study of pH 8.5 using NaOD–D_2O instead of NaOH–H_2O yielded I-d_2 (both methylene protons were replaced by deuterium).

Part 2 was adjusted to pH 13.5 with sodium hydroxide solution and stirred under a nitrogen atmosphere for 8 h. The pH was adjusted to 4.0 followed by evaporation to dryness. The residue was extracted with acetone (4 × 20 mL) and filtered. The combined acetone extracts were evaporated to dryness and the residual yellow oil was dissolved in methylene chloride (50 mL) and filtered. Evaporation of the filtrate yielded a yellow oil (0.8 g, 92%) identified by NMR, IR, and UV as VII.

Reaction of *N*-Nitroso(3-methylamino)propionitrile (IV) with Gaseous Hydrogen Chloride. Compound IV (5.0 g, 40 mmol) was dissolved in dry methanol (40 mL) and dry hydrogen chloride gas was passed through the solution for 2 h; a white precipitate formed. The reaction mixture was evaporated to half its volume under vacuum and the concentrate was cooled in a dry ice–acetone bath for 15 min. Filtration yielded a white solid identified as ammonium chloride (2.1 g, 89%) (sublimation temperature ca. 340 °C, evolution of NH_3 on treatment with NaOH). The filtrate was evaporated to dryness and washed with acetonitrile (3 × 50 mL). The second residue was also NH_4Cl (0.19 g, 8%); total yield of NH_4Cl, 97%. The combined acetonitrile washings were evaporated to dryness to yield a white powder (6.45 g, 95%) which was recrystallized from acetone–ethyl acetate. The resulting product, methyl (3-methylamino)propionate hydrochloride (VIII), was strongly hygroscopic, making it difficult to obtain an accurate or reproducible melting point or elemental analysis. Anal. Calcd for $C_5H_{12}O_2ClN$: C, 39.1; H, 7.82; N, 9.12; Cl, 23.1. Found: C, 37.6; H, 8.45; N, 9.42; Cl, 22.5.

NMR (Me_2SO-d_6): CH_3 (δ 0.04, s, 3 H); CH_2 (0.32, t, 2 H); CH_2 (0.62, t, 2 H); OCH_3 (1.17, s, 3 H); NH_2 (6.80, s, 2 H) (Me_2SO=O). Addition of 1 drop of D_2O to the solution caused the two proton signal due to NH_2 to disappear. IR: intense absorption at 1750 cm^{-1} (C=O) and weak absorption at 3000 cm^{-1} (NH_2).

Reaction of Methyl Cyanomethylamine Hydrochloride (IX) with Gaseous Hydrogen Chloride. This was conducted and worked up as described for IV. The yield of NH_4Cl was 90% and that of methyl (2-methylamino)acetate hydrochloride (X) was 80%. Compound X was also exceedingly hygroscopic. Anal. Calcd for $C_4H_{10}O_2ClN$: C, 34.4; H, 7.17; N, 10.0; Cl, 25.4. Found: C, 33.8; H, 7.07; H, 9.90; Cl, 25.7.

NMR (Me_2SO-d_6): CH_3 (δ 0.06, s, 3 H); OCH_3 (1.44, s, 3 H); CH_2 (1.62, s, 2 H); NH_2 (7.20, s, 2 H) (Me_2S=O = 0). Addition of 1 drop of D_2O to the solution caused the two proton signal due to NH_2 to disappear. IR: intense absorption at 1750 cm^{-1} (C=O) and weak absorption at 2900 cm^{-1} (NH_2).

Denitrosation of *N*-Nitrosamines. General Procedure. Dry hydrogen chloride gas was bubbled through a solution of *N*-nitrosamine (2.0 g) in dry methanol (25 mL) for about 30 min. The solution was evaporated to dryness under vacuum and the residue was washed with cold acetone (3 × 20 mL). The residue was the hydrochloride of the corresponding amine. Recrystallization from ethyl acetate, diethyl ether, or petroleum ether yielded the analytically pure salt identified by analysis and/or NMR.

