An Investigation of the Minimal Structural Conditions for the Dimroth-Type Rearrangement in the Polyazaindolizine Series

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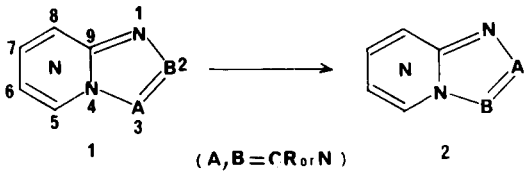
In the imidazo[1,2]diazine series, only the imidazo[1,2-*a*]- and [1,2-*c*]pyrimidine systems were found to undergo a Dimroth-type rearrangement under basic aqueous conditions. The electronic and steric factors influencing the rearrangement rates of methyl substituted imidazo-[1,2-*a*]pyrimidines are discussed.

During the last ten years, the Dimroth-type rearrangement **1** → **2** has been shown to occur in several polyazaindolizine systems (see Table I). However, few specific studies of the rearrangement in this series are found in the literature apart from a very recent investigation in the *s*-triazolo[4,3-*a*]pyridine series (2).



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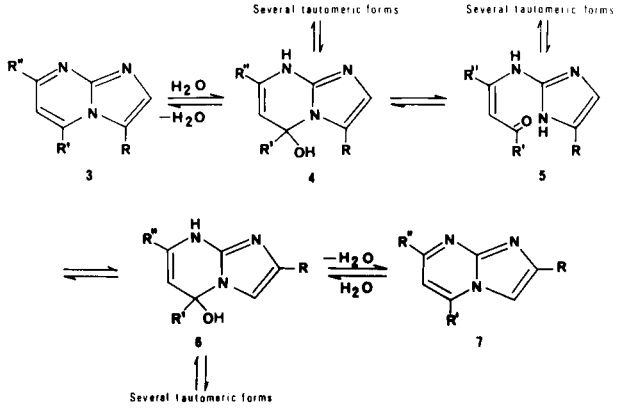
As part of our continuing interest in the chemistry of polyazaindolizines, we have investigated the structural requirements for the occurrence of the rearrangement, and we wish to report some preliminary results of this study.

The rearrangement **1** → **2** can occur in basic as well as acidic media. It is generally accepted that the initial step of the base catalyzed reaction involves nucleophilic attack at position 5 by hydroxide ion. Following hydration, the six-membered ring undergoes tautomeric ring opening; the intermediate **5** then cyclizes to give **7**. This mechanism parallels that proposed for the Dimroth rearrangement (16,17,19). The isolation of an intermediate under basic conditions was possible in the tetrazolo[1,5-*a*]pyrimidine series (12); an intermediate was also isolated in acidic media (13). In brief, the rearrangement appears to be a rather complex sequence of several steps involving two fundamental phenomena: covalent hydration of a C=N bond, and ring-chain tautomerism. Depending on the number and arrangement of the *N*-atoms in the six-membered ring, covalent hydration occurs either at position 5 or 7 (18), or at position 8 (11).



3 4 5 6 7

Results.

Since a nitrogen atom must occupy position 1 of the azaindolizine system, the imidazo[1,2-*a*]pyridine **8** system would be expected *a priori* to undergo the Dimroth-type rearrangement. However, after 24 hours at 90° in aqueous 5% sodium hydroxide, 3-methylimidazo[1,2-*a*]pyridine (20) showed no rearrangement. Substitution of the ring at positions 6 or 8 with electron-withdrawing groups, however, should induce the rearrangement.

