The Reaction of Aryl Chloroformates with Dimethylformamide. A Facile *in Situ* Synthesis of α-Chlorocresols

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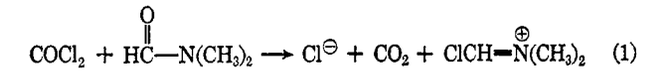
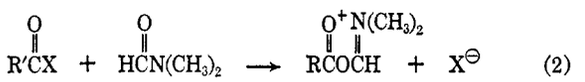
Aryl chloroformates react with dimethylformamide to liberate carbon dioxide and form aryloxy-substituted immonium salts. These in turn react with methanol to generate dimethylformamide, the corresponding phenol, and methyl chloride. An α-chlorotolyl chloroformate yields the α-chlorocresol which reacts with nucleophiles to give good yields of α-substituted cresols.

The reactions of acid halides with amides has been reviewed.[1] Most of these have involved inorganic chlorides (thionyl chloride, phosphorus oxychloride, phosgene) which characteristically yield halogen-substituted immonium salts[2] (eq 1). Some work has been

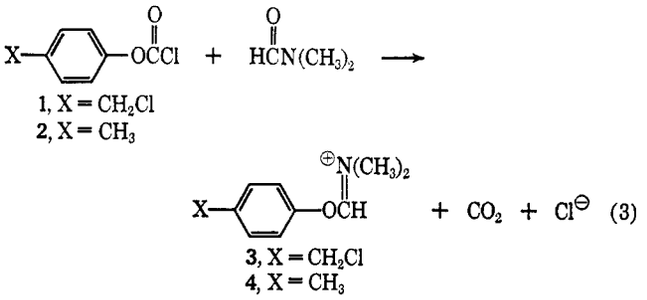


published on the reaction of organic acid halides with amides[1,2] wherein salts have been isolated and the composition designated as shown; however, there is

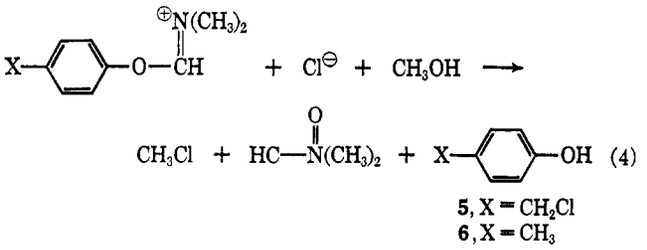


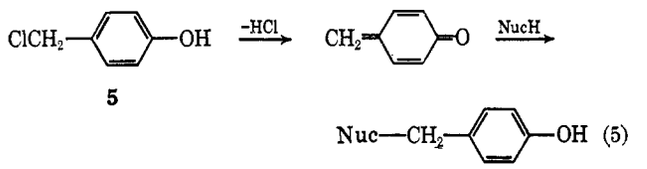
little information on the reaction of chloroformates with amides.[1] Bredereck[3,4] postulates an intermediate analogous to the product in eq 2 in the formation of tris(formylamino)methane from ethyl chloroformate and formamide and also in the amide-catalyzed rearrangement of alkyl cholorformates to alkyl chlorides. Hall[2] also attributes the conductivity of ethyl chloroformate solutions in dimethylformamide to this species.

We present here results of an investigation of the previously unreported reaction of aryl chloroformates with dimethylformamide. Using α-chloro-*p*-tolyl chloroformate (**1**) and *p*-tolyl chloroformate (**2**) the reaction presented in eq 3 occurs. Salts **3** and **4** react



with 1 mol of methanol, giving dimethylformamide and methyl chloride (eq 4). The corresponding phenol,





α-chloro-*p*-cresol (**5**) or *p*-cresol (**6**), is also found in essentially quantitative yield. Product **5** may then be treated with any of a number of nucleophiles to give good yields of α-substituted cresols, perhaps by way of an intermediate quinone methide[5] (eq 5).

