dropwise over a period of 1 hr. and then refluxed with stirring an additional 15 min. On cooling to 0° in an ice bath, the solution was basified with concentrated sodium hydroxide solution and the resulting crude product was collected and recrystallized from petroleum ether from which 2-amino-4-methylpyridine separated as colorless plates, 7.7 g. (78%), m.p. 98°.

Attempted Synthesis of s-Triazolo[1,5-a]pyridin-2-ol by Oxidation of 2-Pyridylurea. A. With Lead Tetraacetate.—2-Pyridylurea (1.0 g., 0.007 mole) and glacial acetic acid (25 ml.) were heated under reflux for 1 hr. The reaction mixture was poured into water, and when no product crystallized, the aqueous solution was concentrated under reduced pressure to a dark brown oil. This residue could not be purified or characterized.

B. With Ferric Chloride.—2-Pyridylurea (4.0 g., 0.03 mole) was dissolved in water (100 ml.) and hydrochloric acid (10 ml.) and the resulting mixture was heated to reflux temperature. To the stirred solution, ferric chloride (16.2 g. in 100 ml. of water) was added dropwise, and after addition, the reaction mixture was stirred an additional 30 min. The contents were then cooled to 0° in an ice bath and sodium carbonate was added until the solution had pH 11. Sodium sulfide was added and the precipitated iron sulfide was removed. No identifiable products were isolated from the reaction mixture.

1,2,4-Triazoles. XIV. Reactions of the s-Triazolo[4,3-a]pyridine Ring System[1a,b]

K. T. POTTS,[1c] H. R. BURTON, AND S. K. ROY

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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s-Triazolo[4,3-a]pyridine was readily oxidized at room temperature with potassium permanganate to s-triazole-3-carboxylic acid and underwent rearrangement to s-triazolo[1,5-a]pyridine on treatment with hot base. This rearrangement occurred readily with a variety of 3-substituents. Bromination took place in the 3-position and only in the six-membered ring when it was activated by at least two methyl substituents. Other electrophilic substitution reactions were unsuccessful and the nucleus was also resistant to nucleophilic substitution. Under neutral conditions the 3-proton only was exchanged with deuterium. Dimethyl acetylenedicarboxylate and tetracyanoethylene did not form Diels–Alder adducts but yielded instead 3-substitution products. A 3-amino substituent readily formed benzal and benzoyl derivatives and, *via* the diazonium salt, was replaced with hydrogen and halogens. The diazonium salt coupled readily with 2-naphthol. 3-Halogen-substituted products were resistant to nucleophilic displacement reactions, did not form Grignard reagents, and were formed in poor yield from the corresponding s-triazolo[4,3-a]pyridin-3-ol. Protonation and salt formation occurred at N-1 except for the 3-amino product, where salt formation occurred at N-2. The salts were readily reduced with sodium borohydride, but the unprotonated nucleus itself was resistant to catalytic hydrogenation and reduction with metal hydrides. Methylation of s-triazolo[4,3-a]pyridin-3-ol with methyl sulfate and alkali and diazomethane gave 2-methyl-s-triazolo[4,3-a]pyrid-3-one, and under comparable conditions s-triazolo[4,3-a]pyridine-3-thiol yielded methyl 3-s-triazolo[4,3-a]pyridyl sulfide.

In an earlier publication,[2] synthetic sequences used to obtain representatives of the s-triazolo[4,3-a]-pyridine ring system were described and, as part of a program studying the properties of bicyclic heterocycles with bridgehead nitrogen atoms, we now report on the reactions and properties of the s-triazolo[4,3-a]pyridine system (**1**).

The behavior of the nucleus under oxidizing conditions is particularly interesting. In contrast to various indolizines which always yield substituted pyridine derivatives,[3] s-triazolo[4,3-a]pyridine (**1**, R = H) was readily oxidized by potassium permanganate (an exothermic reaction) at room temperature to s-triazole-3-carboxylic acid (**2**). The pyrazolo[1,5-a]-pyridine system is similarly oxidized to pyrazole-3-carboxylic acid,[4] and the additional nitrogen atoms in the five-membered ring apparently confer greater stability on that portion of the molecule. This ready oxidation caused us to examine in detail reactions that would give a qualitative estimation of the double bond character present in the pyridine portion of the nucleus, indicated by proton magnetic resonance studies.[5]

The greater stability of the s-triazole ring was again evidenced by the action of hot alkali on various 3-substituted s-triazolo[4,3-a]pyridines. Hot sodium hydroxide solution brought about an interesting rearrangement of the s-triazolo[4,3-a]pyridine nucleus to products that had identical analytical and molecular weight data with their precursors and which have been identified as isomeric s-triazolo[1,5-a]pyridines (**3**). This identity was initially indicated by the characteristic ultraviolet spectra already established for isomeric, fused-ring systems containing the s-triazole nucleus[6] and was confirmed by the various interrelationships and transformations shown in Chart I, as well as by comparison of the products with those of established structure. Thus 3-methyl-s-triazolo[4,3-a]pyridine (**1**, R = CH_3), when heated with 10% sodium hydroxide solution for 48 hr., gave 2-methyl-s-triazolo[1,5-a]-pyridine (**3**, R = CH_3), identical with a sample prepared[7] by the lead tetraacetate oxidation of N-2-pyridylacetamidine (**6**, R = CH_3). The rearrangement of 3-amino-s-triazolo[4,3-a]pyridine (**1**, R = NH_2) to 2-amino-s-triazolo[1,5-a]pyridine (**3**, R = NH_2) under these conditions provided a means of interrelating the isomeric products. Deamination of 2-amino-s-triazolo[1,5-a]pyridine using the diazonium salt and hypophosphorous acid gave s-triazolo[1,5-a]-

(1) (a) Support of this work by Public Health Service Research Grant CA-05973, 01-03, National Cancer Institute, is gratefully acknowledged. (b) Part of this material appeared as a preliminary communication: K. T. Potts and H. R. Burton, *Proc. Chem. Soc.*, 420 (1964). (c) 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) E. T. Borrows and D. O. Holland, *Chem. Rev.*, **42**, 636 (1948); a brief summary of these reactions appears in W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," part 1, Interscience Publishers, Inc., New York, N. Y., 1961, p. 263.