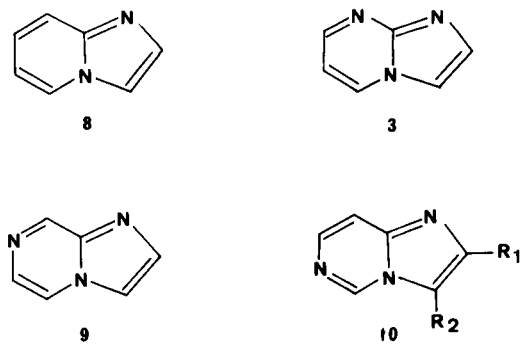


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TABLE I

Survey of Known Dimroth-Type Rearrangements in the Polyazaindolizine Series

Compounds to be rearranged	Conditions
s-triazolo[4,3-*a*]pyridines	Reflux 24 hours in 10% aqueous sodium hydroxide (3); or 30 minutes in 10% sodium hydroxide if a nitro group is present at position 8 (2).
s-triazolo[4,3-*c*]pyrimidines	Sixteen hours in 2*N* sodium hydroxide at 20°, or 15 minutes in 1*N* hydrochloric acid at 20° (4); in 1*N* sodium hydroxide at room temperature or in refluxing formic acid (5).
s-triazolo[4,3-*a*]pyrimidines	Reflux in formic acid (6,7); 30 minutes reflux in 1.25*N* sodium hydroxide or in 1.25*N* hydrochloric acid (8).
s-triazolo[4,3-*a*]pyrazines	Reflux 60 hours in 10% sodium hydroxide (9); in acidic medium a different rearrangement occurs (10,11).
s-triazolo[4,3-*d*]-*as*-triazines	In formic acid, at room temperature or reflux (14).
s-triazolo[3,4-*c*]-*as*-triazines	In acidic or neutral media (15).
tetrazolo[1,5-*a*]pyrimidines	0.1*N* sodium hydroxide at room temperature (14).
tetrazolo[1,5-*c*]pyrimidines	2*N* hydrochloric acid at room temperature: the open chain compound was obtained (13).

Another possible method considered for activating the system was the introduction of an additional nitrogen atom into the six-membered ring, that is, utilizing the imidazo[1,2-*a*]pyrazine (**9**), -pyrimidine (**3**), or imidazo-[1,2-c]pyrimidine (**10**) systems. Because of their electron withdrawing properties, the extra aza-groups of the last two systems should activate the 5-position and indeed it was found that they both underwent a base-catalyzed Dimroth-type rearrangement.

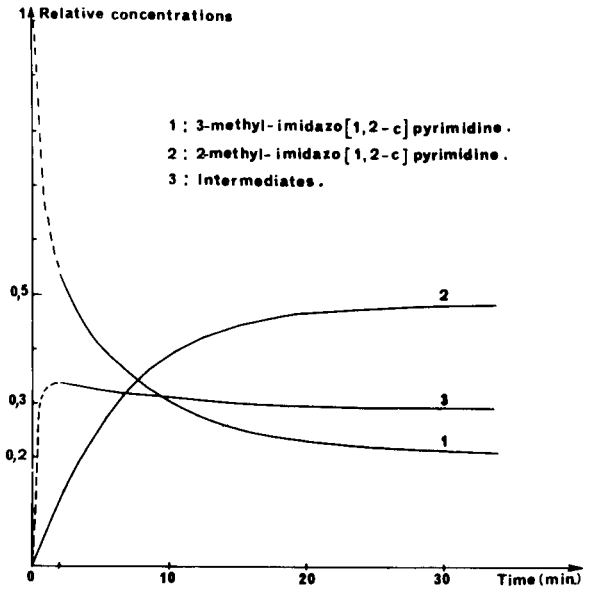
When 3-methylimidazo[1,2-*a*]pyrimidine **3** (R = CH_3, R′ = R″ = H) in aqueous 1% sodium hydroxide was heated at 90° in an nmr tube, it rearranged to 2-methylimidazo[1,2-*a*]pyrimidine **7** (R = CH_3, R′ = R″ = H). The reaction was not complete and the same equilibrium conditions were reached from both 3-methyl- and 2-methylimidazo[1,2-*a*]pyrimidine (Table II). The rearrangement was followed kinetically by nmr and no foreign compound or intermediate was detected. Decomposition was negligible, thus permitting the rate constant to be calculated. However, increasing the proportion of sodium hydroxide to 5 or 10% resulted in appreciable decomposition of these compounds.