α-Chloro-*p*-tolyl Chloroformate (**1**).—On mixing **1** with excess dimethylformamide there is a vigorous reaction and *ca.* 1 mol of carbon dioxide is liberated. A hygroscopic salt precipitates from solution (at 1–2 *M* concentration) for which elemental analyses are in agreement with **3**. The infrared spectrum shows a strong band at 1710 cm^{-1} ($C{=}N^{\oplus}$)[6] and a strong band appears at 1280 cm^{-1} (aryl–oxygen stretching). Nmr studies are confirmatory. After a short reaction time the spectrum of an equimolar mixture of **1** and dimethylformamide shows less than 5% of either starting material. The dimethylformamide portion of the spectrum shows a shift in the aldehydic proton from 8.05 to 10.50 whereas the methyl protons (originally at 2.83 and 2.94) appear at 3.37 and 3.66 ppm. Those at higher field are split (*ca.* 1.5 Hz) probably owing to *trans* coupling with the aldehydic proton although the reciprocal splitting was not resolvable. These data compare with spectra of the salt from dimethylformamide and phosgene presented by Martin and Martin.[7] With respect to the portion of the spectrum derivable from **1**, the benzylic protons are unchanged at 4.70, whereas the A_2B_2 aromatic pattern (7.26 and 7.52 ppm, J = 9 Hz) has collapsed to a single peak at 7.58 ppm. The downfield shifts (relative to starting materials) and also the increased nonequivalence of the N-methyl groups are all in accord with changes expected with **3**.

When a solution of **3** is treated with incremental amounts of methanol, the spectrum diminishes and after 1 mol has been added it is replaced by an entirely new one. This contains peaks representing 1 mol of methyl chloride (3.03 ppm), 1 mol of free dimethylformamide and what appears to be 1 mol of α-chloro-*p*-cresol (**5**). This is not isolable and attempts at isolation gave only resinous products. However it seems

(1) (a) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960); (b) H. Bredereck, R. Gomper, H. v. G. Schuh, and G. Theilig, *ibid.*, **71**, 753 (1959); (c) M. Matzner, R. P. Kurkjy, and R. J. Colter, *Chem. Rev.*, **64**, 645 (1964).

(2) H. K. Hall, *J. Amer. Chem. Soc.*, **78**, 2717 (1956).

(3) H. Bredereck, R. Gomper, H. Rempfer, K. Klem, and H. Keck, *Chem. Ber.*, **92**, 329 (1959).

(4) H. Bredereck, F. Effenberger, and G. Simchen, *ibid.*, **96**, 1350 (1963).

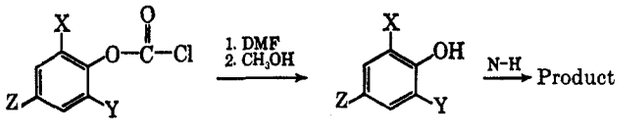
(5) (a) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, No. 25, 9 (1960); (b) A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

(6) A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).

(7) G. Martin and M. Martin, *Bull. Soc. Chim. Fr.*, 1637 (1963).

TABLE I

PREPARATION OF α CHLOROCRESOLS AND REACTION WITH NUCLEOPHILES



X	Y	Z	N	Product	Yield, %
H	H	CH_2Cl	$-CH_3O$	α-Methoxy-*p*-cresol	85
H	H	CH_2Cl	$[CH_3C(=O)]_2CH-$	$[CH_3C(=O)]_2CHCH_2$ 	78
H	H	CH_2Cl	N≡C–	α-Cyano-*p*-cresol	45
H	H	CH_2Cl	$[C_2H_5O]_2P$	4-Diethylphosphonomethyl phenol	93
$-CH_3$	$-CH_2Cl$	H	$[C_2H_5O]_2P$	2-Methyl-6-diethylphosphonomethyl phenol	74
$-CH_2Cl$	$-CH_2Cl$	H	$[C_2H_5O]_2P$	2-Ethoxy-2-oxo-7-diethylphosphonomethyl-1,2-benzoxaphosphole	29

to be quite stable in solution. The nmr spectrum shows two benzylic protons at 4.70 ppm suggesting that their environment is unchanged and that the chloromethyl moiety is intact through the series of reactions. The aromatic protons now appear at 6.93 and 7.23 ppm (J = 9 Hz) with the total envelope shifted to higher field than in **1** and **3** owing to the removal of the deshielding positive group.

