Computer-simulated line shapes were obtained with the program CLATUX[29] and were visually matched to the experimental spectra. From the pre-exchange lifetimes, the free energy of rotation was calculated for each measurement using the equation $\Delta G^{\ddagger} = 4.575T(10.32 + \log T - \log K_r)$. Good agreement was obtained, particularly for measurements made in the coalescence region. From the values between −11 and +38 °C, a $\Delta G^{\ddagger}$ of 14.9 ± 0.2 kcal/mol was obtained.

Registry No.—**11,** 64682-91-3; **12,** 64728-28-5; **13,** 64682-94-6; **14,** 1530-35-4; **15,** 27331-30-2; **16,** 64754-24-1; **17,** 64728-29-6; **18,** 64682-93-5; **19,** 64682-92-4; *m*-chlorobenzaldehyde, 587-04-2; *trans*-dibenzoylethylene, 959-28-4.

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(2) NDEA Title IV Fellow, 1971–1974.
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Centrosymmetric 1,5-Naphthyridine Derivatives: Synthesis, Tautomerism, and Thermal Rearrangements[1]

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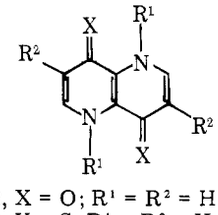
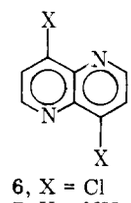
Efficient syntheses of the centrosymmetric 1,5-napthyridine derivatives **2–8** are reported. The 8-methoxy-1,5-naphthyridine **14** has been shown to undergo thermal rearrangement to its *N*-methyl isomer and thermal disproportionation to *N,N*-dimethyl and normethyl compounds. Tautomerism in hydroxy-1,5-naphthyridines has been investigated by UV spectroscopy in aqueous solution. Under these conditions the compounds studied exist predominantly as the pyridone tautomers. A remarkable alkylation reaction of the naphthyridine ring has been observed in the course of Lander rearrangement of **8**. It has been found that **8** via its rearranged isomer **4** gives the centrosymmetric ring-methylated compound **5** when heated in the solid state with methyl iodide.

Introduction

In connection with our studies of organometallic coordination polymers that might prove useful as semiconductors,[3] we needed heteroaromatic compounds potentially capable of functioning as tetradentate ligands. We were particularly interested in obtaining tetradentate analogues of the well-known bidentate chelating agent 8-hydroxyquinoline (**1**). Such analogues could be derived on paper by incorporating two additional coordination sites across a center of symmetry in **1** or by substituting naphthyridine to form appropriate 4,8-disubstituted 1,5-naphthyridines. In the present work, we describe efficient syntheses of the centrosymmetric 1,5-naphthyridine derivatives **2–8**. Hydroxynaphthyridines throughout this work are shown schematically and named as their presumably more stable pyridone (i.e., keto) tautomers, and evidence is presented that the latter tautomers indeed predominate in aqueous solution. Finally, we report novel results obtained during thermal rearrangement studies on alkoxynaphthyridines.



2, X = O; R¹ = R² = H
3, X = S; R¹ = R² = H
4, X = O; R¹ = Me; R² = H
5, X = O; R¹ = H; R² = Me



6, X = Cl
7, X = NH_2
8, X = OMe

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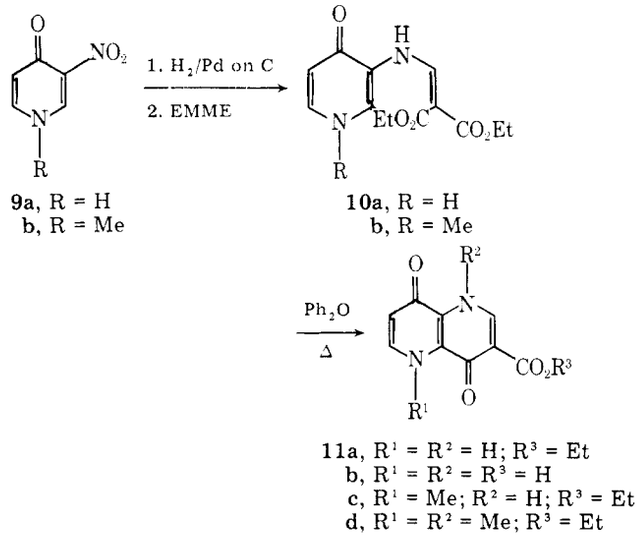
Scheme I

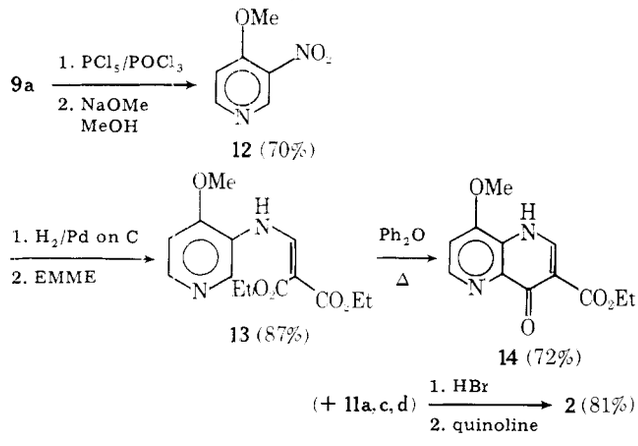


9a, R = H
b, R = Me

10a, R = H
b, R = Me

11a, R¹ = R² = H; R³ = Et
b, R¹ = R² = R³ = H
c, R¹ = Me; R² = H; R³ = Et
d, R¹ = R² = Me; R³ = Et