Similarly 3,5-dimethylimidazo[1,2-*a*]pyrimidine, 3,7-dimethylimidazo[1,2-*a*]pyrimidine and 3,5,7-trimethylimidazo[1,2-*a*]pyrimidine rearranged to the corresponding isomer **7**. 3,7-Dimethyl- and 2,7-dimethylimidazo[1,2-*a*]-pyrimidines were equilibrated at the end of reaction (Table II) and the equilibrium was reached separately from each compound. All the preceding reactions gave overall pseudo-first order kinetics. Moreover, varying the base concentration in the rearrangements of 3,5-dimethylimidazo-[1,2-*a*]pyrimidine gave a first order rate constant (Table II); therefore, one or more rate-determining steps are base catalyzed. As expected, 3-methyl- or 2-methylimidazo[1,2-*a*]pyrazines (*cf.* **9**) failed to rearrange under the same conditions.

Five-membered heterocycles are known to undergo the Dimroth rearrangement (21) but the possibility of an imidazole ring fission was unlikely in our case and was dismissed since the 5- and 7-substituents are not interchanged upon rearrangement.

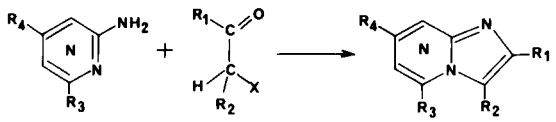
3-Methylimidazo[1,2-*c*]pyrimidine **10** (R_1 = H, R_2 = CH_3) rearranged to 2-methylimidazo[1,2-*c*]pyrimidine **10** (R_1 = CH_3, R_2 = H) about 130 times faster than 3-methylimidazo[1,2-*a*]pyrimidine under the same conditions. 3-Methyl- and 2-methylimidazo[1,2-*c*]pyrimidines were equilibrated under the same conditions used; moreover, a rapid build up (in less than two minutes) of other compounds was observed in the nmr study of this rearrangement (Fig. 1). The total concentration of these compounds remained constant after the first two minutes suggesting that they are intermediates; this allows calculation of the first order rate constant (see Table II). A comparison of the corresponding nmr signals (mainly at 5.64, 6.75, 6.87 and 8.25 δ in water/ethanol = 70/30 with sodium 3-(trimethylsilyl)propanesulfonate as internal reference) with those of tetrazolo[1,5-*c*]pyrimidine covalent hydrate (22) suggests that the detected intermediates result from the covalent hydration of a CN bond in 2-methyl- and 3-methylimidazo[1,2-*c*]pyrimidines. Complementary studies concerning the nature of these compounds will be reported in a future publication.

A few rearrangements were attempted in acidic media with no success. Thus 3-methylimidazo[1,2-*a*]pyridine in 10% aqueous hydrochloric acid, and 3,7-dimethyl-5-oxo-8*H*-imidazo[1,2-*a*]pyrimidine in formic acid were



unchanged after 24 hours at 90°. Further studies of the rearrangements of 3-methylimidazo[1,2]diazines in acidic media are planned.

The 2-methyl- and 3-methylimidazo[1,2-*a*] and [1,2-*c*]-pyrimidines (*cf.* **3** and **10**) were prepared by condensing 2- or 4-aminopyrimidines with a suitable α-halogeno carbonyl compound (23). In methanol, the orientation of the reaction from 2-aminopyrimidine is such that the exocyclic nitrogen atom always attacks the carbonyl group, even when R_2 and R_3 interact sterically (see later). 4-Aminopyrimidine condensed with 2-bromopropanal in methanol to give low yields of both 2-methyl- and 3-methylimidazo[1,2-*c*]pyrimidines. The proportions of the products vary from one run to the other which suggests that a rearrangement takes place rather than a different orientation of the reaction compared to the case of 2-aminopyrimidine. The yields of these reactions probably reflect the differences in basicity between 2- and 4-aminopyrimidines; more precisely, one must consider the nucleophilicities of the nuclear nitrogen atoms towards the sp^3-carbon of the α-halocarbonyl compound and take into account the possibility of tautomerism.