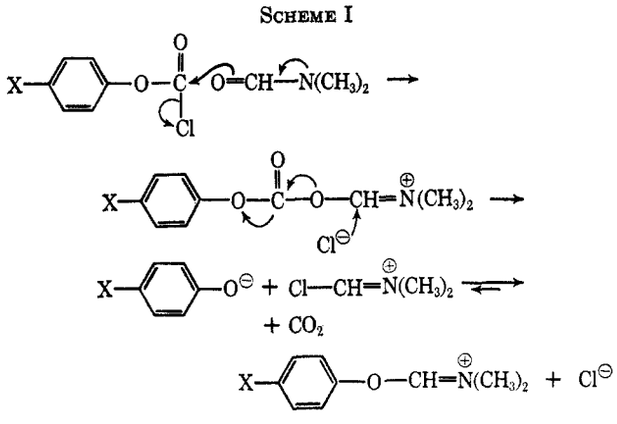
The preparation of simple, unsubstituted α-chlorocresols has been difficult[8] and has been reported infrequently. Thus to further substantiate the above synthesis of **5**, it was desirable to carry out the sequence so that the final product would be a stable, known material.

The reaction of **2** with dimethylformamide gave a product analogous with that formed from **1**, which may be represented by structure **4**. The methyl groups of the dimethylformamide are shifted to 3.36 and 3.65 with the upfield group showing a split of *ca.* 1.5 Hz whereas the aromatic protons are deshielded relative to those in **2** (7.25 ppm) and appear as an A_2B_2 pattern at 7.25 and 7.48 ppm (J = 9 Hz). The protons of the aromatic methyl group remain at 2.35 ppm. On treatment with 1 mol of methanol, the spectrum of a solution of salt **4** disappears and is replaced by one showing 1 mol of methyl chloride, 1 mol of free dimethylformamide, and *p*-cresol (CH_3–, 2.25 ppm; aromatic protons, 7.07 and 6.74 ppm, J = 7 Hz).

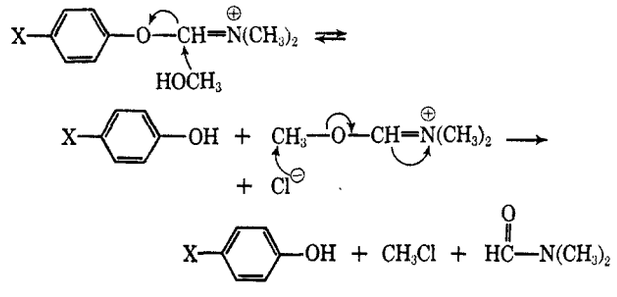
It will be noted that the relationship of the nmr spectra of **2**, **4**, and **6** very closely parallels that of **1**, **3**, and **5** providing further support for the structure of α-chloro-*p*-cresol.

A mechanism for the first reaction may be presented as in Scheme I. The first step, nucleophilic displacement of chloride ion by dimethylformamide, finds analogy in the work of Hall[2] with the reaction of dimethylformamide and acetyl bromide. The second step explains the loss of carbon dioxide and is reasonable since the stability of chloroimonium salts is documented.[7] The final equilibrium should be dependant on the relative basicities of the phenolate and chloride ions and should lie well to the left (in solution) to give the product observed by nmr. Again, in the second reaction (Scheme II) the mechanism accounts for the products and similar mechanisms have been proposed

SCHEME I



SCHEME II



in analogous cases. However, our data do not permit speculation on the more detailed aspects.