Denitrosation of dimethyl-, diethyl-, dipropyl-, and dibutylnitrosamines yielded salts of the corresponding secondary amines. If the effluent gases were passed through an ether solution of 2,3-dimethyl-2-butene, a royal blue color developed within 10 min. I and IV also underwent denitrosation to yield VI and VIII, respectively, as already described.

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Registry No.—I, 3684-91-7; IV, 60153-49-3; VI, 65103-49-3; VIII, 65103-50-6; IX, 25808-30-4; X, 13515-93-0.

References and Notes

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(2) Taken from the Ph.D. dissertation of S. K. Vohra, Temple University, 1977.
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(7) H. C. Hamann and D. Swern, *J. Am. Chem. Soc.*, **90**, 6481 (1968).
(8) Nitrosamines were prepared as described in ref 3 or purchased from Aldrich or Eastman. NMR spectra were recorded with a Varian XL-100 spectrometer using Me_4Si, HOD, or Me_2SO as internal standards. UV spectra were obtained using a Cary Model 14 spectrophotometer. IR spectra were obtained on a Perkin-Elmer 225 or Pye Unicam AP 1000 spectrophotometer. Differential pulse polarography was conducted as described in ref 3. All solvents and reagents were the finest obtainable. All work with nitrosamines was conducted on the smallest scale necessary to obtain the requisite information utilizing efficient hoods and maximum protection of personnel.

Nuclear Magnetic Resonance Studies on σ Adducts of Heterocyclic Systems with Nucleophiles. 18.[1] Proton and Carbon-13 Nuclear Magnetic Resonance Investigations on σ-Adduct Formation between 1,*X*-Naphthyridines and Some Methyl-1,8-naphthyridines with Potassium Amide in Liquid Ammonia

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1,5-, 1,6- and 1,8-naphthyridines dissolved in liquid ammonia containing potassium amide showed the H-2 and C-2 resonances at about 4 and 90 ppm higher field, respectively, than the H-2 and C-2 resonances observed in solutions of these naphthyridines in $CDCl_3$. It indicated that all three naphthyridines underwent addition of the amide ion to position 2, yielding a 2-amino-1,2-dihydro-1,*X*-naphthyridinide ion. The 1,7-naphthyridine showed a more complex reactivity pattern toward amide ions. Besides addition at C-2, addition at C-6 and at C-8 has been found. The relation of this study with that of the Chichibabin amination of the 1,*X*-naphthyridines is discussed. It was further proven that under the influence of the amide ion 2-methyl- and 4-methyl-1,8-naphthyridine only gave deprotonation of the methyl group and that 3-methyl-1,8-naphthyridine gave formation of the 2-amino-1,2-dihydro-3-methyl-1,8-naphthyridinide ion.

Recently there has been great interest in the study of the formation of the 1:1 σ adducts between azines and amide ions[2] and between azinium salts and liquid ammonia.[3,4] This is due to the fact that the many often surprising rearrangements which can take place in these systems[5-7] occur via the intermediacy of these σ adducts. NMR spectroscopy has been found to be a valuable tool for the detection of these adducts, since the newly formed tetrahedral center causes a consider-

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Table I. ^{1}H- and ^{13}C-NMR Data of the 1,*X*-Naphthyridines and Their 1:1 σ Adducts with Amide Ions

