9-Methylacridine.—To a solution of 2.64 g. (0.11 mole) of sodium hydride in 125 ml. of DMSO at 70° was added 2 g. of acridine (0.011 mole) in 80 ml. of DMSO. The reaction mixture was stirred for 4 hr. at 70° under a nitrogen atmosphere followed by addition of 125 ml. of water. The reaction mixture was added to 1500 ml. of water which was extracted three times with chloroform to yield a yellow oil after removal of the chloroform. The yellow oil in chloroform as analyzed by g.l.p.c. on a 3% SE-30 column at 200° indicated a yield in excess of 98% of 9-methylacridine. Upon heating the yellow oil in a flask at 90° under high vacuum, yellow needles formed on walls of the flask. These were collected and resublimed at 93° and 1 mm. and recrystallized from Skellysolve B to yield yellow needles, m.p. 115–117°, lit.[19] m.p. 118–118.5°.

6-Methylphenanthridine.—To a solution of 2.64 g. (0.11 mole) of sodium hydride in DMSO at 70° was added 2 g. of phenanthridine (0.011 mole) in 60 ml. of DMSO. The reaction mixture was stirred for 4 hr. at 70° under a nitrogen atmosphere followed by the addition of 125 ml. of water. The reaction mixture was added to 1500 ml. of water which was extracted three times with chloroform. The chloroform extract yielded an oil which was analyzed by g.l.p.c. on a 3% SE-30 column at 200° to contain more than a 98% yield of 6-methylphenanthridine. The oil dissolved in Skellysolve B was passed through 50 g. of Woelm alumina, grade III. Crystallization of the eluent gave white crystals which were sublimed at 73° and 1 mm. The resulting needles had m.p. 84–85°, lit.[20] m.p. 85°.

1-Methylisoquinoline.—To a solution of 2.64 g. (0.11 mole) of sodium hydride in 100 ml. of DMSO at 70° was added 2.2 ml. of isoquinoline (0.019 mole) in 100 ml. of DMSO. The reaction mixture was stirred at 70° for 4 hr. under a nitrogen atmosphere, 100 ml. of water was added, and the reaction mixture was poured into 1500 ml. of water. The aqueous solution was extracted with benzene. Removal of the benzene yielded an oil which was analyzed by g.l.p.c. Analysis with a 3% SE-30 column at 140° indicated a quantitative yield of 1-methylisoquinoline. The oil distilled at 62–66° at 4 mm. and formed a picrate, m.p. 227°; the picrate of 1-methylisoquinoline is reported to melt at 225–228°.[21]

4-Methylquinoline.—4-Methylquinoline was prepared in 96% yield by a process similar to that employed in the synthesis of 1-methylisoquinoline. The resulting oil distilled at 60–65° at 4 mm. and formed a picrate, m.p. 212–216°, lit.[19] m.p. (picrate) 217°.

2-Methylbenzoxazole.—To a solution of 2.64 g. (0.11 mole) of sodium hydride in 125 ml. of DMSO at 70° was added 2.3 ml. of benzoxazole (0.021 mole). The solution was stirred for 4 hr. at 65° whence 125 ml. of water was added. The reaction mixture was poured into 1500 ml. of water which was extracted with ether. Evaporation of the ether left a crude oil which was analyzed on a 3% SE-30 column at 153°. The analysis indicated a 50% yield of 2-methylbenzoxazole.

***o*-Hydroxyphenylacetylene.**—When the methylation of benzofuran was attempted under the methylation conditions employed for quinoline and isoquinoline, the resulting product after distillation had a n.m.r. spectrum (60 Mc./sec.) with a sharp singlet (intensity 1.0) at 3.34 p.p.m. (relative to tetramethylsilane), a broadened singlet (intensity 1.02) at 4.07 p.p.m. that was exchangable with deuterium oxide, and a complex multiplet at 6.98 p.p.m. (intensity 4.35).

(19) O. Tsuge, M. Nishinohara, and N. Tashiro, *Bull. Chem. Soc. Japan*, **36**, 1477 (1963).

(20) C. L. Arcus and M. M. Coombs, *J. Chem. Soc.*, 4319 (1954).

(21) E. H. White and H. C. Dunathan, *J. Am. Chem. Soc.*, **78**, 6055 (1956).

1,2,4-Triazoles. XII. Derivatives of the s-Triazolo[4,3-*a*]pyridine Ring System[1a]

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Substituted *s*-triazolo[4,3-*a*]pyridines (**2**) containing alkyl, aryl, alkylaryl, heteryl, amino, hydroxyl, mercapto, and halogen substituents at position 3 have been synthesized in a study of the chemistry of this ring system, mainly by cyclization of 2-pyridylhydrazines (**1**) or their derivatives with appropriate reagents, and by modification of groups already present in the 3-position. Methyl substituents have also been placed at all peripheral carbon atoms. Di(3-*s*-triazolo[4,3-*a*]pyridyl)alkanes (**8**) and intermediate products have been obtained by the use of dicarboxylic acids, their anhydrides, or their esters in the above condensations. Substituents containing unsaturation or other functional groups can be introduced into position 3 of the bicyclic system by the use of the appropriate acid or ester. The structures of some interesting, substituted pyridines obtained as by-products in the reaction sequences are discussed.

The *s*-triazolo[4,3-*a*]pyridine ring system[2] (**2**) is one that has been known since 1903 but to which very meager attention has been paid.[3] Our interest in the possible aromatic character of fused ring systems with a nitrogen atom at the ring junction, such as has been shown in the case of the indolizine system, led us to investigate in detail the two possible isomeric *s*-triazolopyridines. In this communication, synthetic sequences used to obtain members of the *s*-triazolo[4,3-*a*]pyridine ring system (**2**) employed in our n.m.r. and other spectral studies, as well as other derivatives of interest, are described. The chemical characteristics of this nucleus and the spectral studies will be reported on in several forthcoming papers. The synthesis of members of the isomeric ring system, the *s*-triazolo[1,5-*a*]pyridine system, are described in a following paper.

Derivatives of similar fused ring systems have been shown to have interesting pharmacological properties,[4] especially in cancer chemotherapy,[5] and included in our study is the evaluation of these products for similar properties.

(1) (a) Support of this investigation by Public Health Service Research Grant CA-05973, 01-03, National Cancer Institute, is gratefully acknowledged. (b) To whom correspondence should be sent: Department of Chemistry, Rensselaer Polytechnic Institute, Troy, N. Y.

(2) A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd Ed., American Chemical Society, Washington, D. C., 1960, System No. 1094.

(3) W. Markwald and K. Rudzik, *Ber.*, **36**, 1111 (1903); R. G. Fargher and R. Furness, *J. Chem. Soc.*, 691 (1915); W. H. Mills and H. Schlinder, *ibid.*, 321 (1923); R. Graf, E. Pouzer-Lederer, V. Kopetz, R. Purket, and P. Laslo, *J. prakt. Chem.*, **138**, 244 (1933); D. S. Tarbell, C. W. Todd, M. C. Paulson, E. G. Lindstron, and V. P. Wystrack, *J. Am. Chem. Soc.*, **70**, 1381 (1948); J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 727 (1957); J. B. Bicking, U. S. Patent 3,050,525 (Aug. 21, 1962); *Chem. Abstr.*, **58**, 1480*e* (1963); R. Huisgen, H. J. Sturm, and M. Seidel, *Chem. Ber.*, **94**, 1555 (1961).

(4) Some of these are described in Farbenfabriken Bayer Akt.-Ger., British Patent 825,514 (Dec. 16, 1959); *Chem. Abstr.*, **55**, 7450*h* (1961); G. W. Miller and F. L. Rose, British Patent 898,408 (June 6, 1962); *Chem. Abstr.*, **57**, 11209*f* (1962); J. B. Bicking, ref. 3; G. W. Miller and F. L. Rose, British Patent 897,870 (May 30, 1962); *Chem. Abstr.*, **58**, 10211*h* (1963); British Patent 873,223 (July 19, 1961); *Chem. Abstr.*, **58**, 10210*d* (1963).

(5) *E.g.*, Y. Makisumi, H. Kano, and S. Takahashi, Japanese Patent 9498 (July 27, 1962); *Chem. Abstr.*, **59**, 5178*e* (1963).

It is possible to synthesize the *s*-triazolo[4,3-*a*]pyridine ring system by two routes: one involving the ring closure of a 2-pyridylhydrazine (**1**) with acidic-type cyclodehydration agents,[3] which also supply the carbon unit for the *s*-triazole ring, and the other utilizing the *s*-triazole nucleus and building up the pyridine portion of the fused ring system. A variation of the former method is the oxidative ring closure of benzal 2-pyridylhydrazone with lead tetraacetate[6] or with bromine in acetic acid in the presence of sodium acetate.[7] Nitrobenzene and ferric chloride have also

1 **2**

been used to bring about this same reaction[8] and this approach has been used successfully in the synthesis of other fused *s*-triazole ring systems.[9] The method involving formation of the pyridine ring introduces the possibility of isomer formation,[10] depending on the particular nitrogen atom of the *s*-triazole nucleus at which cyclization occurs and is of no practical consequence in this series.

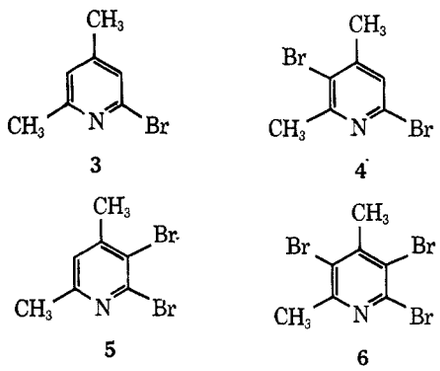
The intermediate 2-pyridylhydrazines (**1**) were prepared by the action of hydrazine[11] on the appropriate 2-bromopyridines, themselves obtained in excellent yield by diazotization of the corresponding 2-aminopyridines[12] in a bromine–48% hydrobromic acid mixture.[13] In the preparation of 2-bromo-4,6-dimethylpyridine (**3**) (66% yield), two more fully brominated products were obtained. Analytical data established the molecular formulas as $C_7H_7Br_2N$ (22% yield) and $C_7H_6Br_3N$ (2% yield). The only two plausible structures for the dibromo product, bromination of the methyl groups having been eliminated by n.m.r. data, were **4** and **5**, differing in the position of substitution of the second bromine atom, and for the tribromo product, structure **6** need only be considered owing to the absence of pyridine ring protons in its n.m.r. spectrum.