The nmr parameters of imidazo[1,2-*a*]pyrimidines **3** have been sufficiently investigated to allow unambiguous assignments of the peaks in the spectra of 2- and 3-methylimidazo[1,2-*a*]pyrimidines (see Table V): thus H_2 is always found at lower field than H_3 (24). The assignments of the nmr spectra of 2- and 3-methylimidazo[1,2-*a*]-pyrazines (*cf.* **9**) and 2- and 3-methylimidazo[1,2-*c*]-pyrimidines (*cf.* **10**) were based on the assumption that the syntheses from aminoazines and 2-bromopropanal or chloroacetone are selective, or on the anticipated existence of a long distance coupling ($0.5 \text{ Hz} < J < 1 \text{ Hz}$) between H-3 and H-8 (as in indolizine (25) or in pyrrolo[1,2-*a*]-pyrazine (26)). Thus 2-methyl- and 3-methylimidazo-[1,2-*c*]pyrimidines were characterized by comparing the splitting and shapes of the H-2 or H-3, and H-8 signals in 3-methyl- or 2-methylimidazo[1,2-*c*]pyrimidines, respectively.

TABLE II

Kinetics of the Rearrangements (90.1°) (a)

Reaction	Solvent	Equilibrium constant (K) and first order rate constant (k)
3 ($R = CH_3$, $R' = R'' = H$) $\overset{k}{\rightleftharpoons}$ **7** ($R = CH_3$, $R' = R'' = H$)	H_2O [NaOH] = 0.24 mole/l	K = 2.3 $k = 7.1 \times 10^{-4}$ sec^{-1}
3 ($R = R' = CH_3$, $R'' = H$) → **7** ($R = R' = CH_3$, $R'' = H$)	aqueous ethanol 30% (b) [NaOH] = 0.17 or 0.032 mole/l	$k = 2.6 \times 10^{-3}$ sec^{-1}
3 ($R = R'' = CH_3$, $R' = H$) $\overset{k}{\rightleftharpoons}$ **7** ($R = R'' = CH_3$, $R' = H$)	aqueous ethanol 30% [NaOH] = 0.16 mole/l	K = 1.3 $k = 1.9 \times 10^{-4}$ sec^{-1}
3 ($R = R' = R'' = CH_3$) → **7** ($R = R' = R'' = CH_3$	aqueous ethanol 30% [NaOH] = 0.17 mole/l	$k = 2.4 \times 10^{-4}$ sec^{-1}
10 ($R_1 = H$, $R_2 = CH_3$) $\overset{k}{\rightleftharpoons}$ **10** ($R_1 = CH_3$, $R_2 = H$)	aqueous ethanol 30% [NaOH] = 0.026 mole/l	K = 2.5 $k = 9 \times 10^{-2}$ sec^{-1}

(a) Under the same conditions, using a sodium hydroxide concentration of 0.16 mole/l in water, 3-methyl- or 2-methylimidazo[1,2-*a*]-pyridines and 3-methyl- or 2-methylimidazo[1,2-*a*]pyrazines were unchanged after 48 hours. (b) Volume/volume: 30% of ethanol. The corresponding compounds were insufficiently soluble in water alone.

Discussion.

The preceding data seem consistent with the accepted mechanism of the Dimroth rearrangement (19) but the question still arises as to whether the observed reactions are real Dimroth rearrangements or not. No intermediate build up was detected within experimental error (except in the imidazo[1,2-*c*]pyrimidine series), in contrast to previous kinetic studies (19) where the involved intermediate was thought to be the open chain compound (corresponding to **5**).

