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Ring Transformations of Heterocyclic Halogeno Compounds with Nucleophiles. 39.[1] Carbon-13 and Proton Nuclear Magnetic Resonance Investigations on the Mechanism of the Ring Transformation Reaction of Pyrimidines into *s*-Triazines[2]

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Treatment of 4-chloro-2-dimethylaminopyrimidine (**1a**) and its 5-phenyl derivative (**1b**) with potassium amide in liquid ammonia and subsequent workup of the reaction mixtures lead to the formation of 2-dimethylamino-4-methyl-*s*-triazine and 4-benzyl-2-dimethylamino-*s*-triazine, respectively. By extensive ^{13}C NMR investigations of both reaction mixtures in liquid ammonia containing potassium amide, a number of unstable intermediates could be identified: from **1a** the 1:1 anionic σ complex **2a** and the anionic open-chain intermediate aminoethynyldiazabutadiene **3**; from **1b**, the σ complex **2b** and the anionic aminodiazabutadiene **7**, but also a redox product of **7**, i.e., the cyanoaminoazabutadiene **8**. Based upon the results of a deuterium labeling experiment it is assumed that the conversion of **7** into **8** occurs by an intramolecular oxidation–reduction process.

Several papers have been published concerning σ-adduct formation between the nucleophilic amide ion and the parent diazines,[3] as well as some of their derivatives, containing a leaving group (Cl, Br, SCH_3, and SO_2CH_3).[4-8]

The results of these studies show that in the absence of a leaving group the σ complex is stable and does not undergo a subsequent reaction[3,5] but that in the presence of such a leaving group, however, further reactions beyond the stage of the σ adduct can occur.[4-8]

A reaction which has attracted our interest for several years is the ring transformation of 2-substituted 4-chloropyrimidines into 2-substituted 4-methyl-*s*-triazines by potassium amide in liquid ammonia.[9] ^1H- and ^{13}C-NMR spectroscopy indicated that the first step in this ring interconversion is the formation of a 1:1 anionic σ complex **2a** in which the amide ion is thus not attached to C-4, the carbon bearing the halogen substituent, but to C-6.[5,6] More examples of this unexpected addition behavior have been found with other diazines.[4,8]

We have investigated by ^{13}C-NMR spectroscopy two reactions in particular, i.e., the ring transformation of 4-chloro-2-dimethylaminopyrimidine (**1a**) into 2-dimethylamino-4-methyl-*s*-triazine (**5a**) (yield 80% with potassium amide) and the hitherto unknown conversion of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) into 4-benzyl-2-dimethylamino-*s*-triazine (**5b**) (yield 60% with potassium amide), specially aiming to obtain information about intermediates beyond the stage of the σ adduct.

Results and Discussion

4-Chloro-2-dimethylaminopyrimidine (1a). From the results of our studies we reached the conclusion that the conversion of **1a** into **5a** occurs by the following reaction sequence **1a** → **2a** → **3** → **4** → **5a** (see Scheme I). Evidence for this mechanism is based on the following data. Addition of **1a** to 2 equiv of potassium amide in liquid ammonia gives the σ adduct **2a** (see Table I). Surprisingly we observed that when the excess of potassium amide is raised to 4 equiv and the reaction time is prolonged, the ^{13}C-NMR spectrum of the resulting reaction mixture is completely different from that of the σ complex **2a.** The new spectral data have been assigned to the intermediate aminoethynyldiazabutadiene anion **3** (see Table I). Two sharp signals at δ 113.3 and 118.5 have been attributed to the acetylenic carbons C-4 and C-5 and two signals at δ 168.4 (J_{C-H} = 157 Hz) and 166.0, both being broadened, to C-2 and C-6, respectively.[10] The broadening observed for the resonances of C-2 and C-6 may well find its cause in *E–Z* isomerism around the N-1–C-6 double bond.