The n.m.r. data[14] (Table I) for these compounds clearly showed that the disubstituted product was **4** and it is interesting to note here the effect that bromine substitution has upon the chemical shifts of the methyl protons. This polybromination of the pyridine nucleus illustrates well the activating effect[15] of methyl substituents in the ring. Of interest, too, in this connection is the recent work[16] describing the action of chlorine on 2-methylpyrazine where nuclear, instead of side-chain, substitution occurred.

TABLE I

N.M.R. DATA FOR BROMO-SUBSTITUTED 4,6-DIMETHYLPYRIDINES IN τ UNITS (DEUTERIOCHLOROFORM)

	Position			
Compd.	3-H	4-CH_3	5-H	6-CH_3
3	3.13	7.82	3.30	7.67
4	2.94	7.69		7.41
6		7.37		7.32



3 **4**

5 **6**

The substituted 2-pyridylhydrazines previously not reported in the literature are described in the Experimental Section.[17] The most effective method of purification of the hydrazines was by distillation,[20] except in the case of 3-methylpyrid-2-ylhydrazine which, because of its high melting point (120–122°), was purified by recrystallization from benzene–petroleum ether. Although these hydrazines are sensitive to air oxidation, they are stable for long periods when stored over nitrogen at low temperatures.

3-Alkyl-*s*-triazolo[4,3-*a*]pyridines (2, R′ = Alkyl).—Products of this type are described in Table II and were readily available from the 2-pyridylhydrazines and the appropriate carboxylic acids,[21] anhydrides, or esters. It was convenient in the case of the lower aliphatic acids to use excess of the acid as a solvent. Several of the 3-alkyl-*s*-triazolo[4,3-*a*]pyridines were contaminated with the intermediate hydrazide which was sometimes difficult to separate by recrystallization because of similar solubility characteristics. Vacuum sublimation and chromatography on neutral alumina (Woelm, activity grade I) were found to be the two most efficient methods of purification in these cases. However, 3,8-dimethyl-*s*-triazolo[4,3-*a*]pyridine (**2**, R

(6) J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 727 (1957).

(7) M. S. Gibson, *Tetrahedron*, **19**, 1587 (1963).

(8) S. Naqui and V. R. Srinwasan, *J. Sci. Ind. Res.* (India), **B21**, 456 (1962).

(9) K. T. Potts and P. J. Nelson, *J. Org. Chem.*, **27**, 3243 (1962); D. Libermann and R. Jacquier, *Bull. soc. chim. France*, 355 (1962); I. Kumashiro, *Nippon Kagaku Zasshi*, **82**, 1068 (1961); G. A. Reynolds and J. A. van Allan, *J. Org. Chem.*, **24**, 1478 (1959).

(10) A summary of this work can be found in K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).

(11) In early experiments it was possible to use anhydrous hydrazine in this reaction with excellent results, but its current unavailability necessitates the use of hydrazine hydrate with a resultant decrease in yield.

(12) Obtained from Reilley Tar and Chemical Co., Indianapolis, Ind., whom we thank for an initial gift of 2-aminopyridine.

(13) L. C. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934); see also C. F. H. Allen and J. R. Tirtle, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 136.

(14) Spectra were measured using a Varian V-4302 dual-purpose, 60-Mc. n.m.r. spectrometer, and chemical shift values are reported in τ units, using tetramethylsilane as internal standard and usual methods of calibration. We are indebted to Dr. T. H. Crawford and Mr. S. Thomas for their assistance in the determination of these spectra.

(15) A discussion of the effect of substituents on the halogenation of pyridines can be found in H. E. Mertel, "Pyridine and Its Derivatives," Part 2, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, Chapter VI.

(16) H. Gainer, M. Kokowidz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

(17) Of the several methods available[18] for the preparation of 2-pyridylhydrazines, the most convenient for this study was the reaction of hydrazine on the 2-bromopyridines. The possibility of isomer formation in the reaction of sodium hydrazide[19] with the various pyridines made this method unsuitable.

(18) A. E. Chichibabin and B. A. Razorenov, *J. Russ. Phys. Chem.*, **47**, 1286 (1915).

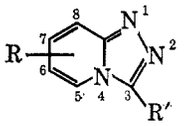
(19) T. Kauffmann and H. Hacker, *Chem. Ber.*, **95**, 2486 (1962); *Ann.*, **656**, 103 (1962).

(20) *Cf.* the method used by N. H. Mills and H. Schlinder, *J. Chem. Soc.*, 321 (1923).

(21) J. D. Bower and F. P. Doyle, *ibid.*, 727 (1957).

TABLE II

3-ALKYL-SUBSTITUTED s-TRIAZOLO[4,3-a]PYRIDINE DERIVATIVES

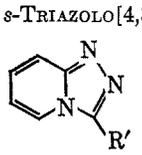


R	R′	Purification method	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
5-CH_3	H	*a*	92–94	41	$C_7H_7N_3$	63.1	5.3	31.6	63.2	5.2	31.1
6-CH_3	H	*a*	78–81	33	$C_7H_7N_3$	63.1	5.3	31.6	62.8	5.6	31.2
7-CH_3	H	*b*	120	64	$C_7H_7N_3$	63.1	5.3	31.6	62.7	5.3	32.0
8-CH_3	H	*c*	90–92	24	$C_7H_7N_3$	63.1	5.3	31.6	63.5	5.6	31.2
5,7-$(CH_3)_2$	H	*a, b*	83–85.5	65	$C_8H_9N_3$	65.3	6.2	28.6	64.8	6.4	28.3
5-CH_3	CH_3	*a, d*	172–174	25	$C_8H_9N_3$	65.3	6.2	28.6	65.7	6.0	28.6
6-CH_3	CH_3	*a, b*	142	41	$C_8H_9N_3$	65.3	6.2	28.6	65.7	5.8	28.6
7-CH_3	CH_3	*a, b*	135	70	$C_8H_9N_3$	65.3	6.2	28.6	65.4	6.2	28.5
5,7-$(CH_3)_2$	CH_3[e]	*b*	163–164	34	$C_9H_{11}N_3$	67.1	6.9	26.1	67.1	6.8	26.6
H	*n*-Pr	*a, b*	55–56	68	$C_9H_{11}N_3$	67.1	6.9	26.1	67.1	6.8	25.8
H	Et[f]	*b*	55	88	$C_8H_9N_3$	65.3	6.2	28.6	65.3	6.6	28.7
5-CH_3	Et	*a, b*	109–111	21	$C_9H_{11}N_3$	67.1	6.9	26.1	67.0	6.8	26.0
6-CH_3	Et	*a, b*	88.5–90	57	$C_9H_{11}N_3$	67.1	6.9	26.1	67.3	7.1	26.0
7-CH_3	Et[e]	*b*	79	87	$C_9H_{11}N_3$	67.1	6.9	26.1	67.5	6.9	26.0
8-CH_3	Et[g]	*b*	116	80	$C_9H_{11}N_3$	67.1	6.9	26.1	67.2	6.2	26.1
5,7-$(CH_3)_2$	Et	*b*	144–145	69	$C_{10}H_{13}N_3$	68.5	7.5	24.0	68.4	7.5	24.2

[a] Sublimation in vacuum. [b] Recrystallization from benzene. [c] Chromatography on alumina. [d] Soxhlet extraction with benzene. [e] Prepared from the ortho ester. [f] Picrate, yellow needles from ethanol, m.p. 206°. *Anal.* Calcd. for $C_{14}H_{12}N_6O_7$: C, 44.7; H, 3.2; N, 22.3. Found: C, 44.8; H, 3.2; N, 22.2. [g] Picrate, yellow needles from ethanol, m.p. 143°. *Anal.* Calcd. for $C_{15}H_{14}N_6O_7$: C, 46.2; H, 3.6; N, 2.15. Found: C, 46.2; H, 3.8; N, 21.7

TABLE III

3-SUBSTITUTED s-TRIAZOLO[4,3-a]PYRIDINES



R′	Hr.[a]	M.p., °C.	Yield, %	Form	Solvent[b]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2-Styryl[c]	16	185–187	30	Plates	B	$C_{14}H_{11}N_3$	76.0	5.0	19.0	76.1	5.1	18.8
2-Thienylvinyl	9	218–219	45	Tan prisms	M–B	$C_{12}H_9N_3S$	63.4	4.0	18.5	63.2	3.9	18.3
2-Thienyl	27	163–164	56	Tan needles	M–B	$C_{10}H_7N_3S$	59.7	3.5	20.9	59.8	3.5	20.8
2-Furyl[c]	48	97	24	Plates	B	$C_{10}H_7N_3O$	64.9	3.8	22.7	64.8	3.7	22.5
2-Pyridyl	24	122–123	62	Prisms	B	$C_{11}H_8N_4$	67.3	4.1	28.6	67.4	4.3	28.6
Methyl-2-pyridyl	28	133–134	57	Needles	M–B	$C_{12}H_{10}N_4$	68.6	4.8	26.7	68.3	4.7	26.7

[a] Reaction time. [b] B = benzene; M = methanol. [c] Reference 23.

= R′ = CH_3) and the corresponding hydrazide resisted all attempts at separation. The purification methods used for particular 3-alkyl-*s*-triazolo[4,3-*a*]pyridines are noted in Table II, and they may be readily characterized by formation of their picrates.