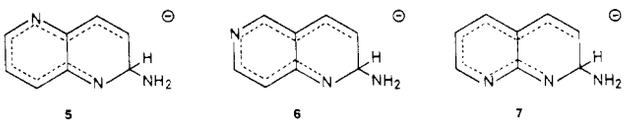
Compd	Registry no.	Solvent	^{1}H-NMR chemical shift (δ) H-2	H-3	H-4	H-5	H-6	H-7	H-8	^{13}C-NMR chemical shift (δ) C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1		$CDCl_3$	8.96	7.55	8.37		8.96	7.55	8.37	151.0	124.1	137.2		151.0	124.1	137.2	144.0	144.0
	254-79-5	NH_2^-/NH_3	4.85	5.27	*a*		6.65	*a*	*a*	65.8	121.3	127.4[b]		125.1	122.7	121.6[b]	151.2	137.3
		Δδ	4.11	2.28			2.31			85.2	2.8	9.8		25.9	1.4	15.6	+7.2	6.7
2		$CDCl_3$	9.03	7.43	8.20	9.22		8.75	7.87	154.9	122.7	135.8	153.0		146.9	122.2	150.5	123.8
	253-72-5	NH_2^-/NH_3	5.05	5.19	6.23	7.15		7.20	5.82	66.1	120.0	124.6	146.1		146.6	112.2	156.2	114.0
		Δδ	3.98	2.24	1.97	2.07		1.55	2.05	88.8	2.7	11.2	6.9		0.3	10.0	+5.7	9.8
3		$CDCl_3$	9.01	7.48	8.14	7.64	8.60		9.50	152.1	125.2	134.7	119.9	144.0		154.5	143.7	131.3
	253-69-0	NH_2^-/NH_3	4.98[c]	5.30[d]	*a*	*a*	4.51[e]		5.15[f]	66.0[c]	*a*	*a*	*a*	80.1[e]		71.0[f]	*a*	*a*
		Δδ	4.03	2.18			4.09		4.35	86.1				63.9		83.5		
4		$CDCl_3$	9.15	7.51	8.21	8.21	7.51	9.15		153.8	122.3	137.3	137.3	122.3	153.8		156.6	123.1
	254-60-4	NH_2^-/NH_3	5.21	5.42	6.32	6.65	5.62	7.60		67.0	122.1	126.0	131.5	100.8	149.3		162.6	112.9
		Δδ	3.94	2.09	1.89	1.56	1.89	1.55		86.8	0.2	11.3	5.8	21.5	4.5		+6.0	10.2

[a] These peaks could not be assigned. [b] The signals may be interchanged. [c] H-2 and C-2 in adduct **8**. [d] H-3 in adduct **8**. [e] H-6 and C-6 in adduct **9**. [f] H-8 and C-8 in adduct **10**.

able upfield shift. In the ^{1}H-NMR spectra upfield shifts of about 3–4 ppm are observed; in the ^{13}C-NMR spectra shifts as large as about 90 ppm are found.[2] The ^{1}H- and ^{13}C-NMR spectra of the parent 1,*X*-naphthyridines have been published,[8,9] but no ^{1}H and ^{13}C data of anionic 1:1 σ adducts, formed between the 1,*X*-naphthyridines and an amide ion, i.e., the aminodihydro-1,-*X*-naphthyridinide ions, are known. Information about the possible existence of these 1,*X*-naphthyridinide ions is of considerable interest, especially in relation to an earlier study on the Chichibabin amination of the 1,*X*-naphthyridines,[10] in which discrepancies were found between a reactivity order for amination in 1,7- and 1,8-naphthyridine, as calculated by the total π-electron density ground state data[10] and the one being experimentally established. Thus 1,7-naphthyridine on amination gave *only* the 8-amino product, while from calculations C-2 was predicted to have about the same reactivity as C-8. Similar discrepancies were also observed in the 1,6-naphthyridine series.

In order to establish which position(s) in the 1,*X*-naphthyridines is (are) vulnerable to attack by amide ions, we have carried out the NMR study on the σ-adduct formation of the parent 1,*X*-naphthyridines, **1–4**, with amide ions. Therefore the ^{1}H- and ^{13}C-NMR spectra of the 1,*X*-naphthyridines in both deuteriochloroform and liquid ammonia containing potassium amide were measured. The ^{1}H and ^{13}C chemical shift data and their assignments are summarized in Table I. The assignment of the proton chemical shifts in the ^{1}H-NMR spectrum of the σ adducts was based on the magnitude of the corresponding coupling constant and on the spectra obtained when deuterated 1,*X*-naphthyridines were used as substrate. The following deuterated compounds were prepared for this spectroscopic study: 2,6-dideuterio-1,5-naphthyridine, 5-deuterio-1,6-naphthyridine, 8-deuterio-1,7-naphthyridine, 2,6,8-trideuterio-1,7-naphthyridine, and 2,7-dideuterio-1,8-naphthyridine (see Experimental Section). The unambiguous assignment of the ^{13}C chemical shifts in the σ adducts was achieved by selective heteronuclear decoupling.