Scheme II



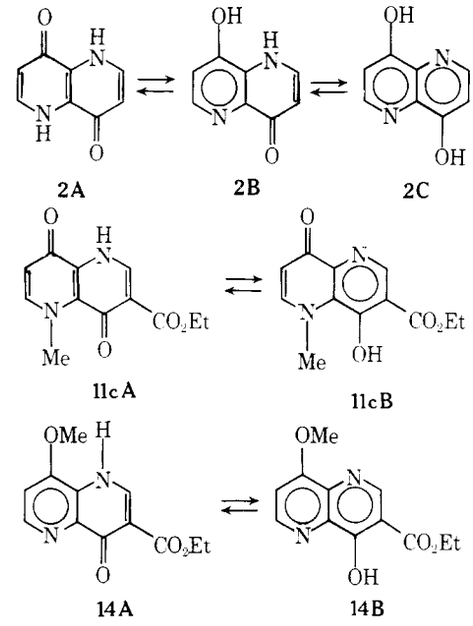
Results and Discussion

Our initial goal was a high-yield synthesis of 1,5-naphthyridine-4(1*H*),8(5*H*)-dione (**2**). Compound **2** had been prepared previously by Brown and Plasz[4] in an overall yield of 1% using the classical ethoxymethylene malonic ester (EMME) method (Scheme I). In this route, 3-nitro-γ-pyridone (**9a**) was catalytically reduced to the amine which was then condensed with EMME to give the adduct **10a** (58%). Thermal cyclization of **10a** gave the naphthyridine **11a** in 50% crude yield but only 4% final yield after purification. Compound **2** was obtained by basic hydrolysis of pure ester **11a** followed by thermal decarboxylation (sublimation) of acid **11b**. Repeating this work, we were not able to improve the procedure by direct hydrolysis of the crude ester **11a** under basic conditions. However, a dramatic increase in the overall yield of **2** resulted when crude **11a** was hydrolyzed in refluxing HCl. The product from the latter reaction, apparently a mixture of **11b** and **2**, was refluxed with quinoline to give **2** in 31% overall yield from **9a**.

We have also synthesized **2** by the somewhat longer route shown in Scheme II. **9a** was converted into 4-methoxy-3-nitropyridine (**12**) which was reduced to the amine and condensed with EMME to yield the adduct **13**. Cyclization to the naphthyridine **14** was accomplished by adding **13** in one portion to refluxing diphenyl ether or Dowtherm A. Reaction of **14** with refluxing HBr gave an excellent yield of the acid **11b** which readily decarboxylated to **2** in refluxing quinoline. The overall yield of **2** from **9a** in this case was consistently 35–45%.

The crucial step in the latter synthesis was the thermal cyclization of **13** to **14**. Yields of **14** were found to depend critically upon the duration of reaction, the isolated yields at various times being 6 (3 min), 38 (17 min), and 65–75% (25 min). Reaction times significantly longer than 25 min led to decreased yields of **14** because of further conversions leading to two other products.

Scheme III



2A 2B 2C

11cA 11cB

14A 14B

The first of these products, isolated in small amounts even after 25–30 min, was the thermodynamically more stable *N*-methyl isomer **11c**, identified by comparison with material synthesized independently according to Scheme I (**9b** → **10b** → **11c**). Thermal rearrangements of the type **14** → **11c** have ample precedent in the pyridine[5] and quinoline[6] series, although few examples have been reported for naphthyridines.[7] Studies on methoxypridines[8] have shown the rearrangement to be an intermolecular process. **11c** could arise by intermolecular reaction involving either **13** or **14**, although **14** has to be the primary source since after 25 min most of the **13** has been consumed.

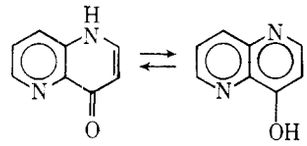
In addition to this rearrangement, we found that as the concentration of **11c** in the reaction mixture increased a disproportionation involving **14** and **11c** became important. Thus, when **13** was refluxed with diphenyl ether for 2 h, a refractory mixture containing **14**, **11c**, and the disproportionation products **11a** and **11d** resulted.[9] Refluxing **14** itself with diphenyl ether for 6.5 h produced qualitatively similar results, except that only traces of **14** remained, a fact facilitating separation of the other compounds. In this case, the *N*,*N*-dimethylnaphthyridone **11d** could be isolated by selective recrystallization followed by gradient sublimation.

The fact that analytically pure **14** did not exhibit a sharp melting point suggests that the aforementioned rearrangement and disproportionation occur more rapidly in the solid state, as might be expected in view of their intermolecular nature. Both **14** and its 8-ethoxy analogue[10] began melting at about 215 °C and were still partially solid at 270 °C.

Reaction of **2** with $POCl_3$ in a sealed tube yielded the known[4] 4,8-dichloro-1,5-naphthyridine **6** (75–82%). Treatment of **6** with ammonia in refluxing phenol gave 4,8-diamino-1,5-naphthyridine **7** (50–60%). Finally, 1,5-naphthyridine-4(1*H*),8(5*H*)-dithione **3** was obtained in essentially quantitative yield by treating **6** with hydrogen sulfide in refluxing aqueous ethanolic potassium hydroxide. Dithione **3** was stable in the solid state for at least six months but autoxidized slowly in dilute solution (see Experimental Section).

The poor solubility of 3 in the usual solvents precluded determination of its NMR spectrum.

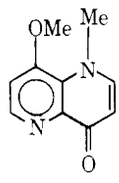
Tautomerism Studies. The γ-hydroxynaphthyridines **2**, **11c**, and **14** are capable of pyridone–pyridinol type tautomerism as depicted in Scheme III. It is well known[11] that, except in certain special cases, pyridone-type tautomers predominate in polar solvents and in the solid phase. The few studies which have been carried out on tautomerism in hydroxynaphthyridines[12] have led to similar conclusions. In particular, it has been shown[12a] by UV spectroscopy that 1,5-naphthyridin-4(1*H*)-one (**15A**) is the major tautomer in polar solvents, while the pyridinol tautomer **15B** predominates in nonpolar ones.



15A **15B**

We have studied tautomerism in the compounds in Scheme III by UV spectroscopy in aqueous solution only. Their UV spectra were compared among themselves and with the spectra of model compounds containing *N*- or *O*-methyl groups. Two appropriate models for compound **2** were 4,8-dimethoxy-1,5-naphthyridine (**8**) and 1,5-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione (**4**). The *O,O*-dimethyl compound **8** was easily synthesized by reaction of **6** with sodium methoxide in methanol. As expected, **8** rearranged readily on heating to the isomer *N,N*-dimethyl derivative **4** (vide infra). The structures of **8** and **4** were established by standard spectroscopic methods and single crystal x-ray analysis.[13]

UV spectral data for all relevant compounds are summarized in Table I. The spectrum of the *N,N*-dimethyl derivative **4** closely resembles that of **2.** Both possess a strong absorption maximum at 232 nm and two further maxima between 315 and 350 nm. Also, both spectra bear a formal resemblance to that of the known pyridone tautomer **15A,** which has a strong maximum at 240 mm and a single maximum at 323 nm. In contrast, the UV spectrum of the *O,O*-dimethyl derivative **8** does not resemble that of **2** but instead is quite similar to the spectrum of pyridinol tautomer **15B.** Both **8** and **15B** absorb strongly around 225 nm and less intensely at about 284 nm.



