inductive electron



(1) W. W. Paudler and L. S. Helmick, *Chem. Commun.*, 377 (1967); *J. Heterocyclic Chem.*, **3**, 269 (1966). (A typographical error caused the incorrect reporting of the melting points of 1,2,4-triazolo[1,5-*a*]pyrimidine and of 1,2,4-triazolo[4,3-*a*]pyrimidine. The correct melting points are 142–143° and 208–210°, respectively.)

(2) W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, **31**, 809 (1966).

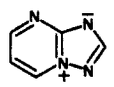
(3) W. W. Paudler and H. L. Blewitt, *ibid.*, **31**, 1295 (1966).

(4) The position of protonation and N-methylation of the 1,2,4-triazolo[1,5-*a*]pyrimidines will be the topic of a forthcoming communication.

(5) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **30**, 4081 (1965).

(6) Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **9**, 804 (1961).

withdrawal at C-3 and C-5, to the ground state of the imidazo compounds **1** and **2**, respectively, base-catalyzed exchange of H-3 and H-5 is to be expected. Similarly, contributions of resonance structures such as **6** to the ground state of the triazole derivative **3** predict facile deuterium–protium exchange at position 5 in this compound. These exchanges have, in fact,



6

been realized and the rate data are presented in Table II. Thus, the observed base exchange processes

TABLE II

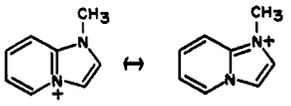
SECOND-ORDER RATE CONSTANTS ($\times 10^3$ l. mol^{-1} sec^{-1}) FOR H–D EXCHANGE IN 0.098 *N* NaOD

Compd[f]	Exchange position 2	3	5	6	Reacn temp, °C
1 (R = H)	*a, d*	0.024[a]	0.0072[a]	*a, d*	65
1·CH$_3$I (R = H)[b]	6.1	9.4	0.033	*d*	35
1·CH$_3$I (R = 5-CH$_3$)[c]	5.2	5.2		*d*	35
1·CH$_3$I (R = 6-CH$_3$)	3.3	8.5	*d*		35
1·CH$_3$I (R = 7-CH$_3$)	3.9	7.8	*d*	*d*	35
1·CH$_3$I (R = 8-CH$_3$)	3.3	8.5	*d*	*d*	35
2 (R = H)	0.025[a]	0.15[a]	1.5[a]	0.048[a]	65
	d	0.145	1.64	*d*	65
2·CH$_3$I (R = H)	Decomposes under basic conditions				35
3 (R = H)[e]	*d*		10.9	0.0098	35
	0.037[a]		>50[a]	0.32[a]	65
3 (R = 2-CH$_3$)			6.1	*d*	35
3 (R = 7-CH$_3$)	*d*		3.8	*d*	35
3·CH$_3$I (R = H)	>50		Decomposes too rapidly		35
3·CH$_3$I (R = 7-CH$_3$)	>50		Decomposes too rapidly		35

[a] 0.5 *M* NaOCH$_3$ in CH$_3$OD. These exchanges are too slow at 35° and in 0.098 *N* NaOD to be measured. [b] All methiodides are the 1-N-methyl derivatives. [c] This is the average rate of exchange of H-2 and H-3 since the nmr signals are insufficiently resolved for an individual determination. [d] No measurable exchange at indicated temperature. [e] H-7, under the condition in footnote *a* exchanges at the same rate as H-2. [f] Respective registry no.: 274-76-0; 15562-25-1; 15639-31-3; 15639-32-4; 15639-33-5; 15639-34-6; 274-95-3; 15562-27-3; 275-02-5; 14388-63-7; 15562-30-8; 15562-31-9; 15562-32-0;

confirm the significant contribution of resonance structures such as **4**, **5**, and **6** to the ground state of compounds **1**, **2**, and **3**, respectively.

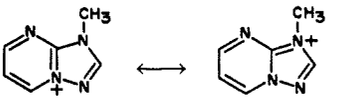
The two major resonance contributing structures of the methiodide of **1** can be pictured as in **7** and **8**.



7 **8**

It is obvious that N-1 no longer possesses a partial negative charge, as is the case in the free bases, and we can consequently predict that base-catalyzed exchange will occur at C-2 in addition to C-3 and C-5. The base-catalyzed exchange in the imidazo[1,2-*a*]pyridine methiodide occurs at a similar rate for H-2 and H-3, with a somewhat faster rate for H-3. The base-catalyzed exchange of H-5 is slower by a factor of about 100 than the H-2 and H-3 exchange. These D–H exchanges do not occur at a measurable rate in the free bases at the conditions employed for the methiodides (65°, 0.098 *N* NaOD). In stronger base, 0.5 *M* NaOMe (65°), the H-3 and H-5 protons of the free base do, however, exchange.[1] Unfortunately, the rate differences in the base-catalyzed exchange reactions of the methiodides and of the free bases is so large, that no suitable set of reaction conditions could be found which allows a direct comparison of the reaction rates. The difference in the reaction rates can, however, be estimated to be in favor of the methiodides by *at least* a factor of 1500. Since the methiodides of the imidazo[1,2-*a*]pyrimidines decompose under basic conditions, no exchange rates can be obtained for these compounds.