1,5- (1), 1,6- (2), and 1,8-Naphthyridine (4). On dissolving the naphthyridines **1, 2,** or **4** (see for the structures, Table I) in liquid ammonia containing potassium amide no trace of the parent compounds **1, 2,** and **4** could be detected in the NMR spectrum; only resonance signals indicating the presence of the anionic 1:1 σ adducts **5, 6,** or **7,** respectively, were found



5 **6** **7**

(see Table I). The adduct spectra showed a very uniform pattern in that the absorptions of all carbon and hydrogen atoms were shifted upfield, compared to the shieldings of the corresponding atoms in the compounds **1, 2,** and **4** in deuteriochloroform. The most striking upfield shifts are of H-2 (about 4 ppm) and of C-2 (about 85–90 ppm). These upfield shifts are ascribed to the rehybridization of C-2 ($sp^2 \rightarrow sp^3$) on adduct formation and are in excellent agreement with the shielding differences reported for chloropyrimidines[11] and substituted pteridines.[12] In accordance with the adduct formation is the change of the $J(C_2\text{–H})$ of 180 Hz in the compounds **1, 2,** and **4** to 150 Hz in the adducts **5, 6,** and **7**.[11b,13] The results given in Table I further showed that from all the remaining carbon atoms, C-6 is the most shielded in both σ adducts **5** and **7,** reflecting a notable contribution of the para quinoid resonance structure in these naphthyridinides. The preferential attack of the nucleophilic amide ion on C-2 in the compounds **1, 2,** and **4** is in accordance with calculations on the total π-electron density of the several atoms in these systems, predicting that C-2 is the most favorable position for nucleophilic attack. It is further in good agreement with the Chichibabin amination of the 1,*X*-naphthyridines **2** and **4,** yielding exclusively the corresponding 2-amino compounds,[10] but not with the amination of the 1,5-naphthyridine (**1**) which has been reported to yield exclusively the 4-amino compound.[14] With **2** no σ adduct at C-5 has been observed despite the fact that above-mentioned calculations predicted that C-5 would have about the same total π-electron density as C-2. Our results indicate that calculations on ground state prop-

Table II. ^{1}H- and ^{13}C-NMR Data of 2-, 3-, and 4-Methyl-1,8-naphthyridines, the Conjugate Base of 2- and 4-Methyl-1,8-naphthyridines, and the Amide Adduct with 3-Methyl-1,8-naphthyridine

Compd	Registry no.	Solvent	^{1}H-NMR chemical shift (δ) H-2	H-3	H-4	H-5	H-6	H-7	H side chain	^{13}C-NMR chemical shift (δ) C-2	C-3	C-4	C-5	C-6	C-7	C-9	C-10	C side chain
11	1569-16-0	$CDCl_3$		7.25	7.97	8.03	7.32	9.00	2.75	163.0	123.0	137.0[a]	136.8[a]	121.4	153.3	156.2	120.9	25.6
		$NH_2^-NH_3$		6.00	6.25	6.69	5.83	7.60	3.05	158.4	125.9	128.1	131.4	107.0	149.4	163.7	117.4	76.1
									3.30									
		Δδ		−1.25	−1.72	−1.34	−1.49	−1.40	+0.30	−4.6	+2.9	−8.9	−5.4	−14.4	−3.9	+7.5	−3.5	+50.5
									+0.55									
12	14759-22-9	$CDCl_3$	8.98		7.94	8.12	7.45	9.07	2.55	155.5	131.9	135.6	136.6	122.2	152.6	155.0	122.5	18.4
		$NH_2^-NH_3$	5.02		6.00	6.55	5.59	7.48	1.90	71.4	130.5	121.8	129.9	101.0	148.1	162.2	113.8	21.0
		Δδ	−3.96		−1.94	−1.57	−1.86	−1.59	−0.65	−84.1	−1.4	−13.8	−6.7	−21.2	−4.5	+7.2	−8.7	+2.6
13	1569-17-1	$CDCl_3$	8.87	7.15		8.17	7.35	9.01	2.56	153.1	122.7	145.9	133.4	121.7	153.0	156.2	122.7	17.6
		$NH_2^-NH_3$	6.72	5.35		7.70	6.42	8.02	3.52	145.7	104.5	145.2	131.3	112.2	149.3	162.7	119.1	74.7
									3.85									
		Δδ	−2.15	−1.80		−0.47	−0.93	−0.99	+0.96	−7.4	−18.2	−0.7	−2.1	−9.5	−3.7	+6.5	−3.6	+57.1
									+1.29									

[a] The signals may be interchanged.

erties can only be used with extreme caution as a method to predict a reactivity pattern. Moreover this argument is reinforced by the fact that it is unknown whether the σ-adduct formation involves a kinetically or thermodynamically controlled process.