Reactions of α-Chlorocresols.—With the preceding spectroscopic evidence that α-chlorocresols could be prepared with ease, it was of interest to demonstrate their synthetic utility. For this reason we prepared several different types from the corresponding chloroformates and utilized them in reaction with nucleophiles. A summary of experimental methods and results is given in Table I.

The reactions were generally carried out by reacting the α-chlorotolyl chloroformate with *ca.* 1 mol of dimethylformamide, then with 1 mol of methanol followed by 1 mol of nucleophile. As shown, the reactions were straightforward and the yields high in most cases. The reaction is general for the preparation of α-substituted cresols. The physical constants for α-methoxy-*p*-cresol and α-cyano-*p*-cresol agree with literature data. Analytical, infrared, and nmr data are consistent with assigned structures in other cases.

(8) G. A. Olah and W. S. Tolgyesi in "Friedel-Crafts and Related Reactions," Vol. 2, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 21.

Experimental Section[9]

Aryl Chloroformates. *p*-Tolyl Chloroformate.—A solution of 1100 g (10.2 mol) of *p*-cresol in 5 l. of toluene was cooled to −10° and 1500 g (15.2 mol) of phosgene was passed into it. The cold solution was then neutralized with 20% sodium hydroxide solution. The product layer was separated and distillation yield 1230 g (71%) of product, bp 97–100° (14 mm) and $n^{25}D$ 1.5100 (lit.[10] bp 108° (30 mm)).

2,6-Xylyl Chloroformate—This material was prepared in the same manner used with *p*-tolyl choroformate using 373 g (3.0 mol) of 2,6-xylenol and 483 g (4.8 mol) of phosgene. Distillation yielded 448 g (81%) of product, bp 155–157° (150 mm) and $n^{25}D$ 1.5023.

Anal. Calcd for $C_9H_9ClO_2$: C, 58.58; H, 4.93; Cl, 19.22. Found: C, 58.58; H, 4.67; Cl, 19.24.

α-Chlorotolyl Chloroformates. α-Chloro-*p*-tolyl Chloroformate.[11]—A mixture of 1110 g (6.5 mol) of *p*-tolyl chloroformate, 23.1 g of phosphorous trichloride, and 2.3 g of benzamide was heated at 135° while a mixture of 12.3 g of benzoyl peroxide and 995 g (7.4 mol) of sulfuryl chloride was added over a period of 6 hr. Distillation yielded 885 g (66%) of product, bp 127–130° (4.5 mm) and mp 60.5–61.5° (from benzene–hexane).

Anal. Calcd for $C_8H_6Cl_2O_2$: C, 46.82; H, 2.95. Found: C, 47.17; H, 3.06.

α-Chloro-2,6-xylyl Chloroformate and α,α′-Dichloro-2,6-xylyl Chloroformate.—These were prepared using the method outlined above in the reaction of 420 g (2.3 mol) of 2,6-xylyl chloroformate, 17 g of phosphorous trichloride, 1.7 g of benzamide, 7 g of benzoyl peroxide, and 740 g (5.5 mol) of sulfuryl chloride. Distillation yielded 124 g (25%) of α-chloro-2,6-xylyl chloroformate, bp 135–145° (10 mm) and $n^{25}D$ 1.5310.

Anal. Calcd for $C_9H_8Cl_2O_2$: C, 49.34; H, 3.68; Cl, 32.4. Found: C, 49.79; H, 3.59; Cl, 32.4.

A second fraction in the distillation yielded 143 g (25%) of α,α′-dichloro-2,6-xylyl chloroformate, bp 162–165° (10 mm) and mp 71.5–73.5 (from benzene–hexane).

Anal. Calcd for $C_9H_7Cl_3O_2$: C, 42.58; H, 2.78; Cl, 42.2. Found: C, 42.02; H, 2.78 Cl, 41.8.