Also the ^1H-NMR spectrum of a solution, obtained by reaction of **1a** with 4 equiv of KNH_2/NH_3 for 30 min, confirms the formation of intermediate **3.** Besides the sharp singlet at δ 2.62 of the dimethylamino substituent, a very broad adsorption band around δ 8 belonging to H-6 is found.

Intermediate **3** is found to be stable for at least 5 h under the reaction conditions. Under these conditions no indication of the formation of the ultimate reaction product 2-dimethylamino-4-methyl-*s*-triazine (**5a**) could be obtained. However, when the reaction mixture was quenched with ammo-

Scheme I

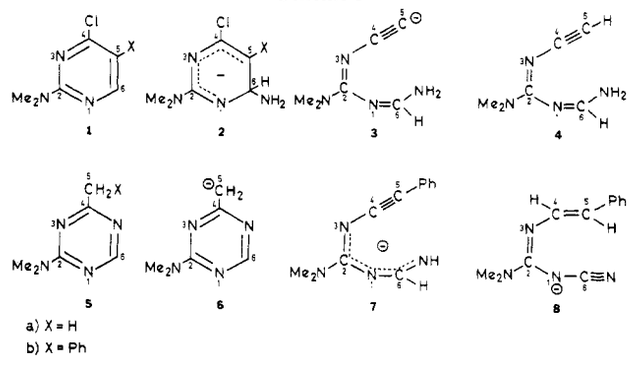

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Table I. Summary of the ^{13}C Chemical Shifts of the Starting Materials 1a and 1b, Intermediates, and Products Obtained in the Reaction of 1a and 1b with KNH_2/NH_3

	Registry no.	C-2	C-4	C-5	C-6	$(CH_3)_2N$	Solvent
1a	23631-02-9	162.3	161.1	108.3	158.7	37.1	$CDCl_3$
1b	65942-50-9	161.1	159.1	121.3	158.9	37.1	$CDCl_3$
2a	57356-50-0	161.2	147.8	86.2	67.3	37.9	KNH_2/NH_3 liq
2b	65942-51-0	160.3	144.4	95.6	70.8	38.3	KNH_2/NH_3 liq
3	65942-52-1	168.4	113.3	118.5	166.0	39.6	KNH_2/NH_3 liq
5a	22404-37-1	163.7	175.8	25.4	166.0	36.1	NH_3 liq
5b	65942-53-2	164.4	176.6	45.5	165.6	36.1	$CDCl_3$
6	65942-54-3	162.4	163.1	66.8	161.7	35.8	KNH_2/NH_3 liq
7	65969-57-5	165.9	105.0	59.7	165.1	37.6	KNH_2/NH_3 liq
		167.6	104.8	59.4	168.0	37.6	KNH_2/NH_3 liq
8	65942-55-4	162.1	141.7	108.8	124.6	38.3	KNH_2/NH_3 liq

nium chloride, the ^{13}C-NMR spectrum of that solution had drastically changed and resonance signals appeared that must be ascribed to the presence of the triazine **5a** (see Table I). Apparently by the addition of ammonium chloride, intermediate **3** is converted to its conjugate acid **4** which easily undergoes the cyclization into **5a.** We have not obtained any evidence for the occurrence of the reverse reaction **5a** → **3.** In fact when **5a** is dissolved in KNH_2/NH_3 anion **6** is formed, as is convincingly shown by the *triplet* splitting found for the side-chain carbon C-5 (J_{C-H} = 153 Hz) and the considerable downfield shift (41.4 ppm) observed on comparison of the chemical shift of this signal with that of the ^{13}C-NMR signal from the methyl group of **5a,** obtained in $CDCl_3$ solution. This downfield shift, together with the value for the J_{C-H} typical for an sp^2 carbon, indicates that in species **6** the negative charge is partly delocalized over the *s*-triazine ring.