1,7-Naphthyridine (3). The ^{1}H- and ^{13}C-NMR spectra of a solution of **3** in liquid ammonia, containing potassium amide, measured at −50 °C were found to be very complex (see both Figures 1 and 2). Although not all ^{1}H and ^{13}C resonance signals could be assigned, it is evident that no unreacted **3** is present

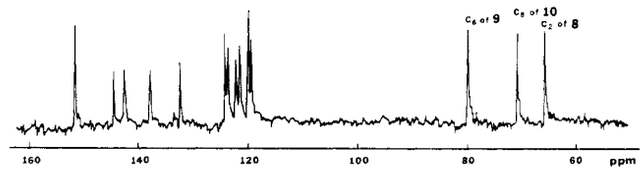


Figure 1. ^{13}C-NMR spectrum of 1,7-naphthyridine (**3**) in liquid ammonia, containing potassium amide.

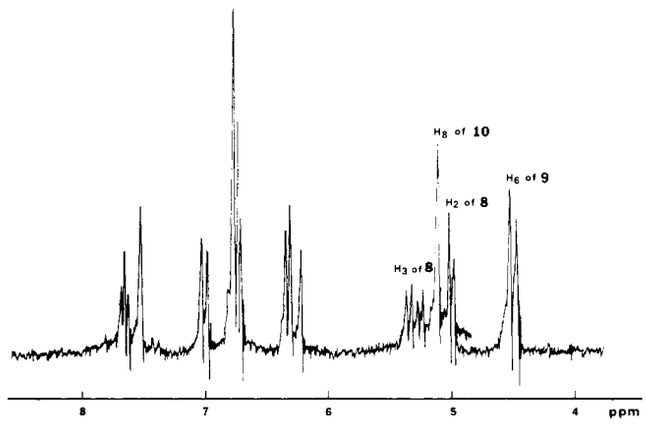
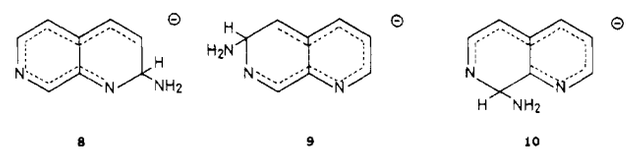


Figure 2. ^{1}H NMR spectrum of 1,7-naphthyridine (**3**) in liquid ammonia, containing potassium amide.

and that the high-field resonance absorptions must be ascribed to the presence of three anionic 1:1 σ adducts, i.e., the aminodihydro-1,7-naphthyridinide ions **8, 9,** and **10.** From the



8 **9** **10**

^{1}H-NMR spectra the ratio in which these three σ adducts are formed is about 1:1:1.

Calculations of the total π-electron densities in the 1,7-naphthyridine (**3**) show[10] that the order of nucleophilic reactivity is C-2 > C-8 > C-4 > C-6. Our experiments nicely confirm the favored addition at C-2 and C-8. However, since the formation of an adduct was found at C-6 and not at C-4, it again indicates the unreliability of ground-state π-electron densities to predict reactivity patterns. Agreement between the experimental data and the results of the calculations may be considered as only fortuitous. It has been reported that adduct formation at C-4, besides C-6 and C-8, occurs with 2-chloro-1,7-naphthyridine.[15] Apparently the presence of the electron-attracting inductive effect of the chloro atom promotes the addition of the amide ion at C-4. Similar observations have been made in pyridine chemistry. 2-Bromopyridine does not give an adduct,[16] but 2-bromo-6-chloropyridine forms an adduct at C-4.[17] The fact that from the reaction mixture containing the three adducts **8, 9,** and **10** only 8-amino-1,7-naphthyridine could be isolated is puzzling.[10] It might be possible that at the temperature which has been used for the Chichibabin amination (25 °C) only the adduct **10** is present. That the temperature can influence the regiospecificity of the addition has been observed with pteridines[12] and 1-methylpyrazinium ions.[4]