The addition of water to the C=N bond can occur by a number of different mechanisms involving specific or general base-catalyzed attack of the unprotonated or protonated imine group (27). In the case of imidazo-[1,2-*a*]- or [1,2-*c*]pyrimidines, the mechanism is further complicated by the possibilities of 1,4-addition or tautomerism. The reaction species could conceivably be either the neutral molecule or the cation by analogy with other heterocyclic systems (28). However, the pK_a values of the investigated heterocycles (29) and the conditions for the rearrangement should favor the mechanism corresponding to the hydration of the neutral molecule.

Our kinetic results are best explained by an initial rate-determining attack at position 5 by hydroxide ion. The driving force of this first step is electronic in nature since it is dependent on the electrophilic properties of the 5 position. On the other hand, the formation of the hydrated compound **4** should relieve the steric interaction between the two *peri* groups R and R′. These two factors, electronic and steric, will be examined successively.

The electron densities of a number of pertinent polyazaindolizine systems have been calculated (Table III); the total π-electron density was obtained from HMO calculations and the total electron density by the CNDO-2 method. The calculation of these values allows a classification of various polyazaindolizines according to their π-electron density at position 5. The results of these calculations show that an aza-group at position 6 or 8 renders the 5 position more electrophilic while at position 7 it has no effect; moreover, an extra nitrogen atom at position 2 decreases the π-electron density at position 5 more than a nitrogen atom at position 3. Assuming that the attack of the hydroxide ion is rate-determining, the experimental results (Table II) can thus be rationalized (30). By contrast, in the methylimidazo[1,2-*a*]pyrimidine series, the results obtained from the CNDO-2 method are not consistent with the electron-donating properties of the methyl groups.

The methyl substituents are known to slow down the rate of ring-opening and it has been proposed that this is a consequence of the reduced polarization of the bond to be hydrated (19). A comparison of the rearrangement rates of **3** (R = CH_3, R′ = R″ = H) and **3** (R = R″ = CH_3, R′ = H) clearly shows the retarding effect of a 7-methyl substituent on the rearrangement of the imidazo[1,2-*a*]pyrimidine system assuming there is no solvent effect.

When a methyl group is attached to the carbon atom of the C=N bond to be hydrated, it has a "blocking effect" on covalent hydration (28). This effect is difficult to detect in the rearrangement of the 5-methylimidazo-[1,2-*a*]pyrimidines because it is masked by the more important steric effect between the 5-methyl group and the necessary 3-methyl group.

TABLE III

Electron Density Calculations

Polyazaindolizines	Electron density at position 5 HMO	CNDO-2
imidazo[1,2-*a*]pyrazine **9**	0.826	–
imidazo[1,2-*a*]pyridine **8**	0.819	–
imidazo[1,2-*a*]pyrimidine **3**	0.711	3.891
2-methylimidazo[1,2-*a*]pyrimidine	–	3.890
3-methylimidazo[1,2-*a*]pyrimidine	–	3.886
3,5-dimethylimidazo[1,2-*a*]pyrimidine	–	3.797
3,7-dimethylimidazo[1,2-*a*]pyrimidine	–	3.883
s-triazolo[1,5-*a*]pyrimidine	0.685	3.875
s-triazolo[4,3-*a*]pyrimidine	0.667	3.884
imidazo[1,2-*c*]pyrimidine **10**	0.626	–
2-methylimidazo[1,2-*c*]pyrimidine	–	3.843
3-methylimidazo[1,2-*c*]pyrimidine	–	3.839
s-triazolo[1,5-*c*]pyrimidine	0.631	–
s-triazolo[4,3-*c*]pyrimidine	0.597	–
imidazo[1,2-*a*]-*s*-triazine	0.528	–
s-triazolo[1,5-*a*]-*s*-triazine	0.520	–
s-triazolo[4,3-*a*]-*s*-triazine	0.484	–