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These observations clearly eliminate the dipyridinol tautomer **2C** and suggest that the dipyridone tautomer **2A** predominates in aqueous solution. The data, however, do not rigorously exclude the pyridinol–pyridone tautomer **2B.** Despite several attempts, we were not able to synthesize the model corresponding to **2B,** namely, the *N,O*-dimethyl derivative **16.** Nevertheless, if **2B** were the major tautomer in solution, then a priori one would expect the spectrum of **2** to show the characteristic absorption maxima present in the spectra of both **4** and **8.** In other words **2** should exhibit a band in the region 250–300 nm corresponding to the long-wavelength band in the spectrum of **8.** This is exactly what happens in the case of **14,** a compound which has one ring only frozen in the pyridinol form. Here there are three bands, at 245, 304, and 317 nm, expected for a compound with a pyridinol–pyridone structure. Consequently, if **14** exists predominantly as the pyridone tautomer **14A,** then the absence of a prominent band around 250–300 nm in the spectrum of **2** is evidence that **2B** is not the principal tautomer in solution. A similar argument can be applied in the case of **11c.** Its spectrum resembles those of **2** and its dipyridone model **4,** in possessing only two prominent long-wavelength bands, both above 300 nm. The spectrum of **11c** is, moreover, virtually identical with that of the dipyridone **11d,** the only model for **11c** available. It therefore seems clear that the predominant tautomer of **11c** in aqueous solution is **11cA.**

Table I. UV Spectral Data for 1,5-Naphthyridine Derivatives

Compd	Registry no.	γ_{max}, nm	ε
15A[a]		240	27 200
		323	10 600
15B[b]		230	36 100
		286	5 940
2	64761-13-3	232	38 500
		262	3 200
		318	19 600
		330	27 400
4	63086-89-5	232	30 700
		267	3 000
		335	19 600
		348	21 300
8	63086-86-2	222	51 400
		282	10 000
11c	64761-17-7	232	29 200
		263	3 800
		319	19 400
		332	19 600
11d	64761-18-8	232	36 100
		265	4 500
		319	22 800
		333	23 000
14	64761-20-2	221	24 300
		245	16 800
		304	15 200
		317	13 600

[a] In H_2O; ref 12a. [b] In dioxane; ref 12a.

Thermal Reactions of 8 and Synthesis of 5. We have studied thermal reactions of the *O,O*-dimethyl compound **8** under a variety of conditions in sealed ampules. When **8** was heated in the solid state for 10 h at 226 °C, the *N,N*-dimethyl isomer **4** was isolated in 62% yield. As expected, the solid-state reaction could be catalyzed by methyl iodide (Lander rearrangement[14]). Heating **8** with 1 molar equiv of methyl iodide (2.5 h/226 °C) gave **4** in 78% isolated yield. Catalysis by methyl iodide even allowed the reaction to be carried out in solution. Thus, when **8** was heated in diphenyl ether with methyl iodide (0.3 molar equiv/20 min/210 °C), **4** was obtained in essentially quantitative yield. In the absence of methyl iodide, no **4** was detected after 2.5 h at 232 °C.

When **8** was heated in the solid state with methyl iodide (0.3 molar equiv/220 °C) for 12 h instead of 2.5 h, a new compound **5** was obtained (53%) which had properties similar to those of **2.** Specifically, **5** sublimed only above 230 °C and possessed at least one acidic hydrogen, the material being soluble in base and reprecipitated with acid. The IR spectrum of **5** resembled closely that of **2** in the region above 1500 cm^{-1}. The UV spectrum of **5** in water suggested that it was a dipyridone, the principal absorption bands appearing at 240 and 343 nm. Elemental analysis showed **5** to be an isomer of **8** and by a process of elimination we concluded that it had to be a ring-methylated derivative of **2.** This was confirmed by its NMR spectrum which showed two singlets at δ 2.61 (6 H) and 8.70 (2 H). Consequently we assigned **5** the centrosymmetric structure 3,7-dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione.

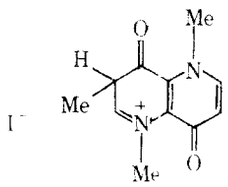
Table II. Mass Spectral Data for the Crude Product from the Reaction of 4 with Methyl-d_3 Iodide

m/e	Rel intensity
190	85
193	100
196	35
204	53
207	82
210	53
218	12
221	24
224	24

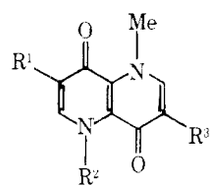
We preferred this structure to the isomeric 2,6-dimethyl derivative because the signals for two ring protons (δ 8.70) resembled those for $H_{2,6}$ (δ 8.65) in the spectrum of **2** (see end of Experimental Section).

The transformation **8** → **5** must take place via **4**, because **4** was isolated in good yield from reactions using shorter reaction times. Furthermore, **4** itself gave **5** in comparable yield when heated in the solid state with methyl iodide. In contrast, no reaction occurred when **4** was heated either in the solid state without methyl iodide or with methyl iodide in diphenyl ether solution (10 h/225 °C).

It is possible that the reaction **4** → **5** involves an electrophilic substitution, attack by methyl iodide leading to the naphthyridinium intermediate **17** which then undergoes loss of a proton and cleavage of the *N*-methyl group by iodide. This mechanism implies the formation of intermediates such as **18a–d**. A compound to which we have assigned the structure



17



18a, R^1 = Me; R^2 = R^3 = H
b, R^1 = R^2 = Me; R^3 = H
c, R^1 = R^3 = Me; R^2 = H
d, R^1 = R^2 = R^3 = Me

18a was indeed isolated in erratic amounts, and apparently contaminated with **4**, when **8** was heated with methyl iodide at temperatures somewhat below 225 °C. As the material was not isolated analytically pure, its identification must remain tentative.[15] More importantly, we have clearly detected tri- and tetramethylated species (presumably **18b–d**) in the mass spectrum of crude **5**. For example, Table II shows mass spectral data for the crude product obtained by heating **4** with methyl-d_3 iodide (0.9 molar equiv/16 h/228 °C). The *m/e* 190–196 series of peaks is due primarily to **5**, the 204–210 series to the trimethylated species, and the 218–224 series to the tetramethylated species. The absence of prominent peaks attributable to d_9 or d_{12} species indicates that no compound contains more than two CD_3 groups and that exchange of the *N*-methyl groups is not significant. The presence of d_0 tri- and tetramethylated compounds is evidence that unlabeled methyl iodide is produced in the course of the reaction. Purification of this crude mixture gave material containing <5% trimethylated compounds and no **18d** as shown by mass spectroscopy. The NMR spectrum showed the expected singlets at δ 2.61 and 8.70 in the peak area ratio of 3.3:2 in good agreement with the expectation based on the mass spectrum.