4,6-Dimethylpyrid-2-ylhydrazine and propionic acid gave only the propionyl derivative which was then cyclized to the fused ring system under more vigorous conditions with phosphorus oxychloride. The reaction of the above hydrazine with an acetic acid–acetic anhydride mixture also resulted in the isolation of a product that was a mixture of the cyclization product and the uncyclized amide. Similarly, in the reaction of 6-methylpyrid-2-ylhydrazine with propionic acid or acetic anhydride, the propionyl and the acetyl derivatives were isolated along with the ring-closed products. The isolation of these uncyclized hydrazides indicates that a methyl group at the 6-position of the pyridine nucleus is bulky enough to provide some steric hindrance to the ring-closure reaction. If the steric effect is due only to a substituent on the pyridine ring, then ring closure takes place without the isolation of the intermediate hydrazide, as in the reaction of formic acid with 6-methyl- and 4,6-dimethylpyrid-2-ylhydrazine. This effect was more noticeable with an aroyl group attached to the hydrazine moiety, and ultraviolet and n.m.r. data clearly indicated steric interaction between the 3- and 5-substituents of the fused ring system.

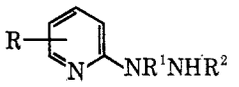
The use of ortho esters as the condensation agent in the above reaction sequence was a less efficient cyclization method, yields being reduced by approximately 20%, which is in contrast to the synthesis of the *s*-triazolo[4,3-*a*]pyrazines,[22] where the ortho ester was the most efficient cyclization agent. The ease of ring closure may be related to the basic strength of the heterocyclic nitrogen atom (pyridine, pK_a = 5.2; pyrazine, pK_a = *ca.* 0.6) since the ring closure should involve the attack of an intermediate carbonium ion on the tertiary nitrogen atom of the heterocyclic system.

3-Alkylaryl- (or Heteryl-) *s*-triazolo[4,3-*a*]pyridines (2, R′ = Alkylaryl or Heteryl).—These products, de-

(22) P. J. Nelson and K. T. Potts, *J. Org. Chem.*, **27**, 3243 (1962).

TABLE IV

BENZOYL DERIVATIVES OF 2-PYRIDYLHYDRAZINES

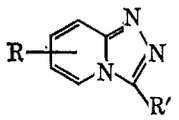


R	R^1	R^2	M.p., °C.	Yield, %	Solvent	Form	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	N.m.r. data (τ) for CH_3 protons[a] CH_3 position 3	4	5	6
3-CH_3	H	Bz	198–200	91	Xylene	Needles	$C_{13}H_{13}N_3O$	68.7	5.8	18.5	68.9	5.8	18.5	7.44 7.79			
4-CH_3	H	Bz	175–180	70	Ethanol	Irreg. prisms	$C_{13}H_{13}N_3O$	68.7	5.8	18.5	68.6	5.7	18.4		7.68 7.81		
5-CH_3	Bz	Bz	165	68	Xylene	Needles	$C_{20}H_{17}N_3O_2$	72.5	5.1	12.7	72.8	5.0	12.5			7.87	
6-CH_3	H	Bz	147–148	37	Xylene	Plates	$C_{13}H_{13}N_3O$	68.7	5.8	18.5	69.0	5.9	18.3				7.60
4,6-$(CH_3)_2$	H	Bz	172–173	82	Ethanol	Plates	$C_{14}H_{15}N_3O$	69.7	6.3	17.4	69.6	6.3	17.3		7.85		7.69

[a] Reference compounds: 2-bromo-3-methylpyridine, τ 7.73 (CH_3); 3-methyl-2-pyridylhydrazine, τ 7.96 (CH_3); 4,6-dimethyl-2-pyridylhydrazine, τ 7.66 (6-CH_3), 7.82 (4-CH_3); 2-bromo-4,6-dimethylpyridine, τ 7.67 (6-CH_3), 7.80 (4-CH_3).

TABLE V

3-PHENYL-*s*-TRIAZOLO[4,3-*a*]PYRIDINE DERIVATIVES (R′ = PH)



R	Purification method[a]	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
5-CH_3	*b*, *c*	154–155	40	$C_{13}H_{11}N_3$	74.6	5.3	20.1	74.3	5.3	19.9
6-CH_3	*b*, *c*	187–188	43	$C_{13}H_{11}N_3$	74.6	5.3	20.1	74.8	5.4	19.7
7-CH_3	*b*	127–128	38	$C_{13}H_{11}N_3$	74.6	5.3	20.1	74.7	5.2	20.2
8-CH_3	*b*	115	20	$C_{13}H_{11}N_3$	74.6	5.3	20.1	74.6	5.6	19.8
5,7-$(CH_3)_2$	*b*, *c*	123–124	45	$C_{14}H_{13}N_3$	75.3	5.9	18.8	75.2	6.0	18.8

[a] All formed colorless plates from benzene. [b] Recrystallization from benzene. [c] Sublimation.

scribed in Table III, were obtained readily when 2-pyridylhydrazine was heated with an equimolar amount of the appropriate acid or its ester at 150° for 2–24 hr. The lower melting points of the solid esters made their use more convenient in these condensations. The lower temperature needed for reaction to occur resulted in less decomposition and in increased yields; occasionally, the presence of polymeric-type material in the crude reaction mixtures made their purification to analytical standards somewhat difficult, but this could be achieved by repeated recrystallizations from a suitable solvent (Table III). 3-(2-Furyl)-*s*-triazolo[4,3-*a*]pyridine (**2**, R′ = 2-furyl),[23] for example, was contaminated with a large amount of polymeric material from the decomposition of the ethyl furoate at the reaction temperature over the extended reaction period.

2-Benzoyl- and 1,2-Dibenzoyl-1-(2-pyridyl)hydrazines.—The reaction of the 2-pyridylhydrazines with an equimolar amount of benzoyl chloride in dry pyridine at 0° using standard procedures[21] gave normal benzoylation products except for 5-methylpyrid-2-ylhydrazine (Table IV). Dibenzoylation under such mild conditions without an excess of benzoyl chloride present was unexpected, though it has been observed with 2-aminopyridine.[24] Similar results have been obtained in the pyrazine series,[9] and, in particular, 3-methylpyrazin-2-ylhydrazine gave the corresponding dibenzoyl product whereas the other mono- and dimethylpyrazin-2-ylhydrazines did not.[25]

(23) J. B. Bicking, U. S. Patent 2,917,511 (Dec. 15, 1959); *Chem. Abstr.*, **54**, 8854*e* (1960).

(24) H. J. Den Hertog and M. Von Ammers, *Rec. trav. chem.*, **74**, 1160 (1955); S. I. Lur'e, *Zh. Obshch. Khim.*, **20**, 195 (1950); *Chem. Abstr.*, **44**, 5880 (1950).

It is possible that in 5-methylpyrid-2-ylhydrazine the methyl group, through a direct hyperconjugation effect, is increasing the basicity of the N-1 of the substituent hydrazino group, but no experimental confirmation of such a postulate has been obtained. In these benzoyl derivatives it is possible for the 3-methyl and 4-methyl groups to be deshielded by the carbonyl group, whereas the 5-methyl and 6-methyl groups could not be deshielded. This is shown in the n.m.r. spectra (Table IV) and it is interesting that under the conditions of measurement the 3- and 4-methyl derivatives exist as an equilibrium mixture of two conformations of the molecule.

3-Phenyl-*s*-triazolo[4,3-*a*]pyridines (2, R′ = Ph).—Derivatives of this type can be formed by the cyclization of the appropriate 2-benzoyl-1-pyrid-2-ylhydrazines with phosphorus oxychloride[21] and are described in Table V. Low yields were obtained by this procedure, but modification of the reaction conditions, such as the use of an inert solvent and chloroform extraction of the basified reaction mixture, did occasionally increase the yields of the products.

It was found that the most efficient method of formation of the 3-phenyl derivatives was the fusion of benzoic acid with the appropriate 2-pyridylhydrazine.[23] When the two reactants were heated together at 180° for 4 hr., there was good conversion of the reactants into the desired product and little decomposition, and no intermediate hydrazide was isolated. The work-up procedure used in the phosphorus oxychloride reactions was virtually eliminated, and this greatly improved the yields in the over-all reaction sequence. Fusion of *o*-toluic acid with 6-methylpyrid-2-ylhydrazine re-

(25) K. T. Potts and S. Schneller, unpublished results.

TABLE VI

DI(3-s-TRIAZOLO[4,3-a]PYRIDYL)ALKANES (7)

n	Reaction temp., °C.	Reaction time, hr.	M.p., °C.	Solvent	Yield, %	Form	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
0	270	5	242–244	DMF[a]	85	Tan plates	$C_{12}H_8N_6$	61.0	3.4	35.6	61.1	3.4	35.6
1[b]	240	3.5	263–264	DMF	70	Needles	$C_{13}H_{10}N_6$	62.4	4.0	33.6	62.7	4.1	33.9
2	170	5.5	234–235	EtOH	76	Plates	$C_{14}H_{12}N_6$	63.6	4.6	31.8	63.4	4.9	31.9
3	230	6	170–171	MeOH	75	Tan prisms	$C_{15}H_{14}N_6$	64.7	5.1	30.2	64.9	5.1	30.4
8	170	6	163–165	MeOH	71	Irreg. prisms	$C_{20}H_{24}N_6$	68.9	6.9	24.1	68.8	7.1	23.8

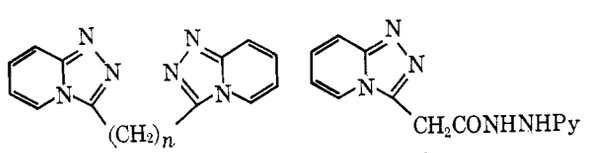
[a] DMF = dimethylformamide. [b] The *Chemical Abstracts* name would be 3,3′-methylenebis-s-triazolo[4,3-a]pyridine.

sulted only in the formation of the intermediate amide. This can be attributed to the steric interaction between the *o*-tolyl group and the 6-methyl group attached to the pyridine nucleus being sufficiently large to prevent cyclization, a fact clearly shown by models.