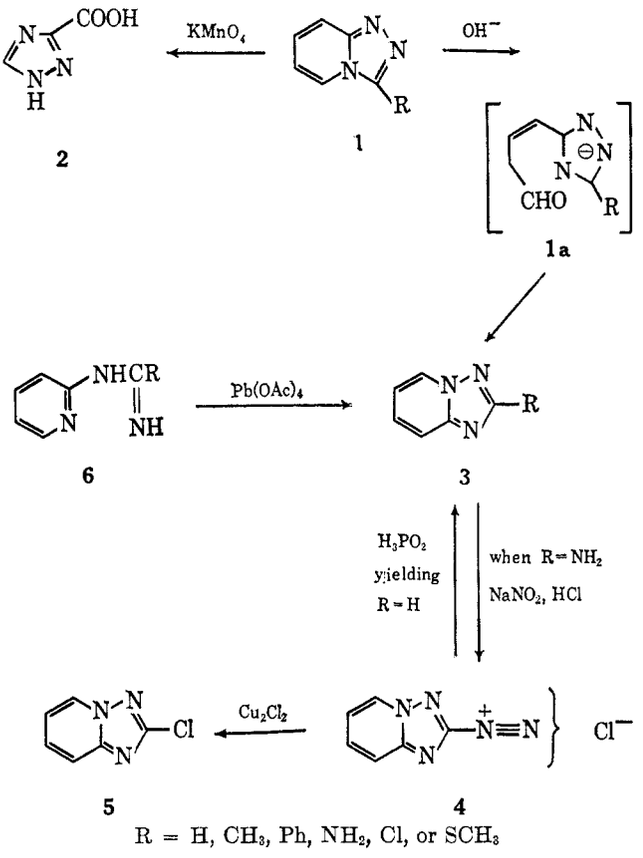
(4) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).

(5) K. T. Potts, H. R. Burton, T. H. Crawford and S. W. Thomas, to be submitted. All these protons occur at lower field than in the unsubstituted product, a fact readily attributable to the 3-substituent.

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

(7) K. T. Potts, H. R. Burton, and J. Bhattacharyya, *ibid.*, **31**, 260 (1966).

CHART I



R = H, CH_3, Ph, NH_2, Cl, or SCH_3

pyridine (**3**, R = H), identical with that obtained by the rearrangement of *s*-triazolo[4,3-*a*]pyridine (**1**, R = H), and also by ring closure of 1,2-diaminopyridinium iodide with formic acid.[7] Preparation of the diazonium solution in the presence of cuprous chloride yielded 2-chloro-*s*-triazolo[1,5-*a*]pyridine (**5**), identical with the product obtained by rearrangement of 3-chloro-*s*-triazolo[4,3-*a*]pyridine (**1**, R = Cl). Similarly, 3-methylthio-*s*-triazolo[4,3-*a*]pyridine underwent rearrangement to the corresponding 2-methylthio-*s*-triazolo[1,5-*a*]pyridine. The rearrangement could not be effected with sodium ethoxide or with dilute acid, and the 3-hydroxy- and 3-mercapto-substituted products underwent degradation under these conditions to pyridine derivatives. It is of especial interest in this connection that the 3-amino product underwent rearrangement (89%) and not hydrolysis, a reaction usually associated with amino–imino tautomerism.

The rearrangement most likely involved an initial hydroxide ion attack at the C-5 position of the nucleus to yield an intermediate such as **1a** which then underwent ring closure in the normal manner at N-1, which is more basic than N-4 in the *s*-triazole anion. The presence of an intermediate such as **1a** in the reaction mixture was indicated by its transient, deep red color and the pronounced aldehyde odor present owing to decomposition of this intermediate, but detailed investigation of the reaction mixture yielded no product such as **1a**, only the isomerized product and the starting material being isolated. Indeed, it was possible to use the appearance and disappearance of this red coloration as a gauge of the progress of the reaction.

In support of this reaction route, the *s*-triazolo[4,3-*a*]pyrazine system was found to undergo rearrangement to the isomeric *s*-triazolo[1,5-*a*]pyrazine system, although in poor yield. However, the *s*-triazolo[4,3-*a*]quinoxaline system was completely resistant to rearrangement, as would be expected from such a ring system in which the position corresponding to that at which the initial attack occurred formed part of a fused ring junction.[8]

This type of isomerization has been reported recently[9] by other workers as occurring in various types of *s*-triazolopyrimidines where it is characterized by the extreme facility with which it occurs. Heat alone is sufficient to cause isomerization as are mild acid reaction conditions, and the latter caused considerable problems in structural assignments to the reaction products in several instances.[9d,10] The extreme ease of rearrangement in this series can be attributed to the increase in the electron deficiency at the C-5 center owing to the second nitrogen atom of the pyrimidine ring. That this effect is considerable is shown by the ready rearrangement of *s*-triazolo[4,3-*a*]pyrimidine-3-thiol to *s*-triazolo[1,5-*a*]pyrimidine-2-thiol under acidic, basic, or thermal conditions, whereas *s*-triazolo[4,3-*a*]pyridine-3-thiol is stable under acidic or thermal conditions and, on prolonged treatment with base, undergoes decomposition to 2-pyridone. Though of no practical significance, it was possible to bring about the rearrangement of the *s*-triazolo[4,3-*a*]pyridine system by heat alone. Decomposition was the predominant reaction and, using thin layer chromatography, 2-aminopyridine was detected along with the isomerization product.