The existence of a *peri*-interaction between two substituents, either at positions 1 and 8, or at 3 and 5, has been previously established in polyazaindolizine systems. Thus, both the 3- and 5-methyl groups of 3,5-dimethylimidazo[1,2-*a*]pyridine are deshielded in the nmr spectrum when compared to the corresponding signals of the monomethyl compounds (31). Similarly, the interaction between the 1- and 8-methyl groups has been used to assign the *N*-methylation products of *s*-triazolo[4,3-*a*]pyridine (32) and imidazo[1,2-*a*]pyridine (33). Such an effect very probably influences the rates of at least two steps in the rearrangement of 3,5-dimethylimidazo[1,2-*a*]pyrimidines. The change in hybridization of carbon-5 upon hydration diminishes the steric interaction between the 3- and 5-substituents thus stabilizing **4** and **6** compared to **3** and **7**, respectively. Then, the ring-chain tautomeric fission of the 4-5 bond is more likely to occur in **4** than in **6** because of the residual interaction between the 3- and 5-substituents. This is in agreement with the increase in rate found in passing from 3-methyl- to 3,5-dimethylimidazo-[1,2-*a*]pyrimidines on one hand, and from 3,7-dimethyl- to 3,5,7-trimethylimidazo[1,2-*a*]pyrimidines on the other.

TABLE IV

Synthesis of Polyazaindolizines

Starting materials	Polyazaindolizines	Chromatographic Solvent	Yield	M.p. °C	Molecular Formulas	Analysis	C%	H%	N%
2-aminopyrimidine and chloracetone	**7** (R = CH_3, R′ = R″ = H)	AcOEt	60	72 (a)	$C_7H_7N_3$	Calcd.:	63.14	5.30	31.56
						Found:	63.08	5.30	31.38
2-aminopyrimidine and 2-bromopropanal	**3** (R = CH_3, R′ = R″ = H)	AcOEt	50	119	$C_7H_7N_3$	Found:	63.18	5.32	31.45
4-methyl-2-aminopyrimidine and chloracetone	**7** (R = R′ = CH_3, R″ = H)	AcOEt/C_6H_6 = 1/1	5	89	$C_8H_9N_3$	Calcd.:	65.28	6.16	28.55
						Found:	65.23	6.16	28.40
	7 (R = R″ = CH_3, R′ = H)	AcOEt	40	127 (b)		Found:	65.25	6.14	28.30
4-methyl-2-aminopyrimidine and 2-bromopropanal	**3** (R = R′ = CH_3, R″ = H)	AcOEt/C_6H_6 = 1/1	20	171	$C_8H_9N_3$	Calcd.:	65.28	6.16	28.55
						Found:	65.12	6.04	28.17
	3 (R = R″ = CH_3, R′ = H)	AcOEt	35	121		Found:	65.25	6.14	28.36
4,6-dimethyl-2-aminopyrimidine and chloracetone	**7** (R = R′ = R″ = CH_3)	AcOEt	50	151 (c)	$C_9H_{11}N_3$	Calcd.:	67.05	6.88	26.07
						Found:	66.94	6.92	26.35
4,6-dimethyl-2-aminopyrimidine and 2-bromopropanal	**3** (R = R′ = R″ = CH_3)	AcOEt	40	169	$C_9H_{11}N_3$	Found:	66.77	6.88	26.28
2-aminopyrazine and chloracetone	2-methylimidazo[1,2-*a*]pyrazine	AcOEt	20	89	$C_7H_7N_3$	Calcd.:	63.14	5.30	31.56
						Found:	63.22	5.37	31.51
2-aminopyrazine and 2-bromopropanal	3-methylimidazo[1,2-*a*]pyrazine	AcOEt	25	159	$C_7H_7N_3$	Found:	63.06	5.24	31.50
4-aminopyrimidine and 2-bromopropanal	3-methylimidazo[1,2-*c*]pyrimidine, and	AcOEt/C_6H_6 = 1/3	25	129	$C_7H_7N_3$	Calcd.:	63.14	5.30	31.56
	2-methylimidazo[1,2-*c*]pyrimidine	AcOEt/C_6H_6 = 1/9		–		Found:	63.41	5.40	

(a) This compound has already been described (23b). (b) *Ibid.* (23b). (c) *Ibid.* (36).