Reaction of Dimethylformamide and α-Chloro-*p*-tolyl Chloroformate.—A mixture of 10.2 g (0.050 mol) of α-chloro-*p*-tolyl chloroformate and 50 ml of dimethylformamide was stirred for 0.5 hr. There was a vigorous reaction, gas was evolved, and a precipitate was formed. The precipitate was collected, washed with ether, and dried *in vacuo*. Spectral data are discussed in the text.

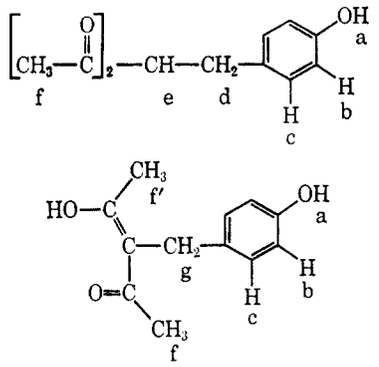
Anal. Calcd for $C_{10}H_{13}Cl_2NO$: Cl, 30.3; N, 6.0. Found: Cl, 30.6; N, 6.0.

In a small-scale experiment, the gas was measured manometrically and amounted to 85% of theory. It was shown to be carbon dioxide by bubbling into limewater and by comparison of the infrared spectrum with that of an authentic sample.

Preparation and Reactions of α-Chloro-*p*-cresol.—As a general procedure 1 mol of α-chloro-*p*-tolyl chloroformate and 1 mol of dimethylformamide were allowed to react for 1 hr in 750 ml of acetonitrile. Methanol (1 mol) was then added and the mixture was stirred for an additional 0.5 hr to form α-chloro-*p*-cresol.

α-Methoxy-*p*-cresol.—A solution of 0.10 mol of the salt of dimethylformamide and α-chloro-*p*-tolyl chloroformate was prepared as above and allowed to react for 1 hr with 125 ml of methanol. The reaction mixture was diluted with water and extracted with ether, and after drying over sodium sulfate, the residue from solvent evaporation was triturated with hexane to yield 14.2 g (85%) of product, mp 79–80° (lit.[12] mp 82.5–83.5°).

3(4′Hydroxybenzyl)-2,4-pentanedione.—A solution of 0.10 mol of α-chloro-*p*-cresol, 10.1 g (0.10 mole) of triethylamine and 10.0 g (0.10 mol) of 2,4-pentanedione was stirred for 1 hr. After the usual treatment the residual oil from solvent evaporation was triturated with benzene to yield 16.0 g (78%) of product, mp 93–94.5° (from ethanol–water). The infrared spectrum was consistent with the assigned structure showing strong hydroxyl absorption and split carbonyl absorption at 1690 and 1720 cm^{-1} (due to keto and enol tautomers). The nmr spectrum is also appropriate and again shows the presence of both the keto and enol structures (δ, ppm (in $CDCl_3$)): a, 8.12; b, doublet, J =

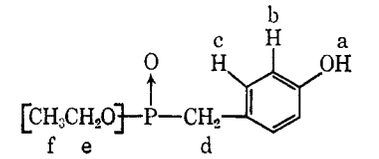


8 Hz, 6.80; c, doublet, J = 8 Hz, 7.12; d, 1.8 protons, doublet, J = 7 Hz, 3.05; e, 0.8 proton, triplet, J = 7 Hz, 4.17; f, 2.12; f′, 2.06; g, 0.4 proton, 3.62.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 70.0; H, 6.84. Found: C, 70.1; H, 6.86.

α-Cyano-*p*-cresol.—A solution of 0.10 mol of α-chloro-*p*-cresol, and 4.9 g (0.10 mol) of sodium cyanide in 75 ml of acetonitrile and 100 ml of methanol was refluxed for 1 hr. The usual procedure yielded 6 g (45%) of product, mp 68–70° (from benzene) and bp 150–155° (1 mm) (lit.[13] mp 69–70°, bp 330.5°).