1-Aryl- (or Heteryl-) 2-(3-s-triazolo[4,3-a]pyridyl)-ethene.—It was of interest to obtain for our detailed spectral study some *s*-triazolo[4,3-*a*]pyridines with extensive conjugation in the 3-substituent. These systems were obtained by heating the α,β-unsaturated acid or its ester with 2-pyridylhydrazine. β-(2-Thienyl)acrylic acid and cinnamic acid[23] yielded the corresponding ring-closed products (Table III), whereas β-(2-furyl)acrylate, ethyl acrylate, methyl methacrylate, ethyl crotonate, and sorbic acid yielded only polymeric products under the reaction conditions used.

Di(3-s-triazolo[4,3-a]pyridyl)alkanes.—When equivalent amounts of 2-pyridylhydrazine and a dicarboxylic acid, its anhydride, or its ester were heated together at elevated temperatures, the di-condensation product **7** was formed readily (Table VI). In this series the melting point decreases as does the polarity of the solvent needed for recrystallization with increase in the value of *n*.

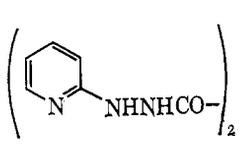
The reaction of 1 equiv. of diethyl malonate with 2 equiv. of 2-pyridylhydrazine yielded not only di(3-*s*-triazolo[4,3-*a*]pyridyl)methane (**7**, $n = 1$), but also the monocyclized product, *s*-triazolo[4,3-*a*]pyridine-3-acetic acid [2-(2-pyridyl)hydrazide] (**8**). This was the only monocyclized product isolated in this study with difunctional acids. When malonic acid was



7

8

Py = 2-pyridyl



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heated with 2-pyridylhydrazine, no identifiable product was isolated; at the high reaction temperature used, it was most likely that the malonic acid underwent decarboxylation. Attempts to form malonic acid bis[2-(2-pyridyl)hydrazide] from 2-pyridylhydrazine and malonyl chloride at 0° in dry pyridine or in dry tetrahydrofuran at 0° with a trace of pyridine failed. The malonyl chloride was so reactive under these conditions that only a black, tarry residue was isolated.

Diethyl oxalate when heated with 2 moles of 2-pyridylhydrazine at 150° formed the intermediate hydrazide, oxalic acid bis[2-(2-pyridyl)hydrazide] (**9**). This product was also formed in good yield from 2-pyridylhydrazine and oxalyl chloride at 0° in an excess of pyridine. Thermal ring closure of the dihydrazide was effected by heating it at 270° for 4 hr.; alternatively, a boiling phosphorus oxychloride–toluene mixture brought about a smooth cyclization. This cyclization could not be effected with commercial polyphosphoric acid, a method which had been employed in the ring closure of N-benzoyl-2,3-diphenyl-6-hydrazinopyrazine to form 3,5,6-triphenyl-*s*-triazolo[4,3-*a*]pyrazine.[26]

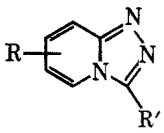
Succinic acid and succinic anhydride when heated with 2-pyridylhydrazine formed only the dicondensation product (**7**, $n = 2$), and no intermediate hydrazide or imide was obtained. Reaction of maleic anhydride or ethyl maleate with the hydrazine resulted only in intractable products. Glutaric and sebacic acids gave only the corresponding dicondensation products (**7**, $n = 3$ and $n = 8$, respectively).

Kauffmann[27] reported recently that when equimolar amounts of oxalic acid and 2-pyridylhydrazine were heated together, a compound with an empirical formula of $C_7H_5N_3O_2$ was isolated and, on the basis of analytical and spectral data (not reported), this product was assigned structure **10**. In view of our work, this structure appeared most unlikely to us and this reaction was investigated further. A crystalline, acidic product, m.p. 166–167°, of the same empirical formula was isolated from the reaction mixture. Its aqueous solution was acid to litmus and readily decomposed sodium carbonate solution; its infrared spectrum, showing strong OH absorption centered at 4000 cm.$^{-1}$ with a broad carbonyl peak centered at 1675 cm.$^{-1}$, and its ultraviolet absorption spectrum [$\lambda_{max}^{CH_3OH}$ 258 (sh), 262 (sh), 268, 281 mμ (log ϵ 3.50, 3.52, 3.58, 3.58)] also indicate that the product has the structure, *s*-triazolo[4,3-*a*]pyridine-3-carboxylic acid (**2**, R^1 = COOH). Using an equivalent amount of diethyl oxalate in this condensation reaction did not result in the formation of the corresponding ester but rather dicondensation occurred as described above. In the oxalic acid condensation, the product actually separated from the reaction melt not long after the reaction commenced and was prevented from undergoing any further condensation with 2-pyridylhydrazine. Using ethyl oxamate in this condensation reaction gave not the

(26) G. M. Badger, P. J. Nelson, and K. T. Potts, *J. Org. Chem.*, **29**, 2542 (1964).

(27) T. Kauffmann, H. Hacker, C. Kosel, and K. Vogt, *Z. Naturforsch.*, **14b**, 601 (1959).

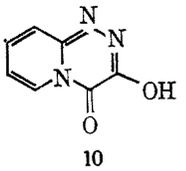
TABLE VII



R	M.p., °C.	Yield, %	Form	Solvent[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
s-Triazolo[4,3-*a*]pyridin-3-ols, R′ = OH											
5-CH_3	179–180	77	Yellow needles	Ethanol	$C_7H_7N_3O$	56.4	4.7	28.2	56.4	4.9	28.3
6-CH_3	190	45	Colorless needles	Ethyl acetate	$C_7H_7N_3O$	56.4	4.7	28.2	56.6	4.4	28.5
7-CH_3	215	85	Pale yellow needles	Ethanol	$C_7H_7N_3O$	56.4	4.7	28.2	56.4	5.1	28.0
8-CH_3	212–213	71	Colorless prisms	Ethanol	$C_7H_7N_3O$	56.4	4.7	28.2	56.3	4.9	28.2
5,7-$(CH_3)_2$	208–209	96	Pale yellow plates	THF–ethanol	$C_8H_9N_3O$	58.9	5.6	25.8	59.0	5.5	25.6
s-Triazolo[4,3-*a*]pyridine-3-thiols, R′ = SH											
5-CH_3	230–231	93	Yellow needles	Methanol	$C_7H_7N_3S$	50.9	4.3	25.5	51.0	4.3	25.4
6-CH_3	224	73	Yellow plates	Methanol	$C_7H_7N_3S$	50.9	4.3	25.5	51.0	4.1	25.6
7-CH_3	245–247	92	Pale yellow needles	Methanol	$C_7H_7N_3S$	50.9	4.3	25.5	51.3	4.6	25.6
8-CH_3	233	85	Colorless needles	Methanol	$C_7H_7N_3S$	50.9	4.3	25.5	50.9	4.4	25.8
5,7-$(CH_3)_2$	265–267 dec.	73	Pale yellow needles	Ethanol	$C_8H_9N_3S$	53.6	5.1	23.5	53.4	5.1	23.2
3-Amino-*s*-triazolo[4,3-*a*]pyridines, R′ = NH_2											
H	228–229	87	Yellow plates	Ethanol	$C_6H_6N_4$	53.7	4.5	41.8	53.9	6.8	41.4
H[b]	246–248	90	Yellow prisms	Ethanol	$C_6H_7BrN_4$	33.5	3.2	26.1	33.7	3.2	26.1
5-CH_3	248–250	84	Pale yellow prisms	Ethanol	$C_7H_8N_4$	56.7	5.4	37.8	57.0	5.6	37.5
6-CH_3	294–296	54	Yellow plates	Ethanol	$C_7H_8N_4$	56.7	5.4	37.8	56.6	5.4	38.0
7-CH_3	298–300	83	Yellow plates	Ethanol	$C_7H_8N_4$	56.7	5.4	37.8	56.8	5.5	37.8
8-CH_3	253–255	78	Pink needles	Ethanol	$C_7H_8N_4$	56.7	4.7	28.2	56.3	4.9	28.2
5,7-$(CH_3)_2$	289–290 dec.	91	Pale pink needles	Ethanol	$C_8H_{10}N_4 \cdot 0.25\ H_2O$	57.6	6.4	33.6	57.9	5.9	33.4

[a] THF = tetrahydrofuran. [b] Hydrobromide.

roduct (**10**) but rather *s*-triazolo[4,3-*a*]pyridine-3-carboxamide (**11**). Infrared absorption frequencies (ν_{NH} 3195, 3044, ν_{CO} 1675, $\nu_{amide\ III}$ 1623 cm.$^{-1}$) and ultraviolet absorption data [$\lambda_{max}^{CH_3OH}$ 283, 237, 231 mμ (log ε 4.00, 3.94, 4.06)] supported this assignment and it was confirmed by alkaline hydrolysis of the 3-carboxamide to *s*-triazolo[4,3-*a*]pyridine (**2**, R = R′ = H), the intermediate 3-carboxylic acid apparently undergoing decarboxylation under these alkaline reaction conditions.