4-Chloro-2-dimethylamino-5-phenylpyrimidine (1b). As we have seen the negative charge on C-5 in **3** plays a vital role in the stability of this species, since not **3** but its conjugate acid **4** is found to be able to undergo cyclization. Therefore we became interested in the influence of a substituent in position 5 of the pyrimidine ring. For that purpose we chose the phenyl group. Reaction of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) with potassium amide in liquid ammonia gave 4-benzyl-2-dimethylamino-*s*-triazine (**5b**) (yield 60%), together with only a small amount of 4-amino-2-dimethylamino-5-phenylpyrimidine. The presence of the phenyl group is found to increase substrate reactivity. Therefore, in order to detect intermediate stages, it was necessary to lower the reaction temperature to −60 °C. Even at this low temperature we could not avoid the fact that two or more intermediate species were simultaneously present in the reaction mixture, making characterization of the reaction intermediates by ^{13}C NMR very troublesome. However, by varying the excess of KNH_2 employed we were able to control the progress of the reaction to some extent. Taking samples at short intervals the rather complex spectra could be analyzed and the rise and fall of three intermediates could be monitored.

It was found that when 1 equiv of KNH_2 is employed first the σ adduct **2b** appears (see Figure 1). The ^{13}C-NMR chemical shifts of this adduct agree well with those recorded for **2a** (see Table I). When **1b** is reacted with 2 equiv of KNH_2 at −60 °C, the ^{13}C-NMR spectrum of a sample of the reaction mixture shows signals that arise from the anionic amino(phenylethynyl)diazabutadiene **7.** Under those conditions only a small number of weak signals of σ adduct **2b** are then observed (see Figure 1).

Of particular interest is the fact that each of the carbon atoms 2, 4, 5, and 6 of intermediate **7** show a pair of singlets in an approximate 1:2 ratio, indicating the existence of two isomers. In these isomers, different values for the C-6–H-6 coupling constants are found, J_{C-6-H} = 169.2 and 162.1 Hz for the major and minor signals, respectively. Based upon the

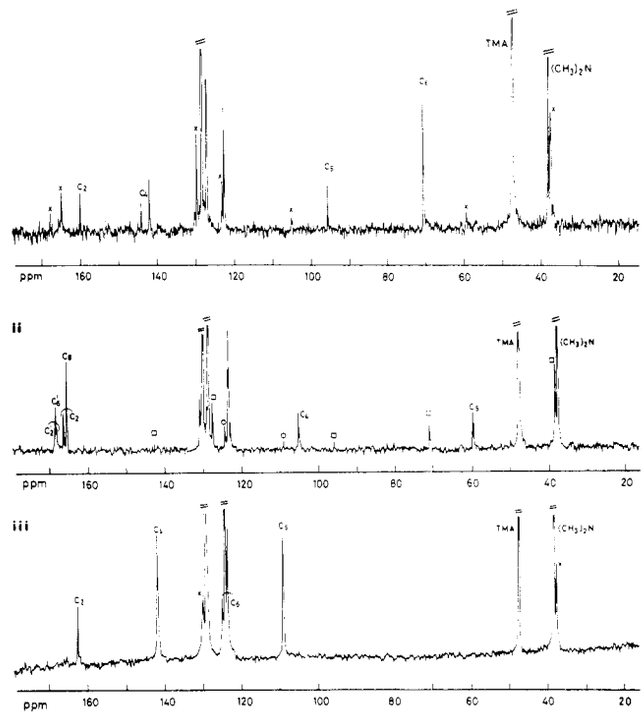


Figure 1. ^{13}C-NMR spectra at 25.2 MHz of reaction intermediates **2b, 7,** and **8** taken in liquid NH_3: (i) signals mainly from **2b,** × refers to signals from **7;** (ii) signals mainly from **7,** □ and ○ refer to signals from **2b** and **8,** respectively; (iii) signals mainly from **8,** × refers to signals from **7.**

relatively large chemical shift differences found between the resonance pairs from C-2 and C-6 ($\Delta\delta$ = 1.7 and 2.9, respectively) *E–Z* isomerism around the N-1–C-6 double bond is proposed, just as has been described for intermediate **3.** Which resonance signals belong to the *E* or *Z* isomer was not determined. C-5 resonates at a somewhat higher field (δ 59.7) compared with the corresponding nucleus in phenylacetylene (δ 84.8). The electron-donating effect, however, exerted by the partly negatively charged N-3 readily accounts for this upfield shift.