2-Methyl- (11), 3-methyl- (12), and 4-Methyl-1,8-naphthyridine (13). When the ^{1}H- and ^{13}C-NMR spectra of solutions of **11** and **13** in liquid ammonia, containing potassium amide, were measured, they were found to be quite different from the anionic σ adduct **7** (see Table II). The resonance of all ring hydrogen and carbon atoms has been shifted

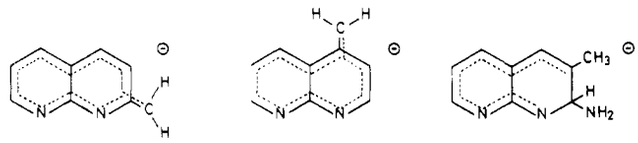
Table III. Results of Hydrogen/Deuterium Exchange in 1,X-Naphthyridines (1–4)

Starting material	Temp, °C	Time, h	Product	% deuterium (position) by ^{1}H-NMR data	Mass spectrum data
1,5-Naphthyridine (1)	220	24	2,6-Dideuterio-1,5-naphthyridine	88 (2 and 6)	0 D 1.2%; 1 D 19.7%; 2 D 78.2%; 3 D 0.7%; 4 D 0.2%
1,6-Naphthyridine (2)	170	12	5-Deuterio-1,6-naphthyridine	95 (5); 22 (2)	0 D 7.1%; 1 D 78.4%; 2 D 14.3%; 3 D 0.2%
1,7-Naphthyridine (3)	170	12	8-Deuterio-1,7-naphthyridine	90 (8)	0 D 9.6%; 1 D 79.7%; 2 D 10.5%; 3 D 0.2%
	220	24	2,6,8-Trideuterio-1,7-naphthyridine	87 (8); 67 (2); 53 (6); 25 (5)	0 D 0.04%; 1 D 1.5%; 2 D 18.7%; 3 D 51.2%; 4 D 28.0%; 5 D 0.5%
1,8-Naphthyridine (4)	220	24	2,7-Dideuterio-1,8-naphthyridine[a]	95 (2 and 7)	0 D 0.5%; 1 D 11.7%; 2 D 83.0%; 3 D 4.3%; 4 D 0.4%; 5 D 0.1%

[a] This compound was also prepared by oxidation of 2,7-dihydrazino-1,8-naphthyridine with a solution of cupric sulfate in deuterated water.[25]

upfield, but the magnitude of the upfield shift did not exceed 2 ppm in the ^{1}H-NMR spectra and 20 ppm in the ^{13}C-NMR spectrum. It is evident that *no* σ adduct is formed.

The downfield shift of the hydrogens ($\Delta\delta$ = 0.3–1.3 ppm) and C atom ($\Delta\delta$ = 50–57 ppm) of the substituent at C-2 or C-4 is remarkable. It strongly indicates the formation of the anions **14** and **15**, formed by deprotonation of the side chain in **11** and



14 **15** **16**

13, respectively. It is further of interest that both hydrogens of the substituent were split into a pair of doublets (J = 2–3 Hz). The coupling is due to the presence of a methylene group in which the free rotation around the C(methylene)–C-2 bond is absent causing a difference in chemical environment of the methylene protons. It indicates further that the charge formed in the side chain is delocalized over the heterocyclic rings. The relatively large upfield shift for C-6 in **14** and C-3 in **15** is in agreement with this charge delocalization. Amide-induced deprotonation of a methyl group α or γ to the ring nitrogen is well established and NMR data of the conjugated base of 4-methylpyrimidine,[18] 4-methyl-5-bromopyrimidine,[18] and 2-methylpyridine[19] are recorded.