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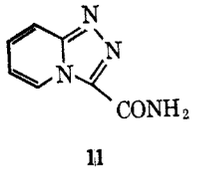

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When ethyl cyanoacetate was heated with 2-pyridylhydrazine, the expected product was 3-cyanomethyl-*s*-triazolo[4,3-*a*]pyridine. The product actually isolated was identified by mixture melting point and infrared data as di(3-*s*-triazolo[4,3-*a*]pyridyl)methane, which had been prepared previously as above. The most likely method of formation of this product involved an initial hydrolysis of the cyanide to the carboxylic acid, which then underwent further reaction as described above to yield the dicondensation product. A reaction sequence involving an intermediate amidine would have been unlikely under these reaction conditions.

dl-Malic acid was found to condense with 2 moles of 2-pyridylhydrazine in such a way that the hydroxyl group was not affected and the dicondensation product, *dl*-1,2-di(3-*s*-triazolo[4,3-*a*]pyridyl)ethanol, was formed. This alcohol was dehydrated readily to 1,2-di(3-*s*-triazolo[4,3-*a*]pyridyl)ethene, a product having the same poor solubility characteristics as the saturated dicondensation products, and the introduction of unsaturation into a side chain *via* the intermediate alcohol is preferable to direct condensation of the unsaturated acid and 2-pyridylhydrazine. As expected, the extended conjugation present in this unsaturated product resulted in a 37-mμ shift of the long wave length absorption band to 350 mμ.

The reactions described above represent a general synthetic route for the introduction of functional groups at the 3-position of the *s*-triazolo[4,3-*a*]pyridine nucleus or a side chain containing a functional group. It should be noted that halogenoacetic acids are not suitable for obtaining the corresponding 3-halomethyl compounds. The reaction of trichloroacetic acid with 2-pyridylhydrazine resulted in the isolation of chloroform since the acid underwent ready decarboxylation when the anion was formed in the presence of the basic 2-pyridylhydrazine. Reaction of ethyl dichloro- and trichloroacetate resulted only in isolation of tarry material when the mild exothermic reaction was carried out at room temperature. However, mercaptoacetic acid resulted in the formation of a small amount of product which appears to be 3-*s*-triazolo[4,3-*a*]-pyridylmethanethiol from its infrared spectrum.

***s*-Triazolo[4,3-*a*]pyridin-3-ols (2, R′ = OH).**—Fusion of the 2-pyridylhydrazines with urea[23] or ethyl allophanate or reaction with excess ethyl chloroformate[28] readily gave the 3-hydroxyl compounds (**2**,

(28) O. Shiho and S. Tagami, *J. Am. Chem. Soc.*, **82**, 4044 (1960).

R′ = OH) (Table VII). In this project, the *s*-triazolo[4,3-*a*]pyridin-3-ols were obtained primarily from the fusion of the appropriate 2-pyridylhydrazine with urea because of the favorable yields and the ease of reaction. Evidence that the reaction with urea involves a semicarbazide intermediate was obtained when 1-(5-methylpyrid-2-yl)semicarbazide was isolated from the reaction of 5-methylpyrid-2-ylhydrazine with urea.[29] This semicarbazide underwent ring closure to 6-methyl-*s*-triazolo[4,3-*a*]pyridin-3-ol when heated above its melting point (205°). Spectral data indicate that these compounds exist predominantly in the keto form.

***s*-Triazolo[4,3-*a*]pyridine-3-thiols (2, R′ = SH).**—Carbon disulfide, thiophosgene,[30] or potassium trithiocarbonate[20] is equally effective in causing cyclization of the 2-pyridylhydrazines to the 3-thiols (Table VII), and in this study the general method employed was the use of carbon disulfide in chloroform solution. It was noticed that when carbon disulfide was added to a solution of the 2-pyridylhydrazine, an initial precipitate of the intermediate dithiocarbamic acid soon separated and this slowly underwent cyclization with elimination of hydrogen sulfide.

When the hydrazine was heated with thiourea, a reaction analogous to that involved in the formation of the 3-hydroxy compounds, the only product isolated was 2-aminopyridine thiocyanate. This was identified by analytical data and from the presence of an infrared band characteristic of thiocyanates at 2020 cm.$^{-1}$. It is appropriate to note that our physical data for this product supports an earlier suggestion of Panouse[31] that a 2-aminothiocyanopyridine was in actual fact the thiocyanate salt.[32] Isolation of this product at such an elevated temperature is not surprising in view of the ease with which 2-pyridylhydrazine will form 2-aminopyridine on prolonged heating.

The 3-thiols can also exist in tautomeric forms. Spectral data, coupled with solubility characteristics,[33] indicate that the thione form is predominant.

3-Amino-*s*-triazolo[4,3-*a*]pyridines (2, R′ = NH$_2$).—Ring closure of the 2-pyridylhydrazines with cyanogen bromide in methanol or benzene yielded the hydrobromide of the 3-amino-*s*-triazolo[4,3-*a*]pyridines[34] in good yields. The products (Table VII) were usually isolated as the free base by neutralization with sodium acetate. This exothermic reaction proceeded with great ease and apparently occurred *via* an intermediate cyanohydrazine which rapidly underwent cyclization to the bicyclic system. Cyanogen bromide also reacts readily with 2-pyrimidinylhydrazines to form the 3-amino-*s*-triazolo[4,3-*a*]pyrimidines or 2-amino-*s*-triazolo[2,3-*c*]pyrimidines,[35] depending on the reaction conditions. Related ring-closure reactions between a mercapto and an amino group, such as in 3-aminoquinoline-4-thiol to form 2-aminothiazolo[5,4-*c*]quinoline,[36a] and in 4-amino-*s*-triazole-3-thiols yielding 2-amino-*s*-triazolo[3,4-*b*]-1,3,5-thiadiazoles[36b] also proceed in excellent yield and illustrate the potential of cyanogen bromide as a ring-closure reagent in heterocyclic synthesis.

In contrast to the 3-hydroxyl and 3-mercapto groups, the amino group appears to exist predominantly in the amino rather than the imino form, though these products do have unexpectedly high melting points and unusual solubility characteristics. The amino group can be converted into its benzoyl derivative and also into its benzal derivative (zinc chloride catalyst) and replacement by a chlorine or bromine atom takes place with ease using the Gatterman procedure.

Experimental Section[37]

2-Bromo-4,6-dimethylpyridine.—This preparation illustrates the general procedure used.[18] 2-Amino-4,6-dimethylpyridine (194 g., 1.59 moles), dissolved in hydrobromic acid (790 ml. of 48% aqueous solution), was cooled to −10° (at this temperature some hydrobromide salt crystallized) and was treated with bromine (240 ml., 4.4 moles), keeping the temperature below 0°. Sodium nitrite solution (275 g. in 400 ml. of water) was added over 1 hr. with the reaction temperature being kept below 0°. After a further 30 min. stirring, sodium hydroxide solution (600 g. in 600 ml. of water) was added, keeping the temperature below 10°, and then a further 200 g. of sodium hydroxide was added to make the solution strongly alkaline. After ether extraction (five 500-ml. portions) and drying (Na_2SO_4) of the ether extract, the residual light-colored oil was fractionated under reduced pressure. Fraction 1 was identified as 2-bromo-4,6-dimethylpyridine, 196 g. (66%), b.p. 60–69° (0.4 mm.).

Anal. Calcd. for C_7H_8BrN: C, 45.2; H, 4.3; N, 7.5. Found: C, 45.1; H, 4.3; N, 7.5.

Fraction 2, 2,5-dibromo-4,6-dimethylpyridine, 91 g. (22%), distilled at 70–85 (0.09 mm.), and crystallized from ethanol as colorless needles, m.p. 63°.

Anal. Calcd. for $C_7H_7Br_2N$: C, 31.7; H, 2.7; Br, 60.3; N, 5.3. Found: C, 32.0; H, 2.6; Br, 60.5; N, 5.2.

Fraction 3, 2,3,5-tribromo-4,6-dimethylpyridine (2%), b.p. 87–95° (0.09 mm.), solidified in the condenser and, on crystallization from ethanol, formed colorless needles, m.p. 124–125°.

Anal. Calcd. for $C_7H_6Br_3N$: C, 24.5; H, 1.8; N, 4.1. Found: C, 24.6; H, 1.9; N, 4.0.

The following bromo compounds were prepared in superior yields by this procedure: 2-bromo-3-methylpyridine (94%), b.p. 45–50° (0.2 mm.) [lit.[38] b.p. 82–86° (9 mm.)]; 2-bromo-4-methylpyridine (85%), b.p. 50° (0.45 mm.) (lit.[39] b.p. 223–224°); 2-bromo-5-methylpyridine (80%), m.p. 49–50° [lit.[38] b.p. 73–77° (78 mm.)]; and 2-bromo-6-methylpyridine (80%), b.p. 46–49° (91 mm.) [lit.[40] b.p. 102–103° (120 mm.)].

4,6-Dimethyl-2-pyridylhydrazine.—2-Bromo-4,6-dimethylpyridine (196 g.) was heated under reflux with a tenfold excess of 95% anhydrous hydrazine (480 g.) for 6 hr. After cooling to room temperature, the solution was extracted with ether (four 200-ml. portions), and excess hydrazine was then removed from the mother liquor by evaporation under reduced pressure. Basification of the residue with 50% sodium hydroxide solution and extraction with ether (four 200-ml. portions) yielded an extract

(29) *Cf.* G. A. Reynolds and J. A. Van Allen, *J. Org. Chem.*, **24**, 1478 (1959), in which heating of 1-(2-benzthiazolyl)-4-phenylsemicarbazide was reported to effect ring closure to the hydroxy compound readily.

(30) D. S. Tarbell, C. W. Todd, M. C. Paulson, E. G. Linstrom, and V. P. Wystrack, *J. Am. Chem. Soc.*, **70**, 1381 (1948).

(31) J. J. Panouse, *Compt. rend.*, **230**, 846 (1950).

(32) J. A. Kolmer, H. Brown, and G. W. Raiziss, *J. Pharmacol. Exptl. Therap.*, **61**, 253 (1937).

(33) An interesting discussion can be found in W. Pfleiderer, "Physical Methods in Heterocyclic Chemistry," A. R. Katritzky, Ed., Vol. I, Academic Press, New York, 1963, pp. 179–183.