In contrast to **1a,** the reaction of **1b** with KNH_2 does not stop at the stage of **7;** in the presence of a fourfold amount of KNH_2 a new intermediate arises, which we assigned structure **8** (see Figure 1 and Table I). From the proton-coupled ^{13}C-NMR spectra the presence of two C-H entities can be easily seen; their absorptions at δ 141.7 and 108.8 are attributed to C-4 and C-5 (J_{C-H} = 152 and 150 Hz, respectively). The signal at δ 124.6 belongs to the nitrile carbon C-6, so the signal at δ 162.1 must originate from C-2.

The ^1H-NMR spectrum showed an AB pattern; chemical shifts were found at δ 8.38 and 5.82, showing a coupling con-

stant of J = 13.3 Hz. Since interproton coupling is known to have its origin in the indirect intramolecular interaction of nuclear moments through bonds,[14] the assumption seems justified that the negative π charge in intermediate **8** does not affect the value of the $J_{H,H}$ to a significant extent, compared with the uncharged conjugate acid of **8**. Comparing the value of the coupling constant of 13.3 Hz with those published for both cis and trans isomers of uncharged 1,2-disubstitute olefines[15,16] (containing methoxy or amino groups, coupling constants for cis isomers range from 6 to 9 Hz and for trans isomers from 12 to 14 Hz) intermediate species **8** is assumed to possess a trans substituted double bond.[17]

The formation of **8** takes place from **7**. This rearrangement involves a redox reaction in which reduction of the triple bond of **7** to a double bond occurs simultaneously with oxidation of the amino substituted C-6. This reaction is similar to the self oxidation–reduction process which aldehydes can take place in the presence of strong bases. The conversion of **7** → **8** can be described to occur by a reversible addition of the amide ion to the C-6–N-1 double bond. The resulting charged tetrahedral complex can act as a hydride donor and transfers the hydride ion in a six-membered cyclic transition state to C-4. After protonation at C-5 and loss of ammonia **8** is formed.

In order to test this hypothesis, we synthesized 4-chloro-6-deuterio-2-dimethylamino-5-phenylpyrimidine. This substrate was reacted with 2 equiv of KNH_2 at first to the level of the open-chain compound **9**. ^{13}C-NMR spectroscopy of a sample of the reaction mixture showed all resonance signals of **7**, except the one originating from C-6. This is because carbon–deuterium multiplets are very weak or lost in the noise of ^{13}C NMR spectra, since they lack nuclear Overhauser effects.[18]

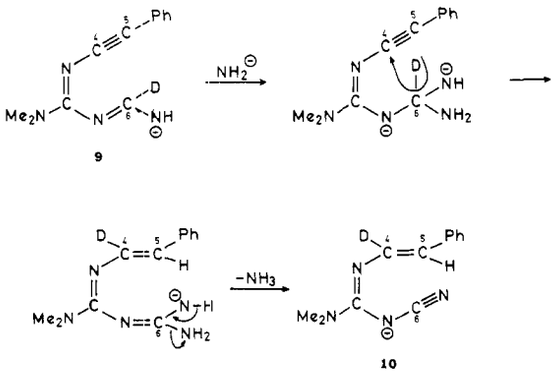
Increasing the excess of potassium amide to fourfold, the signals of **10** appear at the expense of **9**, but now the resonance signal of C-4 is missing, indicating the presence of deuterium at that position (see Scheme II).