As seen from Table II, 3-methyl-1,8-naphthyridine (**12**) surprisingly shows a completely different behavior. From the spectrum it became evident that the formation of the 1:1 σ adduct **16** is favored over deprotonation. The ^{1}H- and ^{13}C-NMR signals data are in agreement with those of **7**; H-2 and C-2 show considerable upfield shift to be expected for conversion of an sp^2 center into an sp^3 center.

Experimental Section

All carbon spectra were obtained with a Varian XL-100-15 spectrometer operating at 25.2 MHz. The spectrometer was equipped with a Varian Fourier transform unit. The pulse separation was chosen as 0–1.2 s. The spectral width was 5000 Hz (1.25 Hz/point). In $CDCl_3$ solutions ^{13}C chemical shifts were measured from internal Me_4Si, while in ammonia solutions ^{13}C chemical shifts were measured from internal $(CH_3)_3N$ and were converted to the Me_4Si scale by adding 47.5 ppm. The $CDCl_3$ solvent was used as field frequency lock; in case of liquid ammonia as solvent field frequency lock was based on the ^{19}F-NMR signal of a capillary of hexafluorobenzene position along the longitudinal axis of the 12 mm (o.d.) sample tubes employed. The probe temperature when measuring samples in liquid ammonia was −55 °C. Downfield shifts are indicated by a positive sign.

The ^{1}H-NMR spectra were recorded on a Jeol JNM C-60H spectrometer, using Me_4Si (δ = 0) as internal standard. In the case of adduct measurement the apparatus was equipped with a JES-VT-3 variable temperature controller. Spectra were obtained at temperatures between −40 and −60 °C. Trimethylamine was used as an internal standard (δ = 2.13 ppm). The procedure for measuring the NMR spectra in liquid ammonia, containing potassium amide, was performed as described before.[18]

Starting Materials. The following compounds were prepared according to the procedures described before: 1,5-naphthyridine (**1**),[20,22] 1,6-naphthyridine (**2**),[20,21] 1,7-naphthyridine (**3**),[22] 1,8-naphthyridine (**4**),[20,23] 2-methyl-1,8-naphthyridine (**11**),[20,23] 3-methyl-1,8-napthyridine (**12**),[24] and 4-methyl-1,8-naphthyridine (**13**).[23]

Deuterated 1,X-Naphthyridines. The deuterated 1,X-napthyridines were prepared by heating of the appropriate naphthyridine with deuterated water in a sealed tube at a temperature and for a period of time as given in Table III. It was not possible to obtain by this procedure a selective hydrogen/deuterium exchange on just one position.

Under the heading "product" in Table III only the compound that is formed in the largest amount is mentioned. The position of labeling was determined by ^{1}H-NMR spectroscopy and the amounts of deuterium present in the deuterated 1,X-napthyridines were established by mass spectrometry, using an AEI MS-902 instrument.

Registry No.—Ammonia, 7664-41-7.

Supplementary Material Available: NMR spectra of compounds **1**, **2**, **3**, and **4** in KNH_2–NH_3 (2 pages). Ordering information is given on any current masthead page.

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Synthesis and Properties of [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine Derivatives Including Their Mesoionic Compounds. A New Class of Heterocycles[1]

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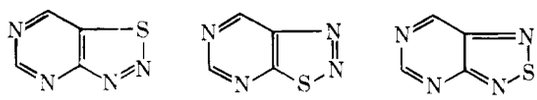
Treatment of 6-hydrazino-1,3-dimethyluracil (**1a**) with thionyl chloride gave 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**5a**), a new class of heterocycles. Reaction of 6-hydrazino-3-methyluracil (**8a**) with thionyl chloride afforded 6-methyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**), which was subsequently converted to 6-methyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (**14a**) by a novel 1,3-sulfur migration. Treatment of 3-methyl-6-(1-methylhydrazino)uracil (**8d**) with thionyl chloride provided the mesoionic compound, *anhydro*-3,6-dimethyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d**), via the 1,3-sulfur migration of 3,6-dimethyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10d**). Several other thiadiazolo[4,5-*d*]pyrimidines including their mesoionic compounds were also synthesized. Thiation of **5a** with phosphorus pentasulfide in pyridine yielded 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**17**). Nucleophilic displacement of **17** with hydrazines furnished the corresponding 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one 7(6*H*)-hydrazones (**18a–c**). The photolysis of **5a** in ethanol gave 1,3-dimethyl-5-mercaptouracil disulfide (**22**), while the thermolysis of **5a** in Dowtherm A yielded both 1,3,5,7-tetramethyl[1,4]dithiino[2,3-*d*;5,6-*e'*]dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (**26**) and 1,3,5,7-tetramethylthiopheno[2,3-*d*;4,5-*e'*]dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (**27**) probably via the thiirene intermediate **25**.