(34) This method was first mentioned briefly in ref. 27, but no details were given.

(35) G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 5642 (1963).

(36) (a) G. B. Bachman, D. E. Welton, G. L. Jenkins, and J. E. Christian, *J. Am. Chem. Soc.*, **69**, 365 (1947); (b) K. T. Potts and R. Huseby, *Chem. Ind.* (London), 1414 (1964).

(37) Petroleum ether is the fraction of b.p. 60–110°. Evaporations were carried out under reduced pressure on the steam bath and microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Drs. Weiler and Strauss, Oxford, England. Ultraviolet spectra were determined using a Beckman DK-2 spectrophotometer and infrared spectra were measured on a Baird IR 2 and a Perkin-Elmer 421 spectrophotometer. Melting points were determined in capillaries using a liquid bath or, at high temperatures, an electrically heated block.

(38) H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, **14**, 509 (1949).

(39) F. H. Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).

(40) R. Adams and S. Migano, *ibid.*, **76**, 3168 (1954).

that was combined with the previous ether extract, and dried (Na_2SO_4), and the ether was removed, leaving a viscous oil which was distilled under reduced pressure. The hydrazine (111 g., 77%) tended to crystallize in the condenser, b.p. 91–95° (0.3 mm.), m.p. 65°.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.3; H, 8.1; N, 30.6. Found: C, 61.1; H, 7.9; N, 30.6.

The picrate crystallized from ethanol as yellow needles, m.p. 184° dec.

Anal. Calcd. for $C_{13}H_{14}N_6O_7$: C, 42.6; H, 3.85. Found: C, 42.4; H, 3.9.

The following hydrazines were prepared in the same manner: pyrid-2-ylhydrazine (68%), b.p. 105° (0.5 mm.), m.p. 49–50° [lit.[41] b.p. 140° (20 mm.), m.p. 46°]; 3-methylpyrid-2-ylhydrazine (98%), crystallized from benzene as colorless plates, m.p. 120–122.5° (*Anal.* Calcd. for $C_6H_9N_3$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.4; H, 7.4; N, 34.4.); 4-methylpyrid-2-ylhydrazine (94%), b.p. 115° (1 mm.) [lit.[13] b.p. 88–89° (0.01 mm)]; 5-methylpyrid-2-ylhydrazine (71%), b.p. 90–95° (0.03 mm.), crystallized from benzene as colorless needles, m.p. 71–72° (*Anal.*. Calcd. for $C_6H_9N_3$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.6; H, 7.3; N, 34.1.); and 6-methylpyrid-2-ylhydrazine (83%), b.p. 80–85° (0.5 mm.) [lit.[13] b.p. 65–71° (0.2 mm.)].

3-Alkyl-*s*-triazolo[4,3-*a*]pyridines (2, R′ = Alkyl). A. Ring Closure with Aliphatic Acids.—The 2-pyridylhydrazine (0.16 mole) was heated under reflux with the aliphatic acid (0.75 mole) for 4–10 hr. The excess acid was removed under reduced pressure on a steam bath and the residual viscous oil was basified with 30% sodium hydroxide solution. The alkaline solution was extracted with chloroform (three 60-ml. portions) and the combined extracts were dried (Na_2SO_4). On removal of the chloroform, the dark brown product was purified by crystallization from benzene, sublimation *in vacuo*, chromatography on alumina, or by a combination of these methods as designated in Table II.

The following are examples when this procedure was modified because of the separation of the intermediate hydrazide.

1-Propionyl-2-(6-methylpyrid-2-yl)hydrazine.—6-Methylpyrid-2-ylhydrazine (20 g., 0.16 mole) was refluxed with propanoic acid (50 ml., 0.75 mole) for 9 hr. After removal of the excess acid and basification with sodium hydroxide solution, the alkaline solution was extracted with chloroform (four 100-ml. portions) and the combined extracts were dried (Na_2SO_4). Removal of the chloroform gave a light brown, crystalline residue which on boiling with benzene left an insoluble portion, fraction A, 6.2 g. (21%). Fraction A was recrystallized several times from ethanol and separated as colorless prisms, m.p. 184–185°. The infrared spectrum and analytical data established this product as 1-propionyl-2-(6-methylpyrid-2-yl)hydrazine: infrared, cm.$^{-1}$, 3268 (NH), 1667 (C=O), 1534 (amide II), 1339 (amide III).

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.3; H, 7.3; N, 23.5. Found: C, 60.7; H, 7.2; N, 23.2.

Fraction B, 5.5 g. (24%), which was soluble in hot benzene, was recrystallized several times from benzene and finally sublimed *in vacuo*. It formed colorless prisms, m.p. 109–111°, and was identified as 3-ethyl-5-methyl-*s*-triazolo[4,3-*a*]pyridine: infrared, cm.$^{-1}$, 3003 (CH), 1642 (C=C), 1550, 1502, 1447 (aromatic), other strong bands at 1416, 1330, 1164, 1100, 1053.

In a similar way, **1-propionyl-2-(4,6-dimethylpyrid-2-yl)-hydrazine** was obtained from 4,6-dimethylpyrid-2-ylhydrazine (20 g., 0.13 mole) and propanoic acid (50 ml., 0.75 mole). Crystallization from ethanol yielded colorless prisms: 7.0 g. (24%); m.p. 211–213°; infrared, cm.$^{-1}$, 3279 (NH), 2857 (CH), 1661 (C=O), 1555 (amide II), 1342 (amide III).

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.2; H, 7.8; N, 21.8. Found: C, 60.7; H, 7.4; N, 22.1.

1-Acetyl-2-(3-methylpyrid-2-yl)hydrazine, prepared from the hydrazine and acetyl chloride in pyridine, crystallized from benzene as colorless needles: m.p. 132–133°; infrared, cm.$^{-1}$, 3247, 3096 (NH), 1658 (C=O), 1468 (amide II), 1311 (amide III).

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.2; H, 6.7; N, 25.4. Found: C, 57.6; H, 6.9; N, 25.1.

B. Ring Closure of the 1-Acyl-2-pyrid-2-ylhydrazines with Phosphorus Oxychloride.—Phosphorus oxychloride (30 ml., 0.33 mole) was added slowly to 1-propionyl-2-(4,6-dimethylpyrid-2-yl)hydrazine (6.0 g., 0.03 mole), and the mixture was refluxed for 7 hr. After removal of the excess phosphorus oxychloride on a steam bath under reduced pressure, the residue was cautiously made alkaline with ice and sodium hydroxide solution. This solution was extracted with chloroform (three 75-ml. portions), and the combined extracts were dried (Na_2SO_4). After removal of the chloroform, the light brown residue crystallized from benzene as colorless prisms, 3.7 g. (71%), m.p. 144–145°, and was identified as 3-ethyl-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine (Table II): infrared, cm.$^{-1}$, 2899 (CH), 1653 (C=C), other strong bands at 1553, 1449, 1408, 1377, 1323, 1094; n.m.r. ($CDCl_3$), τ 2.69 (8-H), 3.69 (6-H), 6.67 (quartet, CH_2), 7.22 (7-CH_3), 7.68 (5-CH_3), 8.49 (triplet, CH_3).

C. Ring Closure with Ortho Esters.—The 2-pyridylhydrazine (0.12 mole) was refluxed with the ortho ester (0.31 mole) for 6 hr. The excess ortho ester and alcohol were removed on a steam bath under reduced pressure, and the residue was recrystallized several times from benzene to yield the products described in Table II.

2-Benzoyl- and 1,2-Dibenzoyl-1-(2-pyridyl)hydrazines.—The 2-pyridylhydrazine (0.2 mole) was dissolved in dry pyridine (250 ml.), and the solution was cooled to 0° in an ice bath. Benzoyl chloride (0.2 mole) was added slowly, and after the addition was complete, the reaction mixture was stirred at room temperature for 30 min. After heating for 1 hr. on a steam bath, the product was isolated by pouring the reaction mixture onto cracked ice (200 g.). The mono- or dibenzoyl derivative was purified by crystallization from the appropriate solvent shown in Table IV.

3-Phenyl-*s*-triazolo[4,3-*a*]pyridines. A. Cyclization of the 2-Benzoyl-1-(2-pyridyl)hydrazines with Phosphorus Oxychloride.—Phosphorus oxychloride (0.04 mole) was added cautiously to 2-benzoyl-1-(2-pyridyl)hydrazine (0.04 mole), and the reaction mixture was refluxed for 4 hr. and then worked up essentially as described in part B above. The product was purified by recrystallization from benzene and sublimation *in vacuo* (Table V). In the preparation of 3-phenyl-4,6-dimethyl-*s*-triazolo[4,3-*a*]pyridine from 1-benzoyl-2-(4,6-dimethylpyrid-2-yl)hydrazine (0.04 mole), toluene (125 ml.), and phosphorus oxychloride (0.4 mole) (10-hr. reflux), the product separated after basification of the reaction mixture. Recrystallization from benzene and sublimation *in vacuo* yielded 4.1 g. (45%) of 3-phenyl-4,6-dimethyl-*s*-triazolo[4,3-*a*]pyridine as colorless plates, m.p. 123–124°.

B. Fusion with Aromatic Acids.—2-Pyridylhydrazine (6.0 g., 0.051 mole) and benzoic acid (6.7 g., 0.051 mole) were heated at 170° for 4 hr. After cooling to room temperature, the dark viscous oil was dissolved in aqueous ethanol, the solution made alkaline with dilute sodium hydroxide solution, and the resultant solid was collected by filtration. Crystallization from benzene yielded white plates, 6.4 g. (65%), m.p. 172°, of 3-phenyl-*s*-triazolo[4,3-*a*]pyridine[23] which had a superimposible infrared spectrum and which gave no melting point depression with a sample of 3-phenyl-*s*-triazolo[4,3-*a*]pyridine prepared by method A.