Supporting evidence for the presence of deuterium at position 4 is obtained by ^1H-NMR spectroscopy showing the absence of the resonance signal from H-4; H-5 now appears as a singlet.

All the data support the proposal of the internal oxidation–reduction mechanism as a reasonable pathway for the formation of **8** from **7**.

^{13}C-NMR spectroscopy of a sample of a reaction mixture containing **8** that has been quenched with ammonium chloride revealed that no cyclization takes place at this level of the reaction (contrary to what has been found for **3** upon quenching). Only if the solvent ammonia has been evaporated will the *s*-triazine **5b** form as is found in the chloroform extract of the resulting residue. The question why **7** undergoes an internal redox reaction into **8** and **3** does *not* may be explained by the fact that, although the first step in this conversion, i.e., addition of the amide ion to C-6, can occur in both species (see Scheme II), the subsequent hydride transfer to C-4 is prevented by the negative charge present in the acetylene group of **3**.

Scheme II



Experimental Section

^{13}C and ^1H spectra were obtained with a Varian XL-100-15 spectrometer, equipped with a Varian 620/L16K computer, operating at 25.2 MHz in the FT mode and at 100.1 MHz in the CW mode, respectively.

In $CDCl_3$ solution the deuterium resonance of the solvent was used as an internal field-frequency lock signal. In the case of liquid ammonia as solvent, field-frequency lock was obtained from the ^{19}F-NMR signal of a capillary of hexafluorobenzene positioned along the longitudinal axis of 12 mm (o.d.) sample tubes employed. Spectra were taken at ambient temperature, but when measuring liquid ammonia samples the probe temperature was −50 °C. In $CDCl_3$ solutions ^{13}C and ^1H chemical shifts were measured from internal Me_4Si. In NH_3 solutions ^{13}C and ^1H chemical shifts were measured from internal trimethylamine and they were converted to the Me_4Si scale adding 47.5 and 2.13 ppm, respectively. Typical ^{13}C spectral parameters were as follows: spectral width 5120 Hz (1.25 Hz/point), acquisition time 0.8 s, pulse delay 1.2 s, pulse width 10 μs. All samples were run as approximately 1 M solutions in NH_3 and they were prepared according to the method described in ref 7. The average accumulation time was 60 min. The IR spectra were recorded with a Hitachi Model EPI-G.3. Mass spectra were obtained with an AEI MS-902 instrument. Melting points are uncorrected.

Preparation of Starting Materials. 4-Chloro-2-dimethylaminopyrimidine (1a) was prepared according to ref 9. **4-Chloro-2-dimethylamino-5-phenylpyrimidine (1b).** 2-Ethylthio-5-phenyl-4-pyrimidone[19] (14.8 g) was heated with dimethylammonium acetate[20] (60 mL) at 160 °C for 2.5 h. The mixture was left overnight and filtered under suction. The white crystals (83 g of crude 2-dimethylamino-5-phenyl-4-pyrimidone) were twice thoroughly washed with water, dried, and subsequently refluxed with freshly distilled phosphorus oxychloride (75 mL) for 2 h. The excess of phosphorus oxychloride was evaporated and the residue was treated with ice water. The resulting mixture was carefully neutralized with aqueous ammonia (0 °C < t < 5 °C) and extracted with ether. After evaporation of the solvent the residue was distilled in vacuo. The fraction boiling between 130 and 135 °C (0.4 mmHg) was collected; yield 11.9 g. Anal. Calcd for $C_{12}H_{12}ClN_3$: C, 61.7; H, 5.2. Found: C, 61.8; H 5.1.