The major resonance contributing structures (**9** and **10**) of the methiodides of the 1,2,4-triazolo[1,5-*a*]-pyrimidines suggest that the D–H exchange in these compounds should occur at positions 2 and 5. This



9 **10**

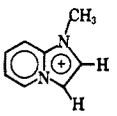
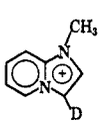
prediction is verified for H-2 by experiment (*cf.* Table II). Unfortunately, these methiodides decompose too rapidly to obtain a valid rate constant for the exchange of H-5. We find that the exchange rate of the methiodides of these compounds is faster, by at least a factor of 1000, than the exchange rate of the corresponding free bases.

The D–H exchange rate of various methiodides of methyl-substituted imidazo[1,2-*a*]pyridines, compared with the exchange rates of the 2 and of the 3 proton of the methiodide of the parent compound itself, is of some interest. The substitution of any of the protons in the six-membered ring by a methyl group has essentially the same rate decreasing effect upon the exchange of H-2, while it has very little, if any, effect upon the exchange rate of H-3 (*cf.* Table II).

The rate data reported in Table II represent second-order rate constants with first-order dependency in both base and heterocycle (see Table III). The results

TABLE III

KINETIC DATA FOR BASE-CATALYZED H–D EXCHANGE AT 35° IN D$_2$O

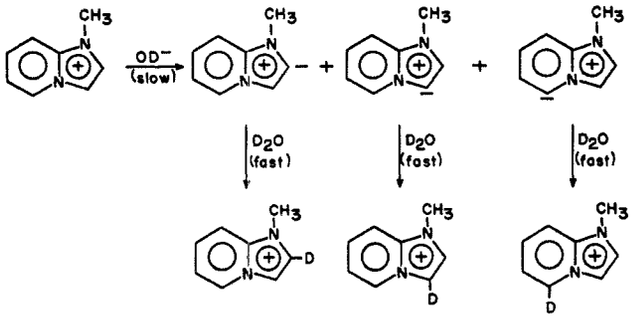
	Concn of methiodide, *M*	Concn of NaOD, *M*	Second-order rate constants ($\times 10^3$ l. mol^{-1} sec^{-1}) H-2	H-3
	0.260	0.098	6.12	9.33
	0.260	0.050	6.22	9.38
	0.260	0.025	6.15	9.60
	0.250	0.098	5.62	8.93
	1.04	0.098	5.95	10.3
	0.262	0.100[a]		4.27

[a] Concentration of NaOH in H$_2$O.

of the base-catalyzed D–H exchanges are certainly consistent with the proposal that an ylide-type intermediate is involved in these reactions. The primary deuterium kinetic isotope effect (see Table III) for the exchange of the methiodide of the 3-deuterioimidazo[1,2-*a*]pyridine as compared to the exchange of the protio compound is 2.19 at 35°. Thus, proton transfer occurs in the rate-determining step. One might

well envision the reaction sequence in Scheme I to account for these base-catalyzed exchange reactions.[7]

SCHEME I



(7) Related studies dealing with some five- and six-membered ring nitrogen heterocyclic compounds have been the subject of several recent publications cited in ref 1. Some more recent publications in this area are Y. Kawazoe and M. Ohnishi, *Chem. Pharm. Bull.* (Tokyo) **15**, 826 (1967); R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967).

Experimental Section

Nmr spectra were obtained with a Varian A-60 spectrometer. Elemental analyses were done on all new compounds by Mrs. K. Decker of this department.

General Procedure of H–D Exchange.—A weighed sample of the appropriate polyazaindene was placed in an nmr tube and dissolved in a measured quantity of standardized acid or base. The nmr spectrum was immediately run and integrated. Exchange was followed by repeated integrations at selected time intervals. Exchange at 35° was obtained by allowing the sample to remain in the nmr probe. Exchange at 65 and 100° was obtained by placing the sample in refluxing methanol or water, respectively, and by removing the sample periodically for nmr analysis. All exchanges were followed to 85% completion.

3-Deuterioimidazo[1,2-*a*]pyridine Methiodide.—Imidazo[1,2-*a*]pyridine was heated at 95° for 19 hr in 3 *M* D_2SO_4, cooled, and neutralized with anhydrous Na_2CO_3 to pH 9. The aqueous solution was extracted with $CHCl_3$, the chloroform extract evaporated to dryness, and the residue dissolved in acetone. Excess iodomethane was added and the solution was allowed to stand overnight. The solution was then filtered, yielding 3-deuterioimidazo[1,2-*a*]pyridine methiodide containing 90% deuterium at position 3 as determined by nmr analysis.