There appears to be no precedent for carbon alkylation either in the Lander rearrangement[14] or in the closely related Hilbert–Johnson reaction.[16] The apparent regiospecificity of the reaction **4** → **5** seems to rule out an alkylation mechanism involving radical intermediates, although this type of evidence is not entirely conclusive.[17]

Electrophilic alkylations of azaaromatic compounds are extremely rare.[19] An interesting example in the pyridine series is the thermal reaction of trityl chloride with 2-pyridone or *N*-methyl-2-pyridone to yield, in both cases, 5-triphenylmethyl-2-pyridone.[20] In view of this, we examined the thermal reaction of **2** itself with methyl iodide (4.5 molar equiv/12 h/228 °C). The crude product contained only traces of mono-, di-, and trimethylated species as shown by mass spectroscopy. This failure is somewhat curious, given the pyridone result. More work will be needed to resolve this anomaly.

Experimental Section

Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. IR spectra were taken on KBr pellets on a Beckman IR8 spectrophotometer. NMR spectra were determined on either a Varian A-60 or a Perkin-Elmer R-12 spectrometer. Absorptions are reported relative to an internal tetramethylsilane standard. Ultraviolet and visible spectra were obtained on a Beckman DK-2A spectrophotometer. Solutions of the rather insoluble compounds **2**, **3**, **5**, and **11d** were prepared for UV determination by warming a weighed amount of compound in the appropriate solvent in a volumetric flask until solution was complete. The solution was then allowed to cool to room temperature and made to volume. All UV/visible extinction coefficients were corrected for extraneous absorption determined by running the solvent in both cells. Low-resolution mass spectra were obtained on a Model 21-491 and high-resolution spectra on a Model 21-110 DuPont-Consolidated Electrodynamics Corp. instrument. Gradient sublimations were run at 0.1-mm pressure in 9-mm glass tubes heated in a cylindrical oven[21] constructed by Mr. F. C. Maseles. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Concentrated hydrobromic acid was distilled from stannous chloride dihydrate immediately before use. Predried quinoline was vacuum distilled (20 mm) from zinc dust and stored over potassium hydroxide pellets.

3-Nitro-γ-pyridone (9a). γ-Pyridone was nitrated by the method of Crowe,[22] except that the product was isolated in 55–65% yield in two crops: the first by filtration of the original acidic reaction mixture which had been poured onto ice and the second by filtration of the cold neutralized reaction mixture. Recrystallization from water and drying in a desiccator (P_2O_5) gave yellow microcrystals, mp 275–277 °C (lit.[22] 279 °C).

3-Nitro-4-chloropyridinium Hydrochloride. 3-Nitro-4-chloropyridine was prepared from **9a** by the method of Bishop et al.[23] The hydrochloride was prepared by bubbling hydrogen chloride gas through a stirred cooled ether solution of the chloro compound. The resulting moisture-sensitive precipitate was quickly filtered and stored in a desiccator in vacuo. Yields were 70–82%.

3-Nitro-4-methoxypyridine (12). The synthesis was a modification of a procedure of Bijlsma and den Hertog.[24] To an ice-cooled solution of sodium metal (5.42 g; 0.236 mol) in dry methanol (200 mL) was added dropwise with stirring a solution of 3-nitro-4-chloropyridinium hydrochloride (22.9 g; 0.117 mol) in dry methanol (200 mL) over a 1-h period. At the end of the addition, the ice bath was removed and the mixture was stirred an additional 1 h. Carbon dioxide gas was bubbled through the liquid for 20 min and then the mixture was filtered. The sodium chloride precipitate was washed several times with dry methanol and then discarded. The yellow-tan filtrate was evaporated to dryness and the residue was boiled with ether and filtered to remove a small amount of residual sodium chloride. The ether filtrate was boiled down to a convenient volume and Skelly B was added to the hot solution until turbidity was evident. Refrigeration of the solution followed by filtration gave **12** as yellow microcrystals (13 g). Two further crops were obtained from the filtrate. Final yield was 16.5 g (91%), mp 73–75 °C (lit.[25] 75 °C).

Diethyl [(4-Methoxy-3-pyridyl)amino]methylenemalonate (13). A mixture of **12** (5 g; 0.0325 mol), 10% palladium on carbon (500 mg), and dry methanol (125 mL) was hydrogenated for 6 h in a Parr apparatus at 50 psi. Filtration of the mixture through Celite and evaporation of the filtrate yielded the crude amine as a light tan oil or solid. The amine was stirred and refluxed in toluene (100 mL) with ethoxymethylenemalonic ester (EMME; 7 g; 0.0325 mol) for 24 h and then the reaction mixture was evaporated to dryness. The residue was dissolved in boiling Skelly B, filtered by gravity, and cooled to room temperature. **13** crystallized as fine, white platelets (8.3 g; 87% based

on **12**), mp 98.5–100 °C, after drying in vacuo. A small amount of this material was dissolved in boiling Skelly B and filtered hot through a thin pad of Norit A on Celite. Cooling the filtrate yielded an analytical sample of **13**: mp 100–101 °C; mass spectrum *m/e* 294.1215 (M^+, calcd for $C_{14}H_{18}N_2O_5$, 294.1216); NMR ($CDCl_3$) δ 1.34, 1.39 (6 H, overlapping triplets, ethyl CH_3), 4.03 (3 H, s, OCH_3), 4.29, 4.36 (4 H, overlapping quartets, ethyl CH_2), 6.95 (1 H, d, J = 5.8 Hz, H_5), 8.34 (1 H, d, J = 5.8 Hz, H_6), 8.53 (1 H, s, H_2), 8.60 (1, H, d, J = 14 Hz, collapses to singlet on shaking with D_2O, vinyl CH), 11.00 (1 M, d, J = 14 Hz, vanishes on shaking with D_2O, NH).