4-Chloro-6-deuterio-2-dimethylamino-5-phenylpyrimidine. 4,6-Dichloro-2-dimethylamino-5-phenylpyrimidine (4.5 g) and hydrazine hydrate (100%) (17 mL) are refluxed in ethanol (40 mL) for 0.5 h. On cooling 3.75 g of 4-chloro-2-dimethylamino-6-hydrazino-5-phenylpyrimidine separate out as white needles (mp 127–128 °C from ethanol). This compound is refluxed in a small volume of CD_3OD, yielding after evaporation of the solvent hydrazino deuterated starting material, 1.6 g of which are dissolved in $CDCl_3$ (30 mL) containing CD_3NO_2 (7 mL) as a D donor and reacted at 40 °C in an inert atmosphere (N_2) with MnO_2/C[21] (30 g) that is added portionwise over 2 h. The reaction mixture is kept at 40 °C for another 0.5 h and then filtered under suction. The residue is washed well with chloroform. The oil obtained after evaporation of the filtrate is purified twice by column chromatography over Silica with $CHCl_3$ and benzene–ethyl acetate (4:1), respectively, as eluent, yield 0.5 g. The deuterium content at position 6 was about 90% as determined by ^1H NMR using the signal from the dimethylamino group as an internal standard.

4,6-Dichloro-2-dimethylamino-5-phenylpyrimidine. To a boiling mixture of *N,N*-dimethylguanidine·HCl (24.6 g) in methanol (absolute) (150 mL) containing sodium methoxide (21.6 g) was added with stirring diethyl phenylmalonate (47.2 g). After 4 h of reaction time, the mixture is left overnight at ambient temperature. The white precipitate is filtered off and the filtrate is acidified with acetic acid. The resulting voluminous paste is washed with water and dried at 80 °C over phosphorus pentoxide in vacuo. This crude 4,6-dihydroxy-2-dimethylamino-5-phenylpyrimidine is treated with phosphorus oxychloride (360 mL) as described before. (See the preparation of 4-chloro-2-dimethylamino-5-phenylpyrimidine.)

After evaporation of the excess of phosphorus oxychloride and neutralization, the precipitate is collected and extracted with ether. Evaporation of the solvent afforded a colorless oil that solidified upon standing. Recrystallization from aqueous ethanol yielded 17.7 g, mp 80–81 °C (lit.[22] 81–82 °C) (overall yield 33%). Anal. Calcd for $C_{12}H_{11}Cl_2N_3$: C, 53.7; H, 4.2. Found: C, 53.6; H, 4.4.

Reaction of 1b with Potassium Amide into 4-Benzyl-2-dimethylamino-*s*-triazine (5b). Dry liquid ammonia (20 mL) con-

densed in a 50-mL three-neck round-bottom flask, equipped with a dry ice/acetone condenser. Potassium (390 mg) and a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst were added. After stirring for 30 min at reflux temperature 0.58 g of 4-chloro-2-dimethylamino-5-phenylpyrimidine (**1b**) was added at −60 °C. After 4 h the reaction was quenched with ammonium chloride and the ammonia was evaporated. The residue was extracted with ether and the extract was evaporated to dryness. Separation from the by-product 4-amino-2-dimethylamino-5-phenylpyrimidine (yield 0.037 g (7%); mp 119–120 °C. Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.3; H 6.6. Found: C, 67.2; H, 6.8) was performed by column chromatography (silica): yield 0.32 g; oil; picrate mp 143–144 °C. Anal. (picrate) Calcd for $C_{18}H_{17}N_7O_7$: C, 48.8; H, 3.9. Found: C, 48.8; H, 4.0.

Acknowledgment. We are indebted to Dr. C. A. Landheer and Mr. W. P. Combé for mass spectroscopic data, to Mr. W. Ch. Melger for chromatographic advice, and to Mr. H. Jongejan for carrying out the microanalyses.

Registry No.—**5b** picrate, 65942-58-7; 2-dimethylamino-5-phenyl-4-pyrimidone, 65942-56-5; 4,6-dichloro-2-dimethylamino-5-phenylpyrimidine, 61769-99-1; 4-chloro-2-dimethylamino-6-hydrazino-5-phenylpyrimidine, 65942-57-6; *N,N*-dimethylguanidine hydrochloride, 22583-29-5; diethyl phenylmalonate, 83-13-6.