TABLE V

NMR Spectra of Polyazaindolizines (Deuteriochloroform)

Compounds	R_2	R_3	R_5	R_6	R_7	R_8	J_{23}	J_{56}	J_{67}	J_{57}	J_{58}	J_{78}
2-methylimidazo[1,2-*a*]pyrimidine (*cf.* **7**)	2.48d	7.37q	8.47q	6.83q	8.47q	–	0.8	6.7	4.1	2.0	–	–
3-methylimidazo[1,2-*a*]pyrimidine (*cf.* **3**)	7.62q	2.48d	8.27q	6.90q	8.55q	–	0.8	6.8	4.0	2.0	–	–
2,5-dimethylimidazo[1,2-*a*]pyrimidine (a)	2.52d	7.23q	2.60d	6.67d	7.60d	–	0.8	0.8	4.0	–	–	–
3,5-dimethylimidazo[1,2-*a*]pyrimidine (b)	7.58m	2.80	2.90	6.53d	8.33d	–	<0.5	<0.5	4.0	–	–	–
2,7-dimethylimidazo[1,2-*a*]pyrimidine	2.43d	7.20q	8.23d	6.67m	2.57	–	0.8	6.8	–	–	–	–
3,7-dimethylimidazo[1,2-*a*]pyrimidine	7.48q	2.45d	8.02d	6.78d	2.63	–	0.8	7.0	–	–	–	–
2,5,7-trimethylimidazo[1,2-*a*]pyrimidine	2.57d	7.13m	2.47d	6.53m	2.57d	–	0.8	0.8	–	–	–	–
3,5,7-trimethylimidazo[1,2-*a*]pyrimidine	7.25m	2.82d	2.67d	6.33m	2.48	–	0.8	0.8	–	–	–	–
2-methylimidazo[1,2-*a*]pyrazine (*cf.* **9**)	2.52d	7.53	8.04q	7.88d	–	9.00	0.7	4.5	–	–	1.4	–
3-methylimidazo[1,2-*a*]pyrazine	7.61	2.54d	7.88q	7.90d	–	9.09	0.8	4.8	–	–	1.2	–
2-methylimidazo[1,2-*c*]pyrimidine (*cf.* **10**)	2.50d	~7.45m	8.97d	–	7.90d	~7.45m	1	–	–	–	1.4	6.2
3 methylimidazo[1,2-*c*]pyrimidine	7.48m	2.60d	8.90d	–	7.97d	7.52q	1	–	–	–	1.2	6.2

(a) UV max: nm (ϵ): 229 (17200), 278 (3000), 287 (3600), 317 (3800). (b) UV max: nm (ϵ): 232 (19800), 278 (2500), 287 (2200).

Moreover, it is significant that the larger the interaction between the groups R = CH_3 and R′ = H, CH_3 the more the equilibrium is shifted towards **7** (Table II). In addition, the deshielding of the methyl protons in the nmr spectrum of 3,5-dimethylimidazo[1,2-*a*]pyrimidines (see the experimental part) compared to the corresponding monomethyl compounds shows that Van der Waals forces are operative.