Fusing 6-methylpyrid-2-ylhydrazine (5.94 g., 0.048 mole) and *o*-toluic acid (7.43 g., 0.048 mole) at 180° for 14 hr. gave colorless needles (benzene), 2.0 g. (19%), m.p. 162–163°, of 1-*o*-toluyl-2-(6-methylpyrid-2-yl)hydrazine (*Anal.* Calcd. for $C_{14}H_{15}N_3O \cdot {}^1/_6C_6H_6$: C, 70.8; H, 6.3; N, 16.5. Found: C, 70.4; H, 6.5; N, 16.5.). A sample recrystallized from water and dried at 100° and 0.2 mm. for 6 hr. had the elemental analysis (*Anal.* Calcd. for $C_{14}H_{15}N_3O$: C, 69.7; H, 6.3; N, 17.4. Found: C, 69.8; H, 6.3; N, 17.3.); infrared, cm.$^{-1}$, 3300 (NH), 2941 (CH), 1678 (C=O), 1600 (aromatic), 1585 (amide II), 1466 (aromatic), 1385 (CH_3), 1355 (amide III).

3-Alkyaryl- (or Heteryl-) *s*-triazolo[4,3-*a*]pyridines.—The 2-pyridylhydrazine (0.05 mole) was heated with the arylaliphatic acids, heterocyclic acids, or their esters (0.05 mole) at 170–190° from 4–24 hr. The reaction was considered complete when the melt crystallized or when there was no evidence of water being eliminated. The crude products were recrystallized from benzene or a methanol–benzene mixture as described in Table III.

1-Aryl- (or Heteryl-) 2-(3-*s*-triazolo[4,3-*a*]pyridyl)ethene.—2-Pyridylhydrazine (0.05 mole) and the aryl- or the 2-heterylacrylic acid (0.05 mole) were heated at 180° for 9–16 hr. The dark tarry residue was purified by repeated crystallizations from methanol–benzene and by treatment with decolorizing carbon. These products are described in Table III.

(41) R. G. Fargher and R. Furness, *J. Chem. Soc.*, 691 (1915).

Di(3-s-triazolo[4,3-a]pyridyl)alkanes.—2-Pyridylhydrazine (10.9 g., 0.1 mole) and the dicarboxylic acid or ester (0.05 mole) mole) were heated at 170–270° for 2–72 hr. The reaction was considered complete when the product crystallized from the melt or when there was no more indication of water being eliminated. The crystalline product or viscous oil was crystallized from the appropriate solvent listed in Table VI.

Di(3-s-triazolo[4,3-a]pyridyl)methane from the Reaction of 2-Pyridylhydrazine and Ethyl Cyanoacetate.—2-Pyridylhydrazine (10.9 g., 0.1 mole) and ethyl cyanoacetate (8.5 g., 0.1 mole) were heated at 190° for 6 hr. The brown residue was recrystallized from dimethylformamide yielding 7.0 g. (56%) of colorless, irregular prisms, m.p. 263–265°. The infrared spectrum was identical, and there was no depression in the mixture melting point with that of a sample of di(3-s-triazolo[4,3-a]pyridyl)-methane prepared from 2-pyridylhydrazine and diethyl malonate.

s-Triazolo[4,3-a]pyridine-3-acetic Acid [2-(2-Pyridyl)hydrazide].—2-Pyridylhydrazine (10.8 g., 0.1 mole) was heated with diethyl malonate (8 ml., 0.1 mole) at 190° for 6 hr. The crude material was recrystallized from a large volume of ethanol, yielding di(3-s-triazolo[4,3-a]pyridyl)methane, 9.1 g. (72%), as colorless needles, m.p. 263–265°. The decantate was concentrated on a steam bath, and on cooling to room temperature, additional product separated. Crystallization from ethanol yielded colorless prisms, 3.0 g. (22%), m.p. 208–209°, which were shown to be s-triazolo[4,3-a]pyridine-3-acetic acid [2-(2-pyridyl)hydrazide]: infrared, cm.$^{-1}$, 3268 (NH), 1658 (C=O), 1604 (aromatic), 1585 (amide II), 1314 (amide III), other strong bands at 1245, 1136, 1042, 972, 915.

Anal. Calcd. for $C_{13}H_{12}N_6O$: C, 58.2; H, 4.5; N, 31.3. Found: C, 57.9; H, 4.5; N, 31.4.

Oxalic Acid Bis[2-(2-pyridyl)hydrazide]. A. From Diethyl Oxalate.—2-Pyridylhydrazine (10.9 g., 0.1 mole) was heated with diethyl oxalate (7.3 ml., 0.05 mole) at 135°. After 15 min., the product crystallized from solution (8.1 g., 59%) and was recrystallized from dimethylformamide from which it separated as colorless needles, m.p. 256–257°.

Anal. Calcd. for $C_{12}H_{12}N_6O_2$: C, 52.9; H, 4.4; N, 30.9. Found: C, 53.0; H, 4.5; N, 31.2.

B. From Oxalyl Chloride.—2-Pyridylhydrazine (10.9 g., 0.1 mole) was dissolved in dry pyridine (100 ml.) and, with stirring, cooled to 0° in an ice bath. Oxalyl chloride (6.4 g., 0.05 mole) was added dropwise over a period of 15 min., and after the addition was complete, the solution was stirred at room temperature for 30 min. The reaction mixture was heated on a steam bath for 1 hr. and poured over cracked ice, and the product that separated was collected. It crystallized from dimethylformamide as colorless needles, 11.9 g. (83%), m.p. 256–257°, and there was no depression of the melting point when mixed with the product obtained from 2-pyridylhydrazine and diethyl oxalate. The infrared spectrum was superimposable with that of oxalic acid bis[2-(2-pyridyl)hydrazide].

Di(3-s-triazolo[4,3-a]pyridyl). A.—Oxalic acid bis[2-(2-pyridyl)hydrazide] (13.5 g., 0.05 mole) was heated in a Wood's metal bath at 270° for 5 hr. After cooling to room temperature, the dark brown, crystalline product was recrystallized from dimethylformamide from which it separated as tan plates, 10.4 g. (85%), m.p. 343–344°.

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.0; H, 3.4; N, 35.6. Found: C, 61.1; H, 3.5; N, 35.6.

B.—The above hydrazide (7.1 g., 0.026 mole), phosphorus oxychloride (45 ml.), and toluene (120 ml.) were heated under reflux for 4 hr. The toluene and excess of phosphorus oxychloride were removed under reduced pressure on a steam bath and the residue was basified carefully with ice and 30% sodium hydroxide solution. The crystalline product was collected and it crystallized from dimethylformamide as tan plates, 4.9 g. (80%), m.p. 261–263°. The product was identical in all respects with di(3-s-triazolo[4,3-a]pyridyl)prepared by method A.

s-Triazolo[4,3-a]pyridine-3-carboxylic Acid (2, R′ = COOH).—2-Pyridylhydrazine (5.5 g., 0.05 mole) and oxalic acid (4.5 g., 0.05 mole) were heated together at 120° for 22 hr. The reaction commenced with effervescence within 15 min., and after 2 hr. a product separated from the melt. After cooling to room temperature the reaction mixture was dissolved in ethanol from which pale yellow needles, m.p. 166–167° (1.7 g., 21%), of the carboxylic acid separated.

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.5; H, 3.1; N, 25.8. Found: C, 51.5; H, 3.2; N, 26.0.

s-Triazolo[4,3-a]pyridine-3-carboxamide (11).—Ethyl oxamate (5.9 g., 0.05 mole) and 2-pyridylhydrazine (5.5 g., 0.05 mole) were heated at 200° for 2 hr., at which time the product crystallized from the melt. The separated material was recrystallized several times from ethanol until a constant melting point was obtained. s-Triazolo[4,3-a]pyridine-3-carboxamide was obtained as pale yellow needles: 3.5 g. (43%); m.p. 238–239°; infrared, cm.$^{-1}$, 3195, 3044 (NH), 1675 (C=O), 1623 (amide II), other strong bands at 1453, 1397, 1277, 1124, 1095; $\lambda_{max}^{CH_3OH}$ 283, 237, 231 mμ (log ε 4.00, 3.94, 4.06).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.9; H, 3.7; N, 34.6. Found: C, 52.0; H, 3.8; N, 34.4.

s-Triazolo[4,3-a]pyridine by Decarboxylation of s-Triazolo-[4,3-a]pyridine-3-carboxamide.—The above amide (1.0 g., 0.0062 mole) was dissolved in 10% sodium hydroxide solution (20 ml.) and heated gently under reflux until no more ammonia was evolved (1 hr.). The cooled reaction mixture was extracted with chloroform (three 15-ml. portions) and the combined extracts were dried (Na_2SO_4). Removal of the chloroform left a colorless oil which crystallized after standing overnight. The crude material crystallized from ethyl acetate–petroleum ether as colorless plates, 0.5 g. (68%), m.p. 52°, and by its infrared spectrum and mixture melting point was identified as s-triazolo-[4,3-a]pyridine.

***dl*-1,2-Di(3-s-triazolo[4,3-a]pyridyl)ethanol.**—2-Pyridylhydrazine (10.9 g., 0.1 mole) and *dl*-malic acid (6.7 g., 0.05 mole) were heated at 120° for 20 hr. and 130° for 48 hr. As the reaction mixture was cooled to room temperature, the crude product crystallized, and it separated from a large volume of ethanol as colorless, irregular prisms: 5.0 g. (36%); m.p. 232–233° dec.; infrared, cm.$^{-1}$, 3125 (OH), 1650 (C=N).

Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 60.0; H, 4.3; N, 30.0. Found: C, 60.0; H, 4.3; N, 30.0.

1,2-Di(3-s-triazolo[4,3-a]pyridyl)ethene.—The above alcohol (1.0 g.) and acetic anhydride (3 ml.) were heated to the boiling point for 10 min. The crystalline product that had separated crystallized from dimethylformamide as greenish yellow needles: 0.5 g. (53%); m.p. 330° dec.; infrared, cm.$^{-1}$, 1650 (C=N).