Although [1,2,3]thiadiazolo[5,4-*d*]pyrimidines (II)[2] and [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (III)[3] have been extensively studied, primarily as potential purine and pteridine antagonists, nothing has been reported on the isomeric [1,2,3]thiadiazolo[4,5-*d*]pyrimidines (I). The present paper



I II III

describes the synthesis and properties of derivatives of I, including their mesoionic compounds. The derivatives of type I are of interest from a chemical as well as a biological point of view. Thus, they may be considered analogues of various biologically important bicyclic fused pyrimidines, e.g., purines, pyrazolo[3,4-*d*]pyrimidines, *v*-triazolo[4,5-*d*]pyrimidines (by virtue of the fusion of the five-membered ring to the pyrimidine nucleus), pteridines, pyrimido[5,4-*e*]-*as*-triazines, and pyrimido[4,5-*e*]-*as*-triazines (by the isoelectronic relationship between a sulfur atom and an ethylenic group[4]). Moreover, they may also be regarded as cyclic analogues of 5-mercaptopyrimidines[5] and 6-azopyrimidines,[6] which have been known to exhibit interesting biological activities.

Treatment of 1,3-dialkyl-6-hydrazinouracils (**1a**[7] and **1b**[8]) with excess thionyl chloride at room temperature (an exothermic reaction) for 30 min afforded good yields of the corresponding 4,6-dialkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-diones (**5a** and **5b**), which were isolated by evaporation of the thionyl chloride and addition of water. The structures of these products were assigned by elemental analyses and spectral data. In particular, their UV spectra (see Table I) revealed the anticipated analogy with that of the known 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**7**)[9] [λ_{max} (EtOH) 240 (log ϵ 3.98), 324 nm (3.56)].[4] Compounds **5a** and **5b** could also be obtained by similar treatment of 1,3-dialkyl-6-(1-methylhydrazino)uracils (**1c**[10] and **1d**) with thionyl chloride. When 6-hydrazino-1,3-dimethyl-2-thiouracil (**1e**) was used as a starting material, the product isolated was again **5a**. An analogous replacement of a sulfur by an oxygen has recently been reported on the reaction of 6-amino-1,3-diethyl-2-thiouracil with thionyl chloride–dimethylformamide mixture to give 5,7-diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione.[11] The reaction of **1a** or **1b** with thionyl chloride presumably proceeds by the initial formation of the sulfinyl chloride intermediate (**2a** or **2b**), followed by cyclization to the thiadiazoline *S*-oxide (**3a** or **3b**), and subsequent dehydration via the Pummerer reaction intermediate (**4a** or **4b**). A similar mechanism for the conversion of **3** to **5** via **4** has been speculated in the reaction of 6-substituted amino-1,3-dimethyluracils with thionyl chloride, leading to 4,6-dimethylthiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones.[12] In the case of **1c** or **1d** with thionyl chloride, the analogously formed Pummerer reaction intermediate (**4c** or **4d**) would undergo demethylation by the acid hydrolysis of the methylthiadiazolium chloride intermediate (**6c** or **6d**) during the workup (Scheme I).

The reaction of 3-alkyl-6-hydrazinouracils (**8a**,[13] **8b**, and **8c**) with excess thionyl chloride at room temperature (an exothermic reaction) for 30 min also provided the corresponding 6-alkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**14a**, **14b**, and **14c**). However, these reactions appeared to involve a strikingly different and unexpected mechanism with that of the foregoing. Namely, careful treatment of **8a** with thionyl chloride at 0 °C for 30 min gave relatively stable 6-methyl[1,2,3,5]thiatriazolino[5,4-*c*]-pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**), probably via the

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