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.25; H, 6.30; N, 9.34.

Ethyl 8-Methoxy-1,5-naphthyridin-4(1*H*)-one-3-carboxylate (14). Diphenyl ether (200 mL) was heated to reflux in a three-necked flask fitted with an air condenser and a mechanical stirrer. **13** (4.5 g; 0.0153 mol) was added to the flask in one portion and the solution was refluxed and stirred for exactly 25 min. The dark-brown solution was cooled rapidly to room temperature with an air gun and poured into Skelly B (200 mL). The resulting precipitate was collected on a fritted glass funnel, washed well with Skelly B, and then boiled for several hours with benzene to remove residual diphenyl ether and again filtered through a fritted glass funnel. Addition of Skelly B to the benzene filtrate yielded variable amounts of the *N*-methyl isomer **11c** (vide infra). The precipitate on the fritted funnel was dried in a vacuum oven at 80 °C to yield crude **14** 2.72 g; 72%) as a tan powder. A small portion was twice dissolved in boiling nitromethane, filtered hot through a thin pad of Norit A on Celite, and cooled to produce analytically pure **14** as white microcrystals which partially melted beginning at about 215 °C (see Discussion): mass spectrum *m/e* 248.0795 (M^+, calcd for $C_{12}H_{12}N_2O_4$, 248.0797); NMR (F_3AcOH) δ 1.53 (3 H, t, ethyl CH_3), 4.60, 4.68 (5 H, singlet and quartet overlapping, respectively, OCH_3 and ethyl CH_2), 7.94 (1 H, d, J = 7 Hz, H_7), 9.16 (1 H, d, J = 7 Hz, H_6), 9.39 (1 H, s, H_2).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87. Found: C, 57.79; H, 4.99.

1,5-Naphthyridine-4(1*H*),8(5*H*)-dione (2). A solution of 2.74 g (0.011 mol) of **14** in 210 mL of concentrated hydrobromic acid was stirred and refluxed for 24 h. The resulting dark tan solution was evaporated to dryness on a rotary evaporator and the residue recrystallized from a large volume of water. Tan crystals of the acid **11b** were collected by filtration and dried in a vacuum oven at 100 °C. Crude yield was 1.98 g (88%): NMR (F_3AcOH) δ 7.92 (1 H, d, J = 6.5 Hz, H_7), 8.99 (1 H, d, J = 6.5 Hz, H_6), 9.48 (1 H, s, H_2).

The acid **11b** was ground to a powder and added to quinoline (90 mL), and the heterogeneous mixture was stirred and refluxed for 10 h. After cooling to room temperature, the precipitate was collected on a fritted glass funnel, washed well with acetone, and dried in vacuo. The dried precipitate was dissolved in dilute aqueous sodium hydroxide on a steam bath to give a tan solution which was filtered hot through a thin pad of Norit A on Celite. The cooled filtrate was taken to pH 6 with 2 N hydrochloric acid and the resulting precipitate was collected on a fritted glass funnel. Acidification of the filtrate to pH 2 gave a mixture of **2**, and **11b** which could be recycled in subsequent decarboxylation reactions. The precipitate on the fritted funnel was redissolved in dilute aqueous sodium hydroxide on a steam bath and then acidified to pH 2 with 2 N hydrochloric acid. The resulting precipitate was collected on a fritted glass funnel, washed well with water, and dried in a vacuum oven at 100 °C to yield **2** as a white powder (1.38 g; 88%). Recrystallization from water (3 mL/mg) gave white microcrystals: mp >300 °C (sublimes) (lit.[4] >300 °C); NMR (F_3AcOH) δ 7.53 (2 H, d, J = 7 Hz, $H_{3,7}$), 8.65 (2 H, d, J = 7 Hz, $H_{2,6}$).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 57.35; H, 3.55; N, 17.03.

2 was prepared from **11a** essentially as described above except that hydrochloric acid was substituted for hydrobromic acid in the initial hydrolysis step.

Diethyl [(1-Methyl-4-oxo-1,4-dihydro-3-pyridyl)amino]-methylenemalonate (10b). The compound was prepared from *N*-methyl-3-nitro-γ-pyridone **9b**[26] by the same procedure used to make **13** from **12**. Crude **10b** was crystallized by adding Skelly B to a solution in hot benzene and cooling to room temperature. Yields were ca. 60% tan crystals, mp 131–132 °C; the material was used without further purification: NMR ($CDCl_3$) δ 1.30, 1.37 (5 H, overlapping triplets, ethyl CH_3), 3.83 (3 H, s, NCH_3), 4.25, 4.34 (4 H, overlapping quartets, ethyl CH_2), 6.43 (1 H, d, $J_{5,6}$ = 7.2 Hz, H_5), 7.38 (1 H, doublet of doublets,[27] $J_{5,6}$ = 7.2 Hz, $J_{2,6}$ = 2 Hz, H_6), 7.59 (1 H, d, J = 2 Hz, H_2), 8.39 (1 H, d, J = 14.5 Hz, collapses to singlet on shaking with D_2O, vinyl CH), 10.89 (1 H, d, J = 14.5 Hz, vanishes on shaking with D_2O, NH).

Ethyl 5-Methyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione-3-carboxyate (11c). Starting with **10b** the procedure was the same as that used to prepare **14** from **13**, except that the cyclization was performed in Dowtherm A and the reaction mixture was refluxed for only 15 min. Crude **11c** was obtained as a tan powder (mp 250–253 °C) in ca. 35% yield. An analytical sample was prepared by the method used for **14**, yielding white microcrystals: mp 262–264 °C; NMR (F_3AcOH) δ 1.58 (3 H, t, ethyl CH_3), 4.69, 4.81 (5 H, singlet and quartet overlapping, respectively, NCH_3 and ethyl CH_2), 7.42 (1 H, d, J = 7.5 Hz, H_7), 8.55 (1 H, d, J = 7.5 Hz, H_6), 9.50 (1 H, s, H_2).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.86; H, 4.80; N, 11.24.