Synthesis of the 6- and 7-Hydroxy-5,8-dioxocarbostyrils[1a]

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Received October 2, 1967

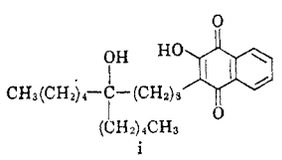
Utilizing a condensation reaction between amine I and methyl propiolate to obtain pyridone III followed by reaction with potassium *t*-butoxide and oxygen in dimethyl sulfoxide, a convenient synthesis of 6-hydroxy-5,8-dioxocarbostyril (V) was achieved. Conversion of 8-hydroxycarbostyril *via* dinitro (XII) and diamino (XIIIa) intermediates provided the isomeric 7-hydroxy-5,8-dioxocarbostyril (XV). The structures assigned to hydroxyquinones V and XV received support from mass spectral and proton magnetic resonance studies.

The potential application[2] of hydroxyquinolinequinones in certain malaria and cancer chemotherapy problems suggested extending our earlier study of carbostyrils[3] to the isomeric 6- (Scheme I) and 7-hydroxy-5,8-dioxocarbostyrils (Scheme II) (V and XV). Whereas syntheses of 6- and 7-hydroxy-5,8-quinolinequinones have been described,[4] no examples of the corresponding carbostyrils appear to have been reported. To allow quinones V and XV to serve efficiently as key intermediates for future studies in this area, initial emphasis was placed upon devising practical routes to both substances.

From a number of potential approaches to quinone V considered, one based on transforming 1,3-dioxocyclohexane to pyridone III appeared most attractive. In 1961, Zymalkowski[5] reported condensing propargyl aldehyde with an amine (I) derivative of 1,3-dioxocyclohexane and obtained the corresponding pyridyl ketone. More recently, the reaction was modified by using methyl propiolate and synthesis of pyridone III by this means was noted, albeit without detail, in a preliminary communication.[6] After brief warming, direct contact between amine I and methyl propiolate led to an exothermic reaction. At the end of 1 hr reaction temperature was raised to approximately 170° to complete cyclization (II → III). Employing lower reaction temperature allowed isolation of *trans*-olefin intermediate IV. The *trans* configuration was supported by a coupling constant of 17 cps for the olefin protons. Heating amino ester IV above 170° caused

(1) (a) This study received support from the U. S. Medical R and D Command under Contract DA-49-193-MD-3010 and National Science Foundation Grant GB-4939. The present manuscript is contribution number 279 from the Army Research Program on Malaria. (b) National Science Foundation Predoctoral Fellow.

(2) For example, from a number of napthoquinones prepared by L. F. Fieser and colleagues for antimalarial evaluation, lapinone (i) proved most promising. For an interesting and valuable review, see L. F. Fieser, J. P.



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Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967), and L. F. Fieser, "The Scientific Method," Reinhold Publishing Corp., New York, N. Y., 1964, p 190. Furthermore, the metabolic products of certain antimalarials have been shown to be quinolinequinones and carbostyrils: refer to R. R. Holmes, J. Conrady, J. Guthrie, and R. McKay, *J. Amer. Chem. Soc.*, **76**, 2400 (1954), and a review by P. B. Russell, "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 814. These facts augmented by an increasing number of naturally occurring quinones with cytotoxic and antibiotic properties enhanced our interest. Recent studies related to the quinolinequinone antitumor agent streptonigrin have been described by T. K. Liao, W. H. Nyberg, and C. C. Cheng, *Angew. Chem. Intern. Ed. Engl.*, **6**, 82 (1967); T. Kametani, K. Ogasawara, M. Shio, and A. Kozuka, *Yakugaku Zasshi*, **87**, 262 (1967); N. S. Nizuno, *Biochem. Pharm.*, **16**, 933 (1967); and C. W. B. Kremer and J. Laszlo, *Cancer Chemotherapy Rept.*, **51**, 19 (1967).

(3) G. R. Pettit and A. B. Neill, *Can. J. Chem.*, **42**, 1764 (1964); G. R. Pettit and M. Kalnins, *J. Org. Chem.*, **25**, 1365 (1960).

(4) The investigations of Drake and colleagues provide a useful summary of prior routes to hydroxyquinolinequinones; *cf.*, Y. T. Pratt and N. L. Drake, *J. Amer. Chem. Soc.*, **79**, 5024 (1957). Interestingly, certain of these quinolinequinones have displayed significant amebicidal activity against induced *E. histolitica* in the guinea pig.

(5) F. Zymalkowski and H. Rimek, *Arch. Pharm.*, **294**, 759 (1961).

(6) M. A. T. Sluyter, U. K. Pandit, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, 87 (1966).