4-Diethylphosphonomethylphenol.—On addition of 16.6 g (0.10 mol) of triethyl phosphite to a solution of 0.10 mol of α-chloro-*p*-cresol there was a gentle exotherm. The reaction mixture was heated to 175°, removing solvent by distillation. The usual procedure yielded 22.8 g (93%) of product, mp 89–91°

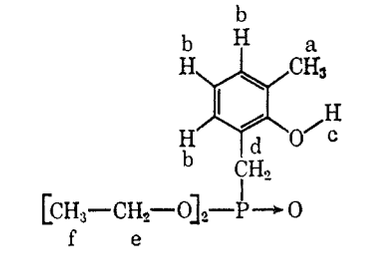


(from tetrahydrofuran–ether–hexane). The infrared and nmr spectra were consistent. Nmr signals (δ, ppm (in $CDCl_3$)) were a, 8.27; b, doublet, J = 8 Hz, 6.65; c, ABX, J_b = 8 Hz, J_P = 3 Hz, 7.05; d, doublet, J = 21 Hz, 3.05; e, ABC, J_f = 8 Hz, J_P = 8 Hz, 3.97; f, triplet, J = 8 Hz, 1.19.

Anal. Calcd for $C_{11}H_{17}O_4P$: C, 54.1; H, 7.03; P, 12.7. Found: C, 54.3; H, 6.98; P, 12.8.

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

2-Methyl-6-diethylphosphonomethylphenol.—A solution of 0.10 mol of α-chloro-2,6-xylyenol and 16.6 g (0.10 mol) of triethyl phosphite in 75 ml of acetonitrile was heated on a steam bath for 1 hr. Following the usual procedure, distillation of the oil from solvent evaporation yielded 19.0 g (74%) of product,



bp 100–125°(1 μ). The infrared and nmr spectra were consistent. Nmr signals (δ, ppm (in CCl_4)) were a, 2.27; b, 6.5–7.2; c, 8.5; d, doublet, J = 21 Hz, 3.08; e, ABC, J_f = 7 Hz, J_P = 7 Hz, 4.00; f, triplet, J = 7 Hz, 1.24.

(9) All melting and boiling points are uncorrected. Infrared spectra were obtained as Nujol mulls or neat smears using a Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were obtained with a Varian Associates Model A-60 spectrometer. Except where otherwise stipulated, these spectra were obtained in acetonitrile solution. In all spectra TMS was used as the standard.

(10) M. Capisarow, *J. Chem. Soc.*, 251 (1929).

(11) This compound was first prepared by E. D. Weil in these laboratories and the preparative method is presented with his gracious permission.

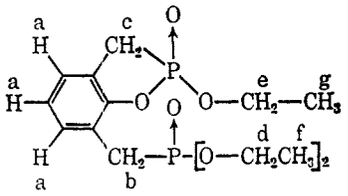
(12) J. deJonge and B. H. Bibo, *Rec. Trav. Chim.*, **74**, 1448 (1955).

(13) H. Will and A. Laubenheimer, *Ann.*, **199**,150 (1879).

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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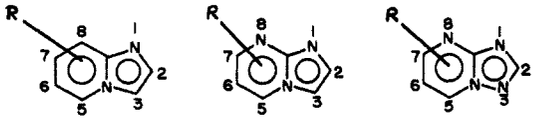
The acid-catalyzed deuterium–protium exchange of compounds **1**, **2**, and **3** occurs at the positions typical for electrophilic substitutions. These substitutions are shown to occur on the free bases. The base-catalyzed deuterium–protium exchange of compounds **1**, **2**, and **3** occurs at positions 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.

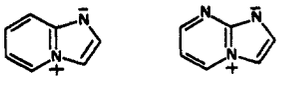
TABLE I

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).