Ethyl 1,5-Dimethyl-1,5-naphthyridine-4(1*H*),8(5*H*)-dione-3-carboxylate (11d). Compound **14** (400 mg) was added to refluxing diphenyl ether (10 mL) and the solution was stirred and heated for 6.5 h. The reaction was worked up with Skelly B in the usual manner and the resulting precipitate was boiled with benzene. Filtration of the hot benzene mixture gave 97 mg of precipitate A, shown by IR to be a mixture of **11a** and **11d.** The yellow benzene filtrate was filtered hot through Norit A on Celite, evaporated to 15 mL, and refrigerated to yield 82 mg of precipitate B, shown by IR to be a mixture of **11c** and **11d.** Precipitate A was recrystallized from nitromethane (Norit A on Celite) to give crude **11d** (23 mg) as yellow microcrystals, mp 274–281 °C. Gradient sublimation at 200 °C yielded an analytical sample as white microcrystals, mp 282–283.5 °C; NMR (F_3AcOH) δ 1.55 (3 H, t, ethyl CH_3), 4.45–4.95 (8 H, multiplet dominated by broad singlet at 4.80, NCH_3 and ethyl CH_2), 7153 (1 H, d, J = 7 Hz, H_7), 8.57 (1 H, d, J = 7 Hz, H_6), 9.17 (1 H, s, H_2).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.39. Found: C, 59.24; H, 5.36.

4,8-Dichloro-1,5-naphthyridine (6). To a heavy-walled glass tube (28-cm long; 2-cm o.d.) was added **2** (335 mg; 0.0021 mol) and phosphorus oxychloride (20 mL). The tube was sealed and immersed to a depth of 4 cm in an oil bath at 175–185 °C. Solid **2** dissolved in about 6 h to yield a green solution. The tube was cooled and opened, and the solution was rinsed out with a little $POCl_3$ and evaporated on a rotary evaporator. The green viscous residue was carefully decomposed with ice and then neutralized with 2 N aqueous ammonia. The resulting gray precipitate was collected and dried in a vacuum desiccator (P_2O_5). The dried precipitate was dissolved in benzene, filtered hot through a thin pad of Norit A on Celite, and evaporated down to a convenient volume. Skelly B was added to the hot solution until turbidity was evident, and the solution was allowed to cool slowly to room temperature and was finally cooled in an ice bath. **6** crystallized as white needles (340 mg; 82%), mp (sealed tube) 274–276 °C (lit.[4] 278–279 °C).

4,8-Diamino-1,5-naphthyridine (7). The procedure was a modification of that described by Case and Brennan[28] for 4-amino-1,5-naphthyridine. To a 50-mL, three-necked flask fitted with an efficient condenser, a thermometer, and a fritted glass gas inlet tube was added warm phenol (20 mL). Ammonia gas passed through a potassium hydroxide drying tower was bubbled into the phenol for 10 min after which **6** (601 mg; 0.003 mol) was added to the flask and the solution was heated to 170–180 °C while the gas flow continued. Periodically, the white precipitate which formed on the gas inlet tube was scraped back into the reaction mixture. After 10 h, the tan solution was cooled, basified with 25% aqueous sodium hydroxide, and poured into a 125-mL flask. Addition of water to the dark-green solution at this point occasionally caused the product to precipitate but the following procedure was more reproducible. Additional 10% aqueous sodium hydroxide was added to the solution to make a final volume of about 75 mL. The flask was placed in a refrigerator for 18 h and the resulting white precipitate was collected and washed twice with ice water. The dried precipitate was dissolved in warm 2 N sulfuric acid, filtered, cooled, and adjusted to pH 8 with saturated aqueous sodium carbonate solution. Care must be taken around pH 5–6, since the mixture then becomes colloidal and froths. The precipitate was collected, washed with ice water, and dried to give **7** as white microcrystals (272 mg; 56%), mp 252–255 °C (dec). An analytical sample, prepared by recrystallization from water, had mp 255–257 °C (dec); NMR (4:1 Me_2SO-d_6/$CDCl_3$) δ 6.58, 6.68 (6 H, singlet and doublet partially overlapping, respectively, $J_{2,3}$ = 5.5 Hz, NH_2 and $H_{3,7}$), 8.22 (2 H, d, $J_{2,3}$ = 5.5 Hz, $H_{2,6}$); UV γ_{max} (H_2O) 235 (ε 37 000), 328 nm (13 600).

Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.73; H, 5.20; N, 34.72.

1,5-Naphthyridine-4(1*H*),8(5*H*)-dithione (3). To a 50-mL, three-necked flask fitted with an efficient condenser and a fritted glass gas inlet tube was added a solution of potassium hydroxide (5.5 g) in ethanol/water (9:1; 35 mL). Hydrogen sulfide gas was passed through the solution for 2 h and then the gas flow was shut off while **6** (1 g;

0.005 mol) was added to the flask. The gas flow was shut off while **6** (1 g; 0.005 mol) was added to the flask. The gas flow was resumed and the mixture was gently refluxed. White crystalline **6** gradually dissolved and the mixture turned deep orange. Periodically, the orange precipitate which formed on the gas inlet tube was scraped off into the reaction mixture. After 12 h, the orange solution was washed into a 125-mL flask with water and any orange precipitate was dissolved by adding a few pellets of solid potassium hydroxide. The solution was filtered and then carbon dioxide gas was passed through the liquid for 20 min. Dark orange crystals of **3** were collected on a fritted glass funnel, washed with water, and dried in a desiccator (P_2O_5). The yellow filtrate, containing traces of **3**, turned colorless in about 25 h as the dithione autoxidized. The dried product weighed 940 mg (96.4%): mp >300 °C; UV γ_{max} (CH_3CN) 246 (sh, ϵ 14 900), 260 (19 400), 328 (6000), 410 (sh, 7400), 450 nm (13 400). Within 30 h the yellowish-orange acetonitrile solution became colorless and exhibited the following UV/visible spectrum: 222 (ϵ 15 900), 238 (sh, 13 500), 263 (sh, 8300), 318 (9200), 330 (10 500). The latter extinction coefficients were calculated on the assumption that the molecular weight of the autoxidized compound remained 194.

Anal. Calcd for $C_8H_6N_2S_2$: C, 49.46; H, 3.11; N, 14.42; S, 33.01. Found: C, 49.54; H, 3.07; N, 14.45; S, 32.82.

4,8-Dimethoxy-1,5-naphthyridine (8). To a magnetically stirred solution of 210 mg (9.13 mmol) of sodium metal in 75 mL of dry methanol was added 834 mg (4.19 mmol) of **6** and the mixture was heated to reflux. Within 2 h **6** had all dissolved and the reaction was thereafter monitored by TLC (silica gel/$CHCl_3$). Refluxing was continued for either 96 h or until the TLC spot corresponding to the monomethoxy- monochloronaphthyridine intermediate had vanished. The solution was cooled and carbon dioxide gas was passed through the liquid for 15 min. The solution was evaporated to dryness and the residue dried in a vacuum desiccator (P_2O_5). The dried residue was boiled three times with 75-mL portions of acetone, the undissolved solid being collected on a fritted glass funnel between each step. The combined acetone filtrates were evaporated to dryness and the residue was dissolved in boiling benzene. Skelly B was added to the boiling solution until turbidity was evident and the solution was allowed to cool slowly to room temperature and was finally cooled in an ice bath. The resulting white crystals were collected and vacuum dried to give 692 mg (87%) of **8**, mp 209–212 °C. An analytical sample prepared by gradient sublimation at 95 °C melted at 214–216 °C. Crystals grown by this method were large enough for x-ray structure determination: NMR (F_3AcOH) δ 4.64 (6 H, s, OCH_3), 8.03 (2 H, d, J = 6.5 Hz, $H_{3,7}$), 9.36 (2 H, d, J = 6.5 Hz, $H_{2,6}$).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.47; N, 14.49.

General Procedures for Thermal Reactions of 4 and 8. All solid-state reactions were carried out in sealed ampules totally immersed in a wax bath. For solid-state reactions employing methyl iodide, the reactants were usually blanketed with a small amount of mineral oil to facilitate sealing the ampule. The reactions were worked up by washing the ampule contents onto a fritted glass funnel with Skelly B. Reactions in diphenyl ether were run in sealed ampules immersed in a wax bath to the level of the liquid in the ampules. The latter reactions were worked up by pouring the ampule contents into Skelly B and filtering.

Thermal Reactions of 8. A. Solid State. Compound **8** (280 mg) was heated at 226 °C for 10 h. The crude product was dissolved in boiling benzene and filtered hot through a thin pad of Norit A on Celite. Cooling the filtrate yielded white crystalline **4** (174 mg; 62%), mp 268.5–272 °C. An analytical sample prepared by gradient sublimation at 110 °C melted at 273–275.5 °C: NMR ($CDCl_3$) δ 4.30 (6 H, s, NCH_3), 6.43 (2 H, d, J = 8 Hz, $H_{3,7}$), 7.37 (2 H, d, J = 8 Hz, $H_{2,6}$); NMR (F_3AcOH) δ 4.79 (s, NCH_3). (The solution was not concentrated enough to distinguish any other peaks. Upon standing, there formed in the solution crystals of the bis(trifluoroacetate salt) of **4** large enough for x-ray analysis.)

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.97; H, 5.40; N, 14.62.

B. Solid State with Methyl Iodide. **8** (140 mg) was heated with methyl iodide (34 mg; molar ratio = 1:0.33) at 220 °C for 12 h. The crude product was boiled with benzene to remove any **4** present and then gradient sublimed at 275 °C. The white crystalline sublimate was dissolved in warm dilute aqueous sodium hydroxide and the resulting violet solution was acidified to pH 2 with concentrated hydrochloric acid. The precipitate was collected and recrystallized from a large volume of water to yield analytically pure **5** (74 mg; 53%): mp >300 °C; NMR (F_3AcOH) δ 2.61 (6 H, s, CH_3), 8.70 (2 H, s, $H_{2,6}$); UV γ_{max} (H_2O) 233 (sh, δ 37 400), 237 (sh, 45 700), 240 (51 600), 273 (4300), 332 (sh, 17 400), 337 (sh, 18 300), 343 nm (23 300).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.98; H, 5.40; N, 14.67.

Heating **8** with methyl iodide at temperatures below 225 °C for 12 h produced complex mixtures of products from which an impure compound identified as **18a** could be isolated in erratic yields by gradient sublimation at 132–150 °C. The material was contaminated with **4** and exhibited: mp 228–235 °C; NMR (F_3AcOH) δ 2.57 (s), 4.79 (s), 7.47–7.87 (m), 8.47–8.95 (m), peak area ratios 7:10:3:5.5, respectively; UV γ_{max} (H_2O) 232 (ϵ 33 600), 267 (3500), 297 (sh, 5000), 325 (20 000), 338 nm (24 800).

Heating **8** (40 mg) with methyl iodide (34 mg; molar ratio 1:1.14) for 2.5 h at 200–220 °C produced **4** (31 mg) which was isolated by gradient sublimation at 132 °C and identified by mp, IR, and UV.

C. Solution. Heating **8** (50 mg) in diphenyl ether (1 mL) for 2.5 h at 232 °C yielded 45 mg of recovered **8** identified by IR.

D. Solution with Methyl Iodide. Heating **8** (45 mg) in diphenyl ether with methyl iodide (9 mg; molar ratio 1:0.27) for 23 min at 210–213 °C yielded 44 mg of **4** which was identified by IR.

Thermal Reactions of 4. A. Solid State. Heating **4** (22 mg) for 10 h at 225 °C yielded 22 mg recovered **4** which was identified by IR.

B. Solid State with Methyl Iodide. **4** (63 mg) was heated with methyl iodide (57 mg; molar ratio 1:1.20) for 17 h at 220–226 °C. The crude product was boiled with benzene and dried to yield 41 mg of material with the IR identical to that of **5**. The mass spectrum showed traces of tri- and tetramethylated derivatives in addition.

When **4** (52 mg) was heated with methyl-d_3 iodide (34 mg; molar ratio 1:0.86) for 16 h at 228 °C, the crude product showed the mass spectrum given in Table II. Purification of the material by dissolution in dilute aqueous sodium hydroxide and reprecipitation with acid yielded material with the following properties: mass spectrum m/e (relative intensity) 190 (95), 193 (100), 196 (32), 204 (4), 207 (9), 210 (3); NMR (F_3AcOH) δ 2.61 (s), 8.70 (s), peak area ratios 3.3:2, respectively.

C. Solution with Methyl Iodide. Heating **4** (32 mg) with methyl iodide (7 mg; molar ratio 1:0.28) in diphenyl ether for 10 h at 225 °C yielded unchanged **4** (29 mg) which was identified by IR.

Attempted Reaction of 2 with Methyl Iodide. Heating **2** (46 mg) with methyl iodide (182 mg; molar ratio 1:4.5) for 12 h at 228 °C gave 47 mg of material which was identified as unchanged **2** by IR. The mass spectrum of the product showed traces of mono-, di-, and trimethylated species in addition.

Assignment of ^{1}H NMR Spectra. All the naphthyridine derivatives with four unsubstituted positions (2,3,6,7) showed two signals for the corresponding CH protons, separated by 1.3–1.5 ppm. These were assigned by analogy with 4-pyridone, where the signals for the protons adjacent to nitrogen appear downfield by 1.3 ppm relative to those adjacent to carbonyl (δ 7.92, 6.62, respectively[29]).

Registry No.—**3,** 64761-22-4; **5,** 63086-87-3; **6,** 28252-80-4; **7,** 64761-26-8; **9b,** 64761-30-4; **10b,** 64761-14-4; **11a,** 64761-28-0; **11b,** 64761-15-5; **12,** 31872-62-5; **13,** 64761-16-6; **18a,** 63086-88-4; 4-methoxy-3-pyridinamine, 33631-09-3; ethyl ethoxymethylenemalonate, 87-13-8; 3-nitro-4-chloropyridinium hydrochloride, 54079-68-4; methyl iodide, 74-88-4.

Supplementary Material Available. Table III, IR spectral data, and Table IV, mass spectral data, for 1,5-naphthyridine derivatives and precursors, (7 pages). Ordering information is given on any current masthead page.

References and Notes

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New Aspects of Intramolecular Hydrogen Transfer in Some Ortho-Substituted Aryl Radicals

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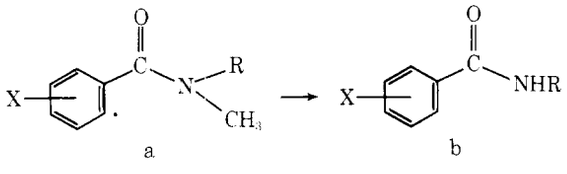
Intramolecular 1,5-, 1,6-, and 1,7-hydrogen transfers are observed when *o*-di-*n*-propylaminosulfonylbenzenediazonium tetrafluoroborate (**1a**) is decomposed in the system: $CuBr_2$–Me_2SO. The reaction competes with the "Sandmeyer-like" aryl bromide formation. The extent of competition is shown, by study of lower homologues, to reflect steric effects which are also evident from a comparison of the similar dediazoniation of *o*-di-*n*-propylamino- and *o*-dimethylaminocarbonylbenzenediazonium ions, **8a** and **8c**, respectively. The stereochemical argument is amplified by the failure of *o*-*n*- and -isopropoxycarbonylbenzenediazonium salts to undergo hydrogen transfer. A large solvent effect is also evident; the substitution of acetone for Me_2SO in decomposition of **8c** decreases hydrogen transfer from near 90 to about 15%, with a corresponding increase in bromoarene formation. The ultimate products of hydrogen transfer are identified and rationalized.

The demethylation of *o*-(dimethylaminocarbonyl)aryl or (*N*-aryl-*N*-methylaminocarbonyl)aryl diazonium salts by intramolecular 1,5-hydrogen transfer in homolytic fashion (Scheme I) was probably first recognized in 1954.[1] Despite extensive study of its mechanism,[2] there are still many unanswered questions which merit further work.[2b,c] It is, however, already apparent that the manner and the medium in which the radical a (Scheme I) is generated play an important role in product determination,[3a] and that when R is a substituted aryl, steric influences have been recognized.[1,3b,c]

In connection with a synthetic project, we happened upon a related reaction which also involved radical transfer, but to a propyl group of a dipropyl sulfonamide (Figure 1). Astonishingly, attack occurred at the α, β, and γ positions! The 6-, 7-, and 8-membered cyclic transition states that were required for this reactivity suggested that there were steric and other influences not previously recognized in this type of process. We have, accordingly, briefly examined some of them. Our experimental method comprised adding a dimethylsulfoxide (Me_2SO) solution of the *o*-diazonium tetrafluoroborates to $CuBr_2$ in Me_2SO, a system which is reported to give bromoaromatics in high yield,[4,5] our original goal. The use of $CuBr_2$–Me_2SO ensured a homolytic reaction, and the high concentration could also be expected to minimize rearrangement of the alkyl radicals[6] prior to oxidation and termination in products. Since this system had not previously been used to generate the analogous carboxamide radicals, we examined two of these, and, for reasons which will become clear, we also studied the behavior of two esters.

Scheme I

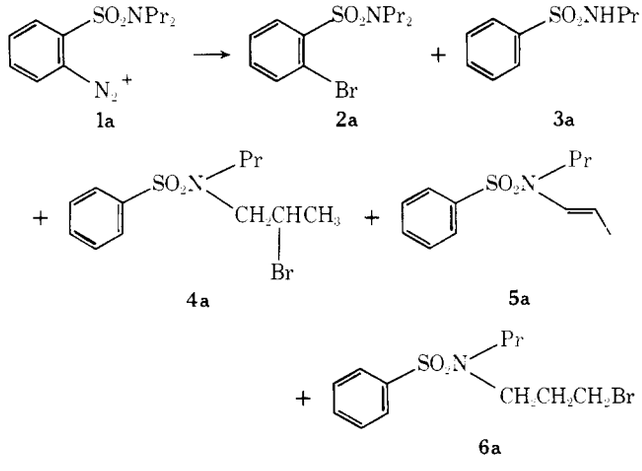


a b

Results

The instantaneous decomposition of *o*-(dialkylaminosulfonyl)benzenediazonium tetrafluoroborates **1** in $CuBr_2$–dry Me_2SO at room temperature furnished *o*-bromobenzenesulfonamides **2** from a Sandmeyer-like[7a] reaction, along with products resulting from transfer of the initially generated aryl radical site to the alkyl side chain.[7b] These latter products included monoalkyl sulfonamides, bromoalkyl sulfonamides, and alkenylalkyl sulfonamides (Scheme II), reflecting hy-

Scheme II



1a 2a 3a 4a 5a 6a