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(10) In order to assign C-4 and C-5 in **3** correctly we acquired ^{13}C-NMR spectral information on the chemical shifts of acetylide anions. It was found by dissolving 3-methoxypropyn ($HC^1{\equiv}C^2C^3H_2OCH_3$) in liquid ammonia containing 2 equiv of potassium amide that in the acetylide anion thus formed the ^{13}C-NMR signals of C-1 and C-2 are shifted downfield 75.7 and 28.2 ppm with respect to the parent compound measured in $CDCl_3$ (74.8 ppm → 150.5 ppm for C-1 and 79.9 ppm → 108.1 ppm for C-2). Distinction between C-1 and C-2 in the acetylide form could be made on the basis of the triplet splitting ($^2J_{C-H}$ = 5.6 Hz) found for C-2 when wide band proton noise decoupling was *not* utilized. A deshielding effect upon anion formation is also found in a number of organolithium compounds, in which the metallated acetylenic carbons are shifted downfield with respect to the parent acetylenes.[11,12] Furthermore we compare the ^{13}C-NMR spectrum of ethoxyethyn (δ_{C-1} 23.2 and δ_{C-2} 89.4)[13] [in this compound the ^{13}C NMR shifts of the acetylenic carbons are strongly subjected to the +M and −I effects due to the neighboring oxygen atom] with that of its anion generated in KNH_2/NH_3. In this medium C-1 and C-2 are found to resonate at δ 72.5 and 116.2, respectively (downfield shifts of 49.3 and 26.8 ppm with respect to the parent compound). These data clearly show that the assignments proposed for C-4 and C-5 in **3** are quite reliable.
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Chemistry of Heterocyclic Compounds. 28. Reactions of Halopyridines with Mercaptide. Synthesis of Multiheteromacrocycles Possessing 2,6-Pyridino Subunits Connected by Carbon–Sulfur Linkages[1]

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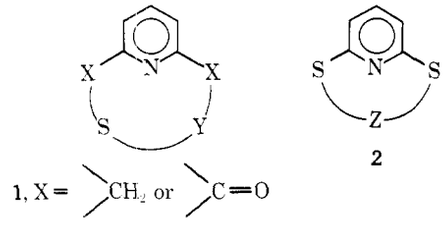
2,6-Dihalopyridines have been successfully incorporated into "crown ethers" (3); however, utilizing similar procedures to prepare the related thio "crown ethers" (e.g., 8) has met with very limited success. The major isolated products from nucleophilic displacement of halide from **7** by mercaptide were derived from numerous competitive reactions of the thiols, such as polymerization, fragmentation, oxidation, and oligomerizations. The desired carbon–sulfur bridged 2,6-pyridino macrocycles were isolated as minor components from these reactions.

Recently, we reported the synthesis of ethereal macrocycles which incorporated the 2,6-pyridino moiety.[2] Although numerous related thioethereal macrocycles have been reported,[3] the vast majority possess a backbone (**1**) in which the sulfur atom is isolated from the pyridine ring by either a methylene[4] or a carbonyl group.[5] Only recently has a second type of macrocyclic system (**2**) been constructed in which the sulfur atoms are directly connected to the 2 and 6 positions of the pyridine nucleus.[6] We herein describe the reactions of 2,6-dihalopyridines with different sulfur nucleophiles as well as the preparation and characterization of carbon–sulfur bridged 2,6-pyridino macrocycles of the latter type (**2**).



2

The preparation of macrocyclic polyethers possessing the 2,6-pyridino subunit (e.g., **3**) has been accomplished,[2] and their general catalytic behavior is currently being studied;[7] however, the corresponding thioethers were yet unknown but were desirable for comparison studies. Important differences

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