Anal. Calcd. for $C_{14}H_{10}N_6$: C, 64.1; H, 3.8; N, 32.05. Found: C, 64.0; H, 3.9; N, 32.0.

s-Triazolo[4,3-a]pyridin-3-ols from 2-Pyridylhydrazine. A. With Urea.—The 2-pyridylhydrazine (15 g.) and urea (15 g.) were heated at 180–210° for 1–2 hr. or until the product crystallized from the melt. Some of the intermediate semicarbazides tended to crystallize soon after the reaction had commenced and the higher temperature range had to be employed in these cases. Thus, when 5-methylpyrid-2-ylhydrazine was heated with urea, the 1-(5-methylpyrid-2-yl)semicarbazide separated. It crystallized from ethanol as pale yellow prisms: m.p. 205° dec.; infrared, cm.$^{-1}$, 3268, 3165 (NH), 1664 (C=O), 1623 (amide II), other strong bands at 1536, 1429, 1351, 1140, 1119, 832.

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.6; H, 6.1; N, 33.7. Found: C, 50.5; H, 5.8; N, 33.4.

1-(5-Methylpyrid-2-yl)semicarbazide (18.2 g., 0.11 mole) was heated at 220° for 1 hr. The crude 6-methyl-s-triazolo[4,3-a]-pyridin-3-ol crystallized from ethyl acetate as colorless needles, 11.6 g. (71%), m.p. 192°.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.6; H, 4.4; N, 28.5. Found: C, 56.4; H, 4.7; N, 28.2.

The alcohols prepared in this fashion are described in Table VII and all crystallized from ethanol as pale yellow needles.

B. With Ethyl Allophanate.—2-Pyridylhydrazine (5.5 g., 0.05 mole) was heated with ethyl allophanate (6.6 g., 0.05 mole) at 190° for 15 min. At this time, a product crystallized from the melt so the temperature was raised to 300° and it was held at this temperature for 2 hr. When the melt cooled, a yellow crystalline material formed. Repeated crystallizations from ethanol gave the product as pale yellow prisms, 5.8 g. (87%), m.p. 225–226°. There was no melting point depression and the infrared spectrum was superimposible with that of s-triazolo-[4,3-a]pyridin-3-ol.[23]

C. With Ethyl Chloroformate.—2-Pyridylhydrazine (2.0 g.) was heated under gentle reflux with excess ethyl chloroformate (10 ml.) for 30 min. The viscous oil crystallized from ethanol as pale yellow prisms, 1.8 g. (72%), m.p. 225–226°. There was no mixture melting point depression and the infrared spectrum was superimposible with that of s-triazolo[4,3-a]pyridin-3-ol.[23]

s-Triazolo[4,3-a]pyridine-3-thiols. A. From 2-Pyridylhydrazines and Carbon Disulfide.—The 2-pyridylhydrazine

(0.2 mole) in chloroform (125 ml.) was treated with carbon disulfide (0.25 mole), a precipitate forming immediately. This dissolved when the reaction mixture was heated under gentle reflux and the heating was continued for 1–7 days, depending on the rate of separation of the product and until no appreciable amount of hydrogen sulfide was being evolved. The insoluble products, described in Table VII, were purified by crystallization from methanol.

B. Attempted Synthesis from Thiourea.—2-Pyridylhydrazine (6.0 g., 0.056 mole) was heated with thiourea (6.0 g., 0.07 mole) at 200° for 3 hr. During this time there was a noticeable amount of ammonia being evolved and, after cooling to room temperature, a dark yellow, viscous oil formed.

The dark yellow semisolid was dissolved in methanol and the small amount of insoluble material was discarded. After removal of the methanol, the residue was distilled under reduced pressure. Fraction I (0.3 g.), b.p. 40–44° (0.1 mm.), crystallized from benzene as colorless plates and was identified as 2-aminopyridine, by mixture melting point data and its infrared spectrum.

Fraction 2, b.p. 125° (0.1 mm.), which collected in the condenser as a pale yellow semisolid, crystallized from methanol–chloroform as pale pink plates, 1.0 g. (12%), m.p. 109–110°. The product was recrystallized twice from acetone–ether, and formed pale pink plates, m.p. 115–119°, infrared (Nujol), cm.$^{-1}$, 2020 (NCS^-). It was identified as 2-aminopyridinium isothiocyanate.

Anal. Calcd. for $C_6H_7N_3S$: C, 47.1; H, 4.6; N, 27.4; S, 20.9. Found: C, 47.1; H, 4.6; N, 27.0; S, 20.7.

3-Amino-*s*-triazolo[4.3-*a*]pyridines.—The 2-pyridylhydrazine (0.1 mole) was dissolved in methanol (125 ml.) and cyanogen bromide (0.1 mole) was added cautiously (mild exothermic reaction) after which the reaction mixture was refluxed for 2–7 hr. The methanol was removed under reduced pressure on the steam bath and the residual, crystalline hydrobromide salt was dissolved in water. The aqueous solution was basified with sodium acetate and a small volume of concentrated sodium hydroxide solution. The base that separated was purified by recrystallization from ethanol (Table VII), and in those cases where the base did not separate from solution, it was obtained by continuous ether extraction (24–48 hr.).

1,2,4-Triazoles. XIII. Derivatives of the *s*-Triazolo[1,5-*a*]pyridine Ring System[1a]

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Cyclization of N-(2-pyridyl)alkyl- (or aryl-) amidines (**1**) with lead tetraacetate resulted in the formation of 2-alkyl- (or aryl-) *s*-triazolo[1,5-*a*]pyridines (**2**) in good yield. The scope of this reaction sequence has been determined. A second method of synthesis of the ring system, from 1,2-diaminopyridinium salts and carboxylic acids or acid chlorides, has also been established. The parent ring and others unsubstituted in the 2-position were readily obtained by this procedure. The pyridinium salts yielded the corresponding 1-amino-2-imino-1,2-dihydropyridines by passage through Amberlite IRA-400 resin; these bases underwent extremely facile cyclizations to the bicyclic system in yields greater than 90%. Potassium permanganate oxidation of *s*-triazolo[1,5-*a*]-pyridine yielded *s*-triazole-3-carboxylic acid. The triazolopyridine nucleus was resistant to the usual electrophilic substitution reactions.

In a previous paper[2] in this series, syntheses of *s*-triazolo[4,3-*a*]pyridine derivatives were described. In a continuation of our interests in the chemistry and pharmacological evaluation of fused bicyclic systems with a common nitrogen atom, we now describe the syntheses of members of the isomeric ring system, the *s*-triazolo[1,5-*a*]pyridine system (**2**) by two methods that make members of this ring system readily available. The spectral characteristics of these derivatives will be described in a later communication, in particular the relationship of their proton magnetic resonance data to various properties associated with heteroaromatic systems.

A synthesis involving ring closure onto a preformed *s*-triazole nucleus to form the pyridine ring is again not practicable,[3a] but a satisfactory route is available by cyclization of an intermediate N-(2-pyridyl)alkyl- (or aryl-) amidine with lead tetraacetate. This oxidative-type ring closure was used by Bower and Ramage[3b] for the synthesis of the only known representatives of this ring system, the 2-methyl- and 2-phenyl-*s*-triazolo[1,5-*a*]pyridines (**2**, R^1 = CH_3 and Ph) and has also found application in the synthesis of the *s*-triazolo[1,5-*a*]pyrazine system.[4] A closely related oxidation reaction is the synthesis of 3-methyl-1-phenyl-*v*-triazolo[3,4-*a*]pyridinium chloride (**4**) from methyl 2-pyridyl ketone phenylhydrazone[5] (**3**). This present study has developed and extended this route to the bicyclic system and determined its limitations, results which are of special interest in view of the recent use[3c] of sodium hypochlorite and base in the oxidative ring closure of N-(2-pyridyl)benzamidine to 2-phenyl-*s*-triazolo[1,5-*a*]pyridine. Using this method, it was found that N′-(3-pyridyl)-4-thiazolecarboxamidine underwent ring closure to 2-(4-thiazolyl)-3H-imidazo[4,5-*b*]pyridine.[3c]

The *s*-triazolo[1,5-*a*]pyridine ring system is now also available from the reaction of aliphatic or aromatic acids (or their chlorides) with 1,2-diaminopyridinium salts (**7**) or the corresponding bases (**8**), and in addition the isomerization of the *s*-triazolo[4,3-*a*]pyridine systems, described in the following publication,[3d] offers an alternative route.

The intermediate N-(2-pyridyl)alkylamidines (Table I) can be prepared by two methods: (a) from the 2-aminopyridines, aluminum chloride, and the alkyl cyanide[6]; or (b) by treatment of an imino ether

(1) (a) This work was supported by Public Health Service Research Grant CA-05973, 01-04, National Cancer Institute, U. S. Public Health Service. (b) To whom correspondence should be sent: Department of Chemistry, Rensselaer Polytechnic Institute, Troy, N. Y.

(2) K. T. Potts and H. R. Burton, *J. Org. Chem.*, **31**, 251 (1966).

(3) (a) A recent example of this approach is the synthesis of 5-azaadenine from 3-amino-*s*-triazole [E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **87**, 1980 (1965)]; (b) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957); (c) V. J. Grenda, R. E. Jones, G. Gal, and M. Stetzinger, *J. Org. Chem.*, **30**, 259 (1956); (d) K. T. Potts, H. R. Burton, and S. K. Roy, *ibid.*, **31**, 265 (1966).

(4) G. M. Badger, P. J. Nelson, and K. T. Potts, *ibid.*, **29**, 2542 (1964).

(5) R. Kuhn and W. Münzing, *Chem. Ber.*, **85**, 29 (1952).