Table I lists the π-electron densities at the various atoms of these ring systems and these data[11] follow the trend of the qualitative experimental observations described above.

2-Phenylimidazo[1,2-*a*]pyridine was found not to undergo rearrangement to 3-phenylimidazo[1,2-*a*]pyridine under comparable alkaline reaction conditions. The greater stability of the *s*-triazole moiety and especially of its anion must be a controlling factor in this rearrangement. It is interesting to compare these results with the hydrolytic rearrangement[12] of pyrazolo[3,4-*d*]pyrimidines to isomeric derivatives. This reaction is a variation of the Dimroth reaction,[13] and the close relationship between all these hydrolytic rearrangements is apparent.

It was found that no reaction occurred with dienophiles such as phenylacetylene and diphenylacetylene, but reaction occurred with tetracyanoethylene and dimethyl acetylenedicarboxylate. In the indolizine (**7**)

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

(9) (a) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. van Allan, *J. Org. Chem.*, **24**, 779, 787, 793, 796 (1959); (b) C. F. H. Allen, G. A. Reynolds, J. F. Tinker, and L. A. Williams, *ibid.*, **25**, 361 (1960); (c) K. Sirakawa, *J. Pharm. Soc. Japan*, **78**, 1395 (1958); **79**, 903,1487 (1959); **80**, 956, 1542 (1960); (d) G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 5642 (1963); 3357, 3369 (1965).

(10) See K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).

(11) These data were obtained by the Hückel LCAO–MO Method, using a Jacobi-type program and assuming a 10π-electron system with the bridgehead nitrogen contributing two electrons to the system. The authors wish to express their sincere appreciation to Dr. S. L. Cooke, Jr., for his advice with these computations and to acknowledge their indebtedness to the University of Louisville Computation Laboratory for the use of their facilities.

(12) E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

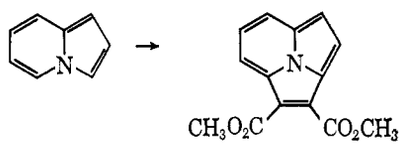
(13) D. J. Brown "Heterocyclic Compounds: The Pyrimidines," John Wiley and Sons, Inc., Interscience Division, New York, N. Y., 1962, pp. 379, 380; D. D. Perrin and I. H. Pitman, *Australian J. Chem.*, **18**, 471 (1965).

TABLE I

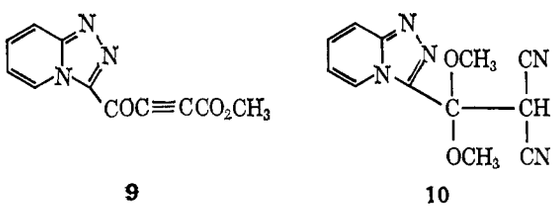
π-ELECTRON DENSITIES AT PERIPHERAL ATOMS OF VARIOUS RING-FUSED s-TRIAZOLE SYSTEMS

Nucleus	Position 1	2	3	4	5	6	7	8	9
s-Triazolo[4,3-a]pyridine	1.347	1.237	0.950	1.596	0.908	1.043	0.959	1.035	0.925
s-Triazolo[4,3-a]pyrazine	1.308	1.230	0.932	1.585	0.926	1.002	1.171	0.914	0.932
s-Triazolo[4,3-a]pyrimidine	1.358	1.236	0.946	1.596	0.830	1.051	0.845	1.250	0.889
s-Triazolo[4,3-c]pyrimidine	1.344	1.234	0.941	1.593	0.779	1.234	0.919	1.043	0.913

series, Boekelheide, *et al.*,[14] found that the products formed from reaction with the acetylenic ester were dimethyl cyclo[3.2.2]azine-1,2-dicarboxylate (**8**) and its 3,4-dihydro derivative. This must have involved an initial electrophilic attack at the 3-position of the nucleus and agrees with theoretical calculations, indicating the greatest electron density to be at the 3-position. No addition across the 5,6–7,8 double bonds was observed.



7 **8**



9

10

With s-triazolo[4,3-a]pyridine, dimethyl acetylenedicarboxylate gave a product that is best represented as 3-(3-methoxycarbonyl-1-oxopropynyl)-s-triazolo[4,3-a]pyridine (**9**). Analytical data indicated this composition and strong support for the presence of these functional groups came from spectral data. In the infrared spectrum, a band at 2223 cm.$^{-1}$ showed the presence of the acetylenic group, two carbonyl bands at 1725 and 1703 cm.$^{-1}$ were due to the ester and ketone carbonyl functions, and absorptions (1626 cm.$^{-1}$) associated with the C=N– system of the nucleus as well as those (1135 cm.$^{-1}$) of a $-COOCH_3$ group were also present. That an intact s-triazolo[4,3-a]pyridine nucleus with an unsaturated 3-substituent was present was evident from comparison of the ultraviolet absorption spectrum [λ_{max} 268, 312 mμ (log ε 3.95, 3.60)] with that of s-triazolo[4,3-a]pyridine [λ_{max} 258 (sh), 262 (sh), 267, 282 mμ (log ε 3.45, 3.48, 3.56, 3.56)] and 2-styryl-s-triazolo[4,3-a]pyridine [λ_{max} 227 (sh), 234 (sh), 263, 307, 326 (sh) mμ (log ε 3.24, 4.11, 4.11, 4.42, 4.41)]. The formation of this product can be rationalized in terms of the greater anionoid activity of the 3-position resulting in attack on the ester carbonyl group instead of on the triple bond function.

The product from the reaction with tetracyanoethylene was found to have the composition $C_{12}H_{11}N_5O_2$ and an ultraviolet absorption spectrum incompatible with any adduct to the bicyclic system. The ultraviolet spectrum [λ_{max} 236, 275 (sh), 283, 295 (sh) mμ (log ε 4.23, 3.82, 3.83, 3.61)] suggested a 3-substituted s-triazolo[4,3-a]pyridine with no further conjugation present in the 3-substituent. Its n.m.r. spectrum showed the presence of two nonequivalent methoxyl groups (τ 5.73 and 6.75) and four sets of aromatic protons (τ 0.27, 1.05, 1.69–1.79, and 2.40) usually associated with this ring system.[5] The presence of the cyanide groups was shown by two bands at 2186 and 2160 cm.$^{-1}$ in the infrared spectrum which was devoid of –NH– and carbonyl absorptions but which showed the characteristic absorptions of the –C=N– grouping of the ring system (1635 cm.$^{-1}$) and of the methoxyl groups (1116 cm.$^{-1}$). These data can best be accommodated by the structure 3-(1,1-dimethoxy-2,2-dicyanoethyl)-s-triazolo[4,3-a]pyridine (**10**).

The nonequivalence of the methoxyl groups requires them to be attached to position 1 of the side chain where they would be affected unequally by the magnetic anisotropic effect of the nuclear nitrogen atoms. In further support of this, the 5-proton absorbed at τ 0.27, a downfield shift of approximately 1.52 p.p.m. (usual absorption, τ *ca.* 1.79), brought about by the deshielding effect of the oxygen atom of the methoxyl group. The interaction between 3- and 5-substituents in this ring system is quite pronounced and results in some interesting, anomalous n.m.r. effects.[5] As methanol was used in the reaction work-up, the presence of the two methoxyl groups in the product can be explained in terms of a prior reaction of the methanol with tetracyanoethylene,[15] the 1,1-dimethoxy-2,2-dicyanoethylene then undergoing reaction at the 3-position of the nucleus. As **10** is relatively unstable and was obtained only in moderate yield, it would be expected that the corresponding tetracyano product would be even more unstable,[16] and this probably accounts for failure to isolate any of this product.

The products obtained from the bromination of the s-triazolo[4,3-a]pyridine system depend on the reaction medium and the substitution pattern of the nucleus. With bromine water or with bromine in acetic acid, s-triazolo[4,3-a]pyridine hydrobromide, also prepared from the base and hydrobromic acid, was obtained by hydrolysis of an initial perbromide. However, use of methanol as solvent gave an excellent yield of 3-bromo-s-triazolo[4,3-a]pyridine, again with the formation of an initial perbromide. Blocking the 3-position with a methyl substituent did not cause bromination to occur in the six-membered ring but simply resulted in formation of the hydrobromide, irrespective of the solvent used. That substitution in s-triazolo[4,3-a]pyridine had occurred in the 3-position was immediately apparent from the n.m.r. spectrum of the product. The characteristic 3-proton absorption at τ 1.14 was absent from the spectrum which was otherwise in reasonably close agreement with that of the

(14) A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.*, **24**, 582 (1959); A. Galbraith, T. Small, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 453 (1961).

(15) W. J. Middleton and V. A. Engelhardt, *ibid.*, **80**, 2788 (1958).

(16) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *ibid.*, **80**, 2783 (1958).

starting product. This position of substitution was confirmed by the bromo product being identical with 3-bromo-*s*-triazolo[4,3-*a*]pyridine obtained by a Sandmeyer reaction from 3-amino-*s*-triazolo[4,3-*a*]pyridine. This bromine atom is particularly inert and in this respect resembles the bromine in 3-bromo-*s*-triazole.[17] The 3-bromo compound will not form a Grignard reagent and the bromine cannot be displaced by nucleophiles, such as the hydroxide and ethoxide ions, amines, and hydrazine. This is in direct contrast to the behavior of a 3-halogen substituent in the imidazo[1,2-*a*]pyridines where it is easily removed[18] and even more so to the lability of halogen substituents in the indolizines.[19]

The introduction of two methyl substituents into the pyridine portion of the nucleus resulted in substitution occurring in that nucleus. Bromination of 5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine readily gave 3,8-dibromo-5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine. The absence of the characteristic 3-proton absorption at τ 1.34 and an absorption at 3.56 (one proton) in the n.m.r. spectrum of the product placed the bromine substituents at the 3- and 8-positions. The latter absorption was attributed to the 6-proton (usual absorption τ 3.12–3.53) as all other protons in this ring system occur at considerably lower field[5] and one would have to postulate a large high-field shift being caused by the bromine atom. Further support for the substituent being in the 8-position came from the pattern of the methyl proton absorptions. A peak at τ 7.07 with ill-defined hyperfine splitting, owing to the 5-methyl group coupled with the 6-proton, has undergone a small downfield shift of 0.27 p.p.m. from the usual position of the 5-methyl protons at τ 7.34 in 5,7-dimethyl-*s*-triazolo[4,3-*a*]pyridine. This can be attributed to the inductive effects exerted by the 3- and 8-bromine substituents. The 7-methyl protons occurred as a sharp singlet at τ 7.58 (usual position τ 7.58) and confirmed an 8-bromo substituent, as the steric interaction between the 7-methyl and 8-bromo substituents is sufficient to displace the 7-methyl group to an extent where coupling with the 6-proton was no longer present. It is interesting that the theoretical electron density calculations favor the 8-position over the 6-position (Table I). The presence of only one methyl group in the six-membered ring, as in 3,6-dimethyl-*s*-triazolo[4,3-*a*]pyridine, was not sufficient to increase the electron density to the point where substitution will occur, and the product isolated in this case was the corresponding hydrobromide.

Except for the above bromination reactions, the nucleus was inert to the usual electrophilic reagents; nitration, sulfonation, the Friedel–Crafts and the Vilsmeier formylation reactions were all unsuccessful.

The nucleus was resistant to attack by sodamide, a result not unexpected in view of the bromination studies described. It also did not undergo a clean metalation reaction with butyllithium, and hydrogen peroxide in acetic acid gave only a very small amount of an unstable product which appeared to be an N-oxide, the *s*-triazolo[4,3-*a*]pyridine being recovered.

s-Triazolo[4,3-*a*]pyridine was not reduced at atmospheric pressure by hydrogen and platinum, under neutral or acid conditions. Possible poisoning of the catalyst by the substrate was considered, but a very large excess of catalyst did not effect reduction. It was also stable to the reducing action of complex metal hydrides, but reduction of the quaternized nucleus with sodium borohydride occurred readily (see below).

3-Amino-*s*-triazolo[4,3-*a*]pyridine (**1**, R = NH_2) is best represented as being in the amino form and not the tautomeric imino form, and spectral data indicate strong hydrogen bonding to be present. This also accounts for the high melting point of the 3-amino-*s*-triazolo[4,3-*a*]pyridines, particularly in comparison to the 2-amino-*s*-triazolo[1,5-*a*]pyridines. The amino group readily formed a benzal and benzoyl derivative and was converted into a diazonium salt which, with hypophosphorous acid lost nitrogen to form *s*-triazolo[4,3-*a*]pyridine, and with cuprous chloride or bromide yielded 3-chloro- or 3-bromo-*s*-triazolo[4,3-*a*]pyridine. The diazonium salt prepared in the presence of mineral acid was relatively unstable, even in the cold, but the use of an oxy acid such as nitric acid imparted stability to the salt. In this behavior, the diazonium salt resembles the *s*-triazol-3-yldiazonium salts and a parallel behavior was observed in the formation of the dark red *s*-triazolo[4,3-*a*]pyrid-3-ylazo-2-naphthol from the diazonium salt and 2-naphthol.

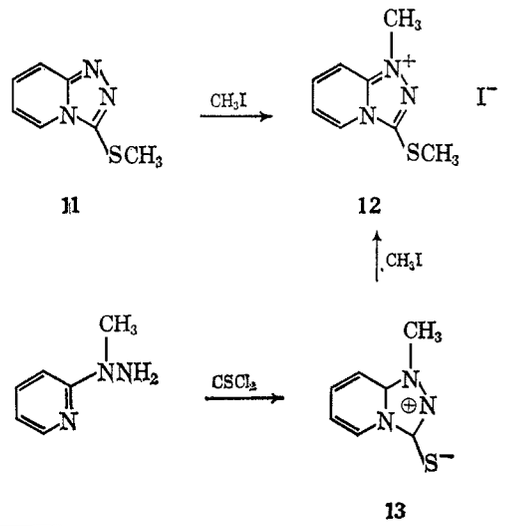
Prolonged boiling with 10% sodium hydroxide solution isomerized the 3-amino compound to 2-amino-*s*-triazolo[1,5-*a*]pyridine, as described above, and did not yield *s*-triazolo[4,3-*a*]pyridin-3-ol (**1**, R = OH). The 3-amino product was also stable to the action of hot, dilute mineral acid. Attempts to introduce a bromine substituent into the nucleus were unsuccessful and there appears to be little contribution from resonance forms utilizing the donor properties of the amino group.

An alternative way of obtaining 3-halogen-substituted compounds in this series was the action of phosphorus halides on the corresponding 3-hydroxy compounds. Of the various methods described in the literature for related systems, that using phosphoryl chloride and dimethylaniline was found to be the most satisfactory, though yields of the order of only 15% were obtained. The use of phenylphosphonic dichloride or of phosphoryl chloride–phosphorus pentachloride was not satisfactory. Methylation of the 3-hydroxy compound gave 2-methyl-*s*-triazolo[4,3-*a*]-pyrid-3-one whether dimethyl sulfate and alkali or diazomethane in methanol was used. No O-methylation product was observed. That N-methylation had occurred was evident from the spectral data, especially the presence of a strong carbonyl band at 1700 cm.$^{-1}$ in the infrared spectrum and a band at τ 6.35 indicative of an N-methyl group in the n.m.r. spectrum. Associated with the 2-methyl product from the dimethyl sulfate and alkali reaction was a high-melting product of unknown constitution whose empirical composition was represented by $C_{14}H_{16}N_6O_3$ and which had a typical amidic-type infrared spectrum, probably formed by further methylation of the 2-methyl product with subsequent ring opening occurring in the presence of alkali.

(17) K. T. Potts and C. Hirsch, unpublished results.
(18) V. K. Matveev, *Bull. Acad. Sci. URSS, Classe Sci. Math. Nat., Ser. Chem.*, 1005 (1936); *Chem. Abstr.*, **31**, 5364[7] (1937).
(19) M. Scholtz, *Ber.*, **45**, 734, 1718 (1912).

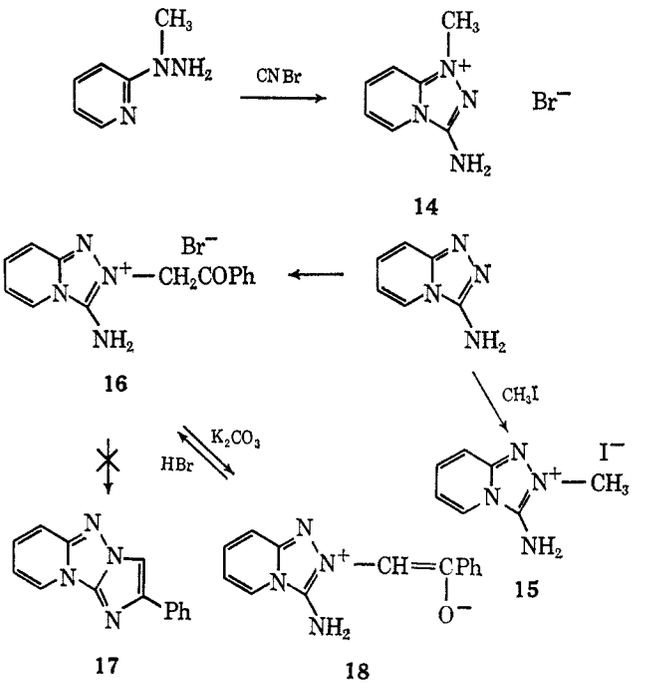
The 3-thiol underwent oxidation reactions very readily. With potassium ferricyanide it formed the corresponding disulfide in excellent yield except when a 5-methyl substituent was present as in 5-methyl-s-triazolo[4,3-a]pyridine-3-thiol. The lower yield obtained in this case would appear to be the result of steric interaction between the substituents in the 3- and 5-positions. With nitric acid the 3-thiol underwent oxidation to an unstable, intermediate sulfinic acid that decomposed rapidly to sulfur dioxide and the corresponding s-triazolo[4,3-a]pyridine. This desulfurization was not successful with commercial Raney nickel. A similar resistance to nucleophilic displacement observed for the 3-halogen substituent was found for the 3-methylthio group in methyl-3-s-triazolo[4,3-a]pyridyl sulfide (**11**), obtained from the 3-thiol and methyl iodide in the presence of base. It is interesting that this same methylthio product was obtained from the thiol and diazomethane in methanol. The methylthio group in s-triazole likewise cannot be displaced with nucleophiles, in contrast to the lability of this group in the pyridine and pyrimidine series. This reaction points out the more effective electron delocalization present in the s-triazole series and also in the s-triazole ring of the bicyclic system.

Protonation and salt formation occurred at N-1 except in the case of 3-amino-s-triazolo[4,3-a]pyridine where salt formation took place at N-2. Molecular orbital calculations (Table I) indicate N-1 to be the most basic nitrogen atom and salt formation at N-2 in the 3-amino product is readily understandable in terms of the partial amidine system present in that molecule. It has not been possible to establish beyond doubt the position of protonation from ultraviolet absorption data,[20] but that salt formation occurred at N-1 was shown unequivocally in the following manner. Treatment of methyl-3-s-triazolo[4,3-a]pyridyl sulfide (**11**) with methyl iodide gave 1-methyl-3-methylthio-s-triazolo[4,3-a]pyridinium iodide (**12**). An identical product was obtained from anhydro-1-methyl-3-mercapto-s-triazolo[4,3-a]pyridinium hydroxide (**13**) and methyl iodide, the mesoionic product having been prepared from 1-methyl-1-(2-pyridyl)hydrazine and thiophosgene.[21] Thus, the methylation product of s-triazolo[4,3-a]pyridine can be confidently assigned the structure represented by 1-methyl-s-triazolo[4,3-a]pyridinium iodide.



1-Methyl-1-(2-pyridyl)hydrazine was also a satisfactory starting point for establishing the structure of the methylation product of 3-amino-s-triazolo[4,3-a]pyridine. With cyanogen bromide, the hydrazine was found[22] to undergo an extremely facile ring closure to yield 3-amino-1-methyl-s-triazolo[4,3-a]pyridinium bromide (**14**). Treatment of 3-amino-s-triazolo[4,3-a]pyridine with methyl iodide readily gave a quaternary iodide which, with silver bromide, yielded the corresponding bromide. This was not identical with the bromide prepared above and, as methylation of the primary amino group was excluded by the presence of amino group bands at 3335, 3280, and 1668 cm.$^{-1}$ in the infrared spectrum, quaternization must have occurred at N-2 to give **15**. Reaction of 3-amino-s-triazolo[4,3-a]pyridine with phenacyl bromide also yielded a quaternary salt, represented as 3-amino-2-phenacyl-s-triazolo[4,3-a]pyridinium bromide (**16**). Reaction at the primary amino group is unlikely, as 2-aminopyridine has been shown to yield 2-phenylimidazolo[1,2-a]pyridine which can only be accounted for by the formation of an intermediate 1-phenacyl-2-aminopyridinium bromide.[23] With 5-amino-1,2,4-thiadiazole reaction has been shown to occur[24] at the N-4 position, and similarly it is the pyrimidine nitrogen atom that is involved in the initial condensation in 2-aminopyrimidine.[25]

CHART II



Treatment of the salt **16** with base was a possible route to the tricyclic ring system (**17**), but instead, an

(20) W. L. F. Armarego, *J. Chem. Soc.*, 2778 (1965).

(21) K. T. Potts and S. K. Roy, unpublished results.

(22) This ring closure with cyanogen bromide has been found to be a general reaction of substituted hydrazines of this type. These results will be reported in another communication; see also ref. 9d.

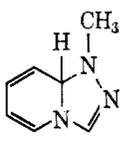
(23) Reaction will occur, however, at the amino group in the form of its lithium salt: F. Kröhnke, B. Kickhöfen, and B. Thoma, *Chem. Ber.*, **88**, 1117 (1955).

(24) J. Goerdeler and W. Roth, *ibid.*, **96**, 534 (1963); T. Pyl, F. Waschk, and H. Beyer, *Ann.*, **663**, 113 (1963).

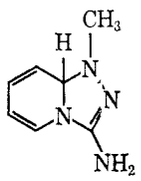
(25) T. Matsukawa and S. Ban, *J. Pharm. Soc. Japan*, **71**, 760 (1951); N. P. Buu-Hoï and N. Dat Xuong, *Compt. rend.*, **243**, 2090 (1956).

unstable solid was obtained which, in view of its red color in solution[26] and its ready reversion to the salt **16** with acid, is probably the enol betaine **18** (see Chart II).

The ultraviolet absorption data for these quaternized derivatives (Experimental Section) were not sufficiently distinctive to make structural assignments solely on the basis of this evidence. Reduction of these quaternary salts was readily effected with sodium borohydride. On the basis of analytical and infrared data (Experimental Section), the unstable base obtained from the reduction of 1-methyl-*s*-triazolo[4,3-*a*]pyridinium iodide was assigned structure **19**. A similar reduction pattern was observed with 1-methyl-3-amino-*s*-triazolo-[4,3-*a*]pyridinium bromide which yielded the base **20**, showing only strong end absorption in its ultraviolet spectrum.



19



20

The 3-methyl group of 3-methyl-*s*-triazolo[4,3-*a*]-pyridine was not sufficiently reactive to undergo condensation with iodine and pyridine to give the corresponding pyridinium salt.[27] The product obtained was 3-methyl-*s*-triazolo[4,3-*a*]pyridine hydriodide, and in this respect the behavior was analogous to that observed with 3-methyl-*s*-triazole.[28] The 3-methyl group was also inert to metalation with butyllithium and did not undergo condensation with benzaldehyde.

Experimental Section[29]

Potassium Permanganate Oxidation of *s*-Triazolo[4,3-*a*]pyridine.—*s*-Triazolo[4,3-*a*]pyridine (1.0 g., 0.008 mole) was warmed at 50–60° with potassium permanganate solution (7.4 g. in 220 ml. of water) for 2 hr. The manganese dioxide was removed by filtration and the filtrate was concentrated to one-fifth of its original volume under reduced pressure, using a rotatory evaporator. The concentrate was just acidified with hydrochloric acid and the product which separated (0.55 g., 58%) by solution and reprecipitation was obtained as colorless prisms, m.p. 136°. This product was identical in all respects with an authentic sample of *s*-triazole-3-carboxylic acid.

Rearrangement of the *s*-Triazolo[4,3-*a*]pyridine System to the *s*-Triazolo[1,5-*a*]pyridine System.—The following procedures illustrate the conditions used.

A. *s*-Triazolo[1,5-*a*]pyridine.—*s*-Triazolo[4,3-*a*]pyridine (2.0 g.) was heated under reflux in aqueous sodium hydroxide solution (50 ml., 50%) for 48 hr. The brown solution was extracted with ether in a continuous extractor for 5 days. The ether solution was dried (Na_2SO_4) and concentrated when a white residue mixed with a little oil was obtained. The solid product was dissolved in ether (50 ml.) and concentrated to give a white crystalline material, 1.3 g., m.p. 97–100°, which crystallized from petroleum ether (b.p. 60–90°) as colorless needles, m.p. 100–102°. The material was identical in all respects with *s*-triazolo[1,5-*a*]pyridine prepared by the method below and by ring closure of 1,2-diaminopyridinium iodide.

The aqueous solution was treated with acetic acid (pH 7) and again extracted continuously with ether for 72 hr. The ether solution afforded an oil (0.15 g.) which was identified as *s*-triazolo[4,3-*a*]pyridine by conversion into its picrate.

B. 2-Amino-*s*-triazolo[1,5]pyridine.—3-Amino-*s*-triazolo-[4,3-*a*]pyridine (20 g., 0.15 mole) was heated under reflux with sodium hydroxide solution (50 ml., 10%) for 48 hr. The alkaline solution was extracted with chloroform in a continuous extractor for 72 hr. After drying (Na_2SO_4) and evaporation of the chloroform extract, a crystalline product, 17.7 g. (89%), was obtained. It crystallized from benzene as colorless needles: m.p. 108–109°; infrared ($CHCl_3$), cm.$^{-1}$, 3448, 3356 (NH_2), 2941 (aromatic); $\lambda_{max}^{CH_3OH}$, mμ (log ε), 313 (3.42), 304 (3.50), 299 (3.55), 292 (3.51), 277 (3.56), 273 (sh) (3.54), 212 (4.39); n.m.r. (saturated solution in $CDCl_3$), τ 1.67 (7-H), 2.65 (4-H and 5-H), 3.26 (6-H), 4.44 (NH_2).

Anal. Calcd. for $C_6H_6N_4$: C, 53.7; H, 4.5; N, 41.8; mol. wt., 134. Found: C, 53.8; H, 4.3; N, 41.9; mol. wt., 140.

By the above method, 2-methylthio-*s*-triazolo[1,5-*a*]pyridine was obtained by rearrangement of 3-methylthio-*s*-triazolo-[4,3-*a*]pyridine as colorless needles from benzene–petroleum ether (b.p. 30–60°), m.p. 67–68°.

Anal. Calcd. for $C_7H_7N_3S$: C, 50.9; H, 4.3; N, 25.5. Found: C, 51.0; H, 4.5; N, 25.3.

Diazotization of 2-Amino-*s*-triazolo[1,5-*a*]pyridine. A. Deamination to *s*-Triazolo[1,5-*a*]pyridine.—A sulfuric acid solution (102 ml. in 50 ml. of water) was cooled to −10 to −15°, and sodium nitrite (3.7 g., 0.054 mole) was added over a period of 15 min. Cooled hypophosphorous acid (19.3 ml., 0.186 mole) was added slowly in small portions over a period of 15 min. and a solution of 2-amino-*s*-triazolo[1,5-*a*]pyridine (2.5 g., 0.018 mole) in acetic acid (100 ml.) was then added over a period of 1 hr. The temperature was kept below −10° and, after the addition was completed, the reaction mixture was stirred for 1 hr. and the temperature was allowed to rise to 0°. The reaction mixture was carefully basified at *ca.* 0° with sodium hydroxide solution and the alkaline reaction mixture was then extracted with ether in a continuous extractor for 72 hr. After drying the ether extract (Na_2SO_4), removal of the ether left the crude product as light tan prisms. Recrystallization from benzene yielded *s*-triazolo[1,5-*a*]pyridine, 0.7 g. (33%), as colorless needles: m.p. 100–102°; infrared ($CHCl_3$), cm.$^{-1}$, 2941 (CH), 1637, 1506, 1443 (aromatic), other strong bands at 1332, 1264, 1178, 1155, 961, 908, 901; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 282 (sh) (3.27), 273 (sh) (3.49), 258 (3.61); n.m.r. (33 mg./0.5 ml. of $CDCl_3$), τ 1.36 (7-H), 1.59 (2-H), 2.23 (4-H), 2.53 (5-H), 3.01 (6-H).

Anal. Calcd. for $C_6H_5N_3$: C, 60.5; H, 4.2; N, 35.3. Found: C, 60.3; H, 4.2; N, 35.1.

B. The Formation of 2-Chloro-*s*-triazolo[1,5-*a*]pyridine.—2-Amino-*s*-triazolo[1,5-*a*]pyridine (2.0 g., 0.015 mole) was dissolved in hydrochloric acid (20 ml.) and water (10 ml.) and cooled to −5° in an ice bath. After addition of a small amount of copper powder (*ca.* 200 mg.), sodium nitrite (2.3 g. in 8 ml. of water) was added dropwise over a period of 45 min., keeping the temperature below −5°, and after the addition was completed, the reaction mixture was transferred to a steam bath and was warmed for 1 hr. The solution was made alkaline with sodium hydroxide solution and extracted with ether (four 60-ml. portions) and the ether extracts were dried (Na_2SO_4). Removal of the ether left a pale yellow oil which crystallized on cooling. The product crystallized from benzene–petroleum ether as pale yellow needles: 1.2 g. (52%); m.p. 110–111.5°; infrared ($CHCl_3$), cm.$^{-1}$, 2950 (CH), 1639, 1506 (aromatic), other strong bands at 1414, 1366, 1333, 1289, 1147, 986; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 283 (3.27), 273 (sh) (3.49), 258 (3.61); n.m.r. (saturated solution in $CDCl_3$), τ 1.45 (7-H), 2.36 (4-H and 5-H), 2.93 (6-H).

Anal. Calcd. for $C_6H_4ClN_3$: C, 46.9; H, 2.6; N, 27.4. Found: C, 47.1; H, 2.7; N, 27.1.

(26) A. E. Tschitschibabin, *Ber.*, **59**, 2048 (1926); K. Schilling, F. Kröhnke, and B. Kickhöfen, *ibid.*, **88**, 1093 (1955); F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

(27) J. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956); W. Rerd and H. Bender, *Chem. Ber.*, **89**, 1893 (1956); W. Rerd and R. M. Gross, *ibid.*, **90**, 2646 (1957).

(28) K. T. Potts and G. Smith, unpublished results.

(29) Infrared spectra were measured with a Baird IR 2 spectrophotometer and with a Perkin-Elmer Model 421 spectrophotometer, and ultraviolet absorption spectra were determined using a Beckman DK2 spectrophotometer. Analyses were by Galbraith Laboratories, Knoxville, Tenn. N.m.r. 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 TMS as internal standard and usual methods of calibration. We are indebted to Dr. T. H. Crawford and Dr. S. W. Thomas for their assistance in the determination of these spectra. All evaporations were carried out using a Rotovap apparatus and products were established as being identical through mixture melting point determinations and infrared and ultraviolet spectral data.

This product was identical in all respects with that obtained by rearrangement of 3-chloro-s-triazolo[4,3-a]pyridine by the method described above.

Reaction of s-Triazolo[4,3-a]pyridine with Dimethyl Acetylenedicarboxