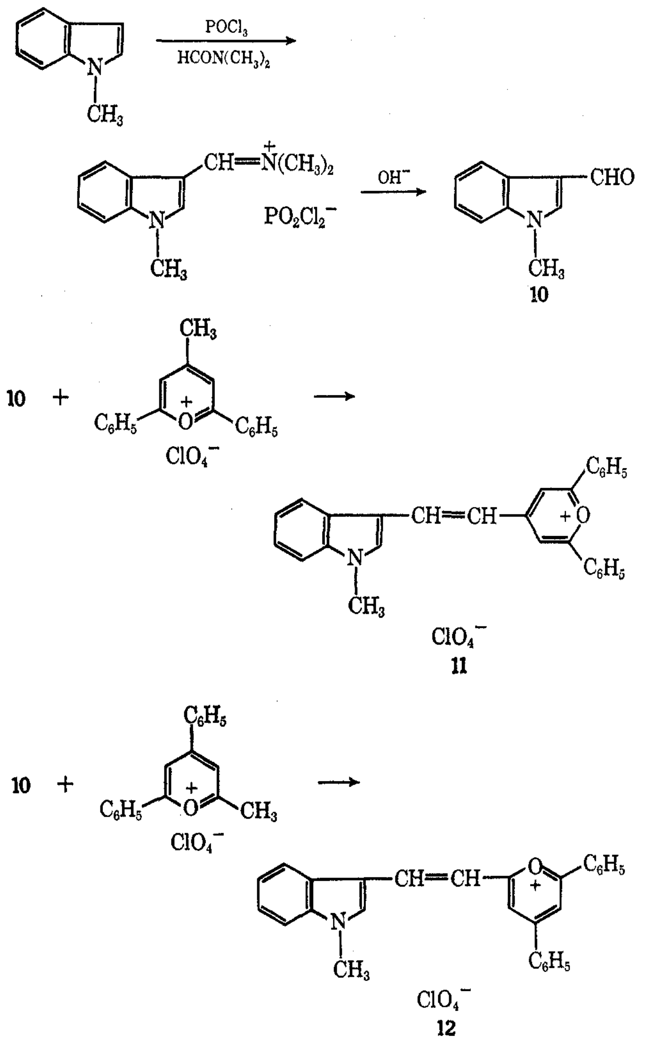
Scheme III



**Registry No.**—2, 27179-40-4; 2 2,4-DNP, 27179-41-5; **3**, 27179-42-6; **4**, 27179-43-7; **5**, 27179-44-8; **6**, 27179-45-9; **7**, 22181-72-2; **8**, 6802-23-9; **9**, 27179-48-2; **11**, 27179-49-3; **12**, 27179-50-6.

**Acknowledgment.**—We are indebted to Dr. T. H. Regan and Mr. R. L. Young for the determination and interpretation of the nmr spectrum.

## Reaction of 2-Thiouracils with Formaldehyde under Acidic Conditions

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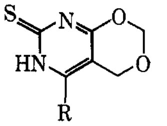
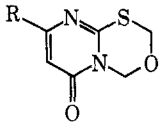
*Received September 26, 1969*

The reaction of 6-methyl- and 6-phenyl-2-thiouracil with formaldehyde under acidic conditions has previously been investigated. Structures **1b** and **1c** were assigned to the products.[1] The basis for this assignment was the observation that the same products were obtained also by reaction of the 5-hydroxymethyl derivatives of these thiouracils with formaldehyde under the same reaction conditions.[1] Thus it appeared that substitution at position 5 of the 2-thiouracil ring had been incontrovertibly demonstrated. Since these results were not in agreement with the available evidence, which indicated that the sulfur atom could be a very reactive center,[2–5] we reinvestigated these reactions and included 2-thiouracil because of its biological significance.

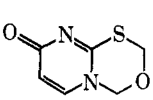
First we ascertained that 2-thiouracil itself reacts with formaldehyde under acidic conditions giving the pyrimidooxathiazine **2a**. Confirmation of the assigned structure seemed necessary not only in order to exclude possible isomeric formulas **1a** and **3**, but also because the reaction product crystallized from water giving two crystalline forms, aggregates of orthorhombic needles and monocline crystals. This was accomplished by X-ray analysis (see Experimental Section). The two crystalline forms were shown to represent a single substance having the assigned structure (**2a**).



**1a**, R = H
**b**, R = CH$_3$
**c**, R = C$_6$H$_5$



**2a**, R = H
**b**, R = CH$_3$
**c**, R = C$_3$H$_7$

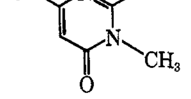


**3**

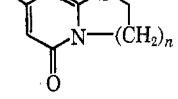
Nmr, ir, and uv data were fully compatible with this assignment. In particular the nmr spectra of the two crystalline forms were identical and fully compatible with structures **2a** and **3**, since position 5 of the original 2-thiouracil ring was shown to be unsubstituted.

The ir spectra in Nujol mull were different because of the different crystal-packing effects while spectra in chloroform solutions were identical; all these spectra showed the presence of the carbonyl bands.

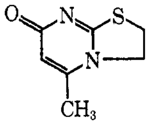
Uv spectra of both crystalline forms of **2a** in water were identical and very similar to the uv spectra of the pyrimidothiazine **5** (methanol), 3,6-dimethyl-2-methylthiopyrimidin-4-one (**4**) (methanol),[6] and the thiazolopyrimidine **6** (water), displaying a maximum in the range 285–295 mμ and two very close maxima in the range 224–245 mμ. Because of this we concluded that all the above-mentioned substances had the same *o*-quinoid chromophore shown to be present in **2a**; structures **5** and **6** were previously supported only by ir analysis.[4]



**4**



**5**, $n = 2$
**6**, $n = 1$



**7**

The presence of two very close maxima in the uv spectrum of **4** in methanol at about 230 and 240 mμ

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[1] L. Monti and C. Pacini, *Gazz. Chim. Ital.*, **78**, 638 (1948).

[2] B. Stanovnik and M. Tisler, *Arzneim.-Forsch.*, **14**, 1004 (1964).

[3] H. F. Andrew and C. K. Bradsher, *J. Heterocycl. Chem.*, **4**, 577 (1967).

[4] N. G. Pashkurov and V. S. Reznik, *Khim. Geterotsikl. Soedin.*, 1918 (1968).

[5] I. Wempen, and J. J. Fox, *J. Org. Chem.*, **34**, 1020 (1969).

[6] P. Galimberti, V. Gerosa, and M. Melandri, *Ann. Chim.* (*Rome*), **48**, 457 (1958).

has been interpreted as resulting from a tautomeric equilibrium in which the N–$CH_3$ bond is being broken and a new O–$CH_3$ bond is being formed.[6,7] Although the uv spectra of **2a** and **6** in water were very similar to that reported for **4** in methanol, this tautomerism cannot operate in the case of **6**. Moreover on changing the solvent to methanol or ethanol the two very close maxima of **2a** and **6** overlapped. Hence the tautomerism most likely does not apply in the case of **4** either.

Starting from 6-methyl- and 6-propyl-2-thiouracil the expected homologs of **2a** were obtained. Structures **2b** and **2c** have been assigned to these compounds on the basis of the following considerations.

Firstly uv spectra of **2b** and **2c** in various solvents were quite similar to the corresponding spectra of **2a**. Secondly, the presence of a *p*-quinoid chromophore characteristic of an isomer of the type **3** was ruled out by comparing the uv spectra of **2b** and **2c** with those of the thiazolopyrimidine **7** in various solvents. The structure of **7** has been previously supported only by ir analysis.[4] Finally the chromophore characteristic of **1a** has been excluded because the ir spectra of **2b** and **2c** showed the presence of a carbonyl group and their nmr spectra demonstrated the presence of a proton bound to the carbon atom adjacent to this carbonyl.

Now that the structure of the product **2b** has been established the role played by the acidity of the medium can be understood. Under conditions of weak acidity 5-hydroxymethyl-2-thiouracils are preferentially formed, as reported in the literature.[1,8] Under conditions of strong acidity the sulfur atom becomes the reactive center and pyrimidooxathiazines like **2a–c** are formed with the unstable 5-hydroxymethyl derivatives serving as intermediates.

The appearance of the new reactive center is also evidenced when uracil and 2-thiouracil respectively are allowed to react with formaldehyde in the presence of concentrated hydrochloric acid. Uracil is reported to form the 5-chloromethyl derivative.[9] Under the same reaction conditions we have now obtained the hydrochloride of the pyrimidooxathiazine **2a** in good yield from 2-thiouracil.

### Experimental Section

Melting points were determined in a Büchi capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 225 spectrophotometer. Ultraviolet spectra were determined on a Hitachi Perkin-Elmer Model 124 spectrophotometer and nmr spectra on a Varian A-60 spectrophotometer with tetramethylsilane as internal reference. Eastman Chromogram 6060 sheets (silica gel with fluorescent indicator) were used for thin layer chromatography and were developed with ligroin–methyl alcohol–ethyl acetate (2:5:2).

**Crystal Structure Determination.**—On the basis of procession photographs, taken with Co K$\alpha$ radiation, the plate-like crystals were found to belong to the monoclinic system. The cell parameters were $a = 11.66 \pm 0.02$ Å, b $= 8.71 \pm 0.02$ Å, $c = 7.32 \pm 0.02$ Å, $\beta = 110.2 \pm 0.3°$, $U = 697.4$ Å$^3$ with eight formula units per unit cell. The systematic extinctions, $0k0$ for $k$ odd and $h0l$ for $l$ odd, indicated the centrosymmetric space group $C_{2h}^5$-$P2_1/c$. Intensity data were collected by the equiinclination Weissenberg technique, using Fe-filtered Co K$\alpha$ radiation. Levels $hk0$ and $h0l$ through $h5l$ were recorded by the multiple film technique. The intensities of 513 independent reflections were measured by visual comparison with a calibrated scale. The usual Lorentz and polarization factors and the spot-shape correction for nonzero levels were applied. No correction for absorption or extinction was made. The observed structure amplitudes were placed in a common scale by Weissenberg cross-level data. The structure was solved by the heavy-atom method and refined by the block-diagonal isotropic method to $R = 0.097$, the atomic parameters of the hydrogen atoms being not allowed to vary.[10] See Table I.

Table I

Final Fractional Coordinates of the Atoms[a]

| Atom | $x$ | $y$ | $z$ |
|---|---|---|---|
| S | 0.5680 (3) | 0.5092 (5) | 0.2761 (5) |
| O(1) | 0.9861 (7) | 0.3592 (13) | 0.2918 (13) |
| O(2) | 0.7226 (7) | 0.6540 (11) | 0.1313 (12) |
| N(1) | 0.6465 (8) | 0.2327 (14) | 0.2743 (14) |
| N(2) | 0.7925 (8) | 0.4197 (14) | 0.2804 (14) |
| C(1) | 0.6777 (11) | 0.3747 (16) | 0.2764 (15) |
| C(2) | 0.7314 (12) | 0.1250 (18) | 0.2843 (19) |
| C(3) | 0.8465 (10) | 0.1554 (17) | 0.2861 (18) |
| C(4) | 0.8849 (11) | 0.3137 (18) | 0.2880 (18) |
| C(5) | 0.8208 (12) | 0.5862 (19) | 0.2812 (23) |
| C(6) | 0.6193 (12) | 0.6809 (17) | 0.1876 (19) |
| H(2) | 0.7049 | 0.0045 | 0.2893 |
| H(3) | 0.9088 | 0.0622 | 0.2853 |
| H(5-1) | 0.8284 | 0.6380 | 0.4208 |
| H(5-2) | 0.9059 | 0.6063 | 0.2570 |
| H(6-1) | 0.6431 | 0.7684 | 0.3016 |
| H(6-2) | 0.5452 | 0.7268 | 0.0640 |

[a] Estimated standard deviations are in parentheses for the nonhydrogen atoms. The esd's were derived from the residuals and the diagonal elements of the inverse matrix of the last least-square cycle.

All calculations were performed on an IBM 7044 computer using programs of Immirzi[11] and Albano, *et al.*[12] A program of our own design (unpublished) was used to calculate best molecular planes according to Schomaker, *et al.*[13] The atomic scattering factors used were those given in the "International Tables for X-Ray Crystallography"[14] for sulfur, those of Berghuis, *et al.*,[15] for nitrogen, and those of Hanson, *et al.*,[16] for oxygen, carbon, and hydrogen.

The results of this analysis showed that the crystals consisted of discrete molecules of the isomer **2a**. A perspective drawing of the molecule is shown in Figure 1. The S and C(5) atoms are coplanar with the pyrimidine ring within 0.05 Å. The conformation of the oxathiazine ring is well described by the torsion angles around its bonds: C(1)–N(2), 0.3; N(2)–C(5), −49.8; C(5)–O(2), 81.8; O(2)–C(6), −56.3; C(6)–S, 5.1; S–C(1), 20.9°.

The needle-like crystals are orthorhombic with cell dimensions, determined from precession photographs, $a = 7.08 \pm 0.02$ Å, $b = 4.02 \pm 0.01$ Å, $c = 24.29 \pm 0.04$ Å, $U = 691.3$ Å$^3$. The crystals appeared to be disordered and the observed extinctions did not allow a sure determination of the space group. However, since we were interested in the overall geometry of the molecule, the space group analysis has not been carried out. The projection of the structure onto (010) is centrosymmetric and belongs

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(7) For a conclusive discussion on the uv spectra of uracil derivatives, see J. Pitha, *J. Org. Chem.*, **35**, 903 (1970); and for 2-thiouracil derivatives, see J. Reiter, P. Sohár, and J. Lipták, *Tetrahedron Lett.*, **17**, 1417 (1970).

(8) G. Poetsch and R. Behrend, *Justus Liebigs Ann. Chem.*, **448**, 89 (1926).

(9) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Amer. Chem. Soc.*, **82**, 991 (1960).

(10) Listings of atomic parameters, bond lengths, and angles and deviation of the atoms from planarity will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(11) A. Immirzi, *Ric. Sci.*, **10**, 846 (1967).

(12) V. Albano, A. Domenicano, and A. Vaciago, *Gazz. Chim. Ital.*, **96**, 922 (1966).

(13) V. Schomaker, J. Waser, R. E. Marsh, and G. Bergman, *Acta Crystallogr.*, **12**, 600 (1959).

(14) "International Tables for X-Ray Crystallography," Vol. 3, Kynoch Press, Birmingham, England, 1962.

(15) J. Berghuis, I. J. M. Haanappell, M. Potters, B. O. Loopstra, C. H. Gillavry, and A. L. Veenedaal, *Acta Crystallogr.*, **8**, 478 (1955).

(16) H. P. Hanson, F. Herman, J. D. Lea, and S. Skilman, *ibid.*, **17**, 1040 (1964).

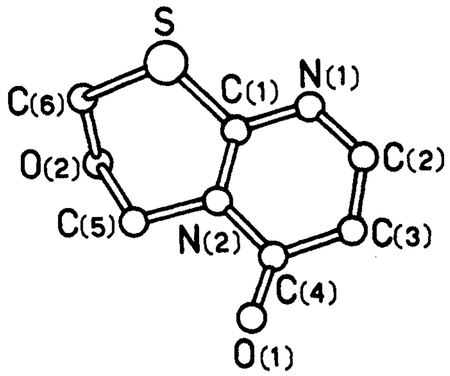

Figure 1.—A sketch of the molecule with a numbering scheme. The hydrogen atoms are not shown.

to the plane space group *pmg*. A two-dimensional analysis, carried out on the basis of 116 independent *h0l* reflections using the heavy-atom method, allowed the location of all the nonhydrogen atoms. After three cycles of isotropic block-diagonal least-squares refinement the *R* factor was 0.21. This value suggests that the deduced model is essentially correct, as shown by the Fourier projection calculated on the basis of these data. Since the geometry of the molecule was univocally determined, no attempt was made to locate the hydrogen atoms in order to inprove the refinement.

Thus the results showed that the orthorhombic needles and the monocline crystals were two crystalline modifications of a single substance having the assigned structure **2a**.

6*H*-**Pyrimido[2,1-*d*][1,3,5]oxathiazin-6-one** (**2a**).—The procedure reported in literature[1] for the homolog **2b** has been followed. 2-Thiouracil (18 g) was dissolved in a mixture of 40 ml of water, 130 ml of concentrated sulfuric acid, and 30 ml of 35% formaldehyde. The solution was allowed to stand at room temperature for 24 hr and was stirred occasionally. After dilution with 800 ml of water, the pH was adjusted to about 8 with diluted ammonia. The precipitate that formed was collected by filtration and crystallized from water. A mixture of monoclinic crystals, mp 132°, and fibrous aggregates of orthorhombic needles, mp 131.5°, was obtained. The monoclinic crystals could be converted into needles by recrystallization from aqueous solutions. The two crystalline forms had identical nmr[17] and uv spectra: $\lambda_{\max}^{\text{hexane}}$ 298 mμ ($\epsilon$ 7496), 228 (6283); $\lambda_{\max}^{\text{water}}$ 293, 240, 226 at pH 6.5; $\lambda_{\max}^{\text{95\% ethanol}}$ 296.5 (240 mμ sh), 228; $\lambda_{\max}^{\text{methanol}}$ 296 (240 sh), 229; $\delta_{\text{TMS}}^{\text{CDCl}_3}$ 7.78 (d, 1 H, CH), 6.21 (d, 1 H, CH), 5.58 (s, 2 H, $CH_2$), 5.31 (s, 2 H, $CH_2$). The ir spectra were different: *e.g.*, monoclinic crystals, $\nu_{\max}^{\text{Nujol}}$ 1690 and 1666 (C=O); needles, $\nu_{\max}^{\text{Nujol}}$ 1678 and 1664 (C=O); $\nu_{\max}^{\text{CHCl}_3}$ 1680 $cm^{-1}$ (C=O) for both forms.

The $R_f$ values obtained by thin layer chromatography for both these crystalline forms were identical.

*Anal.* Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 3.55; N, 16.46; O, 18.80; S, 18.84. Found: C, 42.21; H, 3.59; N, 16.46; O, 19.01; S, 18.76.

The hydrochloride of the base described above has been obtained from 2-thiouracil itself in a 55% yield; the procedure followed was that reported for chloromethylating uracil;[9] and the product was precipitated by addition of acetone to the reaction mixture. After recrystallization from alcohol–ether, the compound had mp 187° with decomposition, depending on the heating speed. This hydrochloride can also be obtained from chloroform solutions of the base by precipitation with hydrogen chloride.

*Anal.* Calcd for $C_6H_7ClN_2O_2S$: C, 34.88; H, 3.41; N, 13.55; Cl, 17.15; S, 15.51. Found: C, 34.92; H, 3.50; N, 13.48; Cl, 17.03; S, 15.64.

6*H*-**8-Methylpyrimido[2,1-*d*][1,3,5]oxathiazin-6-one** (**2b**).—The procedure reported for **2a** was followed starting from 6-methyl-2-thiouracil. After recrystallization from water, the yield was 84%; mp 140° (lit.[1] mp 140–141°); $\lambda_{\max}^{\text{hexane}}$ 294 mμ ($\epsilon$ 6915), 228 (6409); $\lambda_{\max}^{\text{95\% ethanol}}$ 293.5, 240 (230 mμ sh); $\lambda_{\max}^{\text{water}}$ 290, 243.5 (225.5 sh); $\delta_{\text{TMS}}^{\text{CD}_3\text{SO}}$ 6.00 (s, 1 H, CH), 5.46 (s, 2 H, $CH_2$), 5.40 (s, 2 H, $CH_2$), 2.08 (s, 3 H, $CH_3$); $\nu_{\max}^{\text{CHCl}_3}$ 1679 $cm^{-1}$ (C=O).

*Anal.* Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.37; N, 15.20. Found: C, 45.45; H, 4.20; N, 15.32.

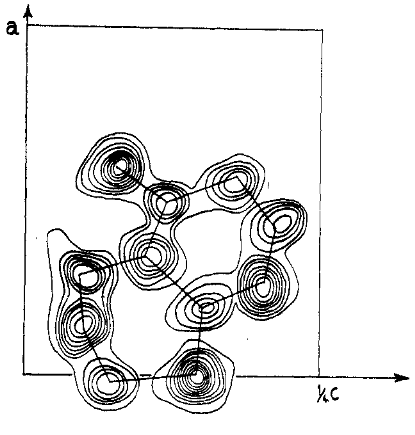

Figure 2.—Fourier projection of the electron density onto (010). Contours are drawn at intervals of 2 e Å$^{-2}$ for the S atom and of 1 e Å$^{-2}$ for the O, N, and C atoms.

6*H*-**8-Propylpyrimido[2,1-*d*][1,3,5]oxathiazin-6-one** (**2c**).—The procedure reported for **2a** was followed starting from 6-propyl-2-thiouracil. After recrystallization from water, the product had mp 97°; $\lambda_{\max}^{\text{hexane}}$ 295 mμ ($\epsilon$ 6770), 229 ($\epsilon$ 6498); $\lambda_{\max}^{\text{water}}$ 288, 242 (221.5 sh); $\lambda_{\max}^{\text{95\% ethanol}}$ 294.5, two overlapping maxima 235; $\delta_{\text{TMS}}^{\text{CDCl}_3}$ 6.0 (s, 1 H, CH), 5.5 (s, 2 H, $CH_2$), 5.26 (s, 2 H, $CH_2$), and with approximated first order 2.37 (tr, 2 H, $CH_2$), 1.60 (m, 2 H, $CH_2$), 0.87 (tr, 3 H, $CH_3$); $\nu_{\max}^{\text{CHCl}_3}$ 1675 $cm^{-1}$ (C=O).

*Anal.* Calcd for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.87; H, 5.60; N, 13.28.

**8-Methyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one** (**5**)[4] had $\lambda_{\max}^{\text{water}}$ 292 mμ, 247; $\lambda_{\max}^{\text{95\% ethanol}}$ 295 (240 sh), 228; $\lambda_{\max}^{\text{methanol}}$ 294, 243.5, 229. The hydrochloride precipitated from a chloroform solution of the base with hydrogen chloride had mp 268–270° (uncor).

*Anal.* Calcd for $C_8H_{11}N_2ClOS$: C, 43.93; H, 5.07; N, 12.81. Found: C, 43.69; H, 4.98; N, 12.90.

**7-Methyl-2*H*,5*H*-thiazolo[3,2-*a*][1,3]pyrimidin-5-one** (**6**)[4] had $\lambda_{\max}^{\text{water}}$ 284.5 mμ (243 and 227 mμ sh); $\lambda_{\max}^{\text{95\% ethanol}}$ 285.5, 227; $\lambda_{\max}^{\text{methanol}}$ 285 (240 mμ sh), 228.

**5-Methyl-2*H*,7*H*-thiazolo[3,2-*a*][1,3]pyrimidin-7-one** (**7**)[4] had $\lambda_{\max}^{\text{water}}$ 262 mμ, 229; $\lambda_{\max}^{\text{95\% ethanol}}$ (257 sh), 229.5; $\lambda_{\max}^{\text{methanol}}$ 264, 228.5.

**Registry No.**—**2a**, 27092-97-3; **2a** HCl, 27092-98-4; **2b**, 27092-99-5; **2c**, 27093-00-1; **5** HCl, 27093-01-2; 2-thiouracil, 156-82-1; formaldehyde, 50-00-0.

**Acknowledgment.**—The authors are very indebted to Dr. E. Trivellone for preliminary nmr spectroscopy and to Mrs. A. Andreassi for her cooperation. This work has been partly supported by Italian National Research Council.

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# Cyclization of Some 2-(Haloacylamino)pyrimidines

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*Received April 24, 1970*

Fozard and Jones[2] reported that heating 2-aminopyridine (**1**) with 4-bromobutyryl bromide led to the formation of 2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*]-diazepinium bromide (**2**, Scheme I). When we at-

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[17] J. P. Kokko, L. Mandell, and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 1042 (1962).

[1] To whom inquiries should be addressed.

[2] A. Fozard and G. Jones, *J. Chem. Soc.*, 2763 (1964).