The ground state total energies of 2-methylimidazo[1,2-*a*]pyrimidine **7** (R = CH_3, R′ = R″ = H), 2,7-dimethylimidazo[1,2-*a*]pyrimidine **7** (R = R″ = CH_3, R′ = H) and *s*-triazolo[1,5-*a*]pyrimidine have been calculated using the CNDO-2 approximation method. These compounds are thus predicted to be more stable than the isomeric 3-methylimidazo[1,2-*a*]pyrimidine, 3,7-dimethylimidazo[1,2-*a*]pyrimidine and *s*-triazolo[4,3-*a*]pyrimidine respectively; this again justifies the preceding experimental data. It also explains the well known experimental fact that *s*-triazoloazines **11** rearranges to *s*-triazoloazines **12** (Table I). This was already expected from

11 12

the calculation of the energies of the triazole tautomers, suggesting that 1,2,4-triazole is more stable than 1,3,4-triazole (34). The driving force of the rearrangement **11** → **12** should therefore originate from the larger interaction between N-1 and N-2 (CNDO total electron densities: 5.22 and 5.09 respectively) in **11** relative to N-3 and N-4 in **12** (electron densities: 5.20 and 4.91 respectively).

In conclusion, this study suggests that suitable polyazaindolizines undergo a Dimroth-type rearrangement closely related to the rearrangement in the pyrimidine series (19). The polyazaindolizines, especially the lower homologs, should be useful as substrates to differentiate between the influences of electronic and steric factors in the Dimroth rearrangement. Finally, the possible occurrence of the rearrangement in the imidazo[1,2-*a*]- and [1,2-*c*]pyrimidine series should be kept in mind whenever nucleophilic substitutions of these heterocycles are studied, particularly in basic aqueous media.

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EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. UV spectra were recorded in 95% ethanol on a Perkin-Elmer 137 apparatus. Nmr spectra were determined on Varian A-60 and T-60 spectrometers; chemical shifts are reported in δ units and coupling constants in Hz using TMS as internal reference.

Preparation and Characterization of Polyazaindolizines.

General Procedure.

The preparation of the starting materials have already been described in the literature.

An equimolar solution of α-halogenocarbonyl compound (0.1 mole) and aminodiazine in anhydrous ethanol (150 ml.) was refluxed until thin layer chromatography showed either that an equilibrium had been reached or that the aminoazine had been entirely consumed. The ethanol was then partly evaporated under reduced pressure and ether added to precipitate the hydrohalides of the products. An aqueous solution of the hydrohalides was neutralized with sodium carbonate and the solution was extracted with chloroform. The crude products in ethyl acetate were then rapidly passed down on a column of grade III alumina. The different isomers were then separated, again by chromatography, on a column of alumina and were finally purified by sublimation. The details for each separation are shown in Table IV and the nmr spectra of the products in Table V. Both 2- and 3-methylimidazo[1,2-*a*]pyridines were prepared according to the method of Paudler and Blewitt (35).

Kinetics (*cf.* Table II).

A sample of 30 to 50 mg. of compound was dissolved in 0.5 to 0.7 ml. of a sodium hydroxide solution; at room temperature no reaction occurs. A hermetically sealed nmr tube containing the solution was then immersed in a thermostatic water bath and the reaction was followed to at least 80% of completion by nmr spectroscopy. The nmr spectra were recorded with careful integration of suitable peaks; this technique is not very accurate, especially at the beginning and end of the kinetic curves but the UV absorptions of **3** and **7** are not sufficiently different for UV spectrometry to be used.

Calculations.

The HMO calculations of the polyazaindolizines were carried out using the Coulomb- and bond-integral parameters recently tested by G. Hafelinger (37) along with an overlap integral of S = 0.25. It must be pointed out that varying the parameters within a reasonable range does not change the qualitative patterns arising from the calculated π-electron densities.

The CNDO-2 method (38) was applied using a program from G. A. Segal which calculates the electronic and total energies, as well as total electron densities and dipole moments, the only required data being the coordinates of the atoms in the molecule. Since no X-ray determination of the molecular geometry is available in the literature, a model system for the polyazaindolizine molecules was used. A diagram was constructed from a regular pentagon and hexagon fused together and exocyclic bonds regularly disposed; bond lengths (Å): ring = 1.40, C-H = 1.09, C-CH_3 = 1.50; the methyl groups had a C-H bond in the plane of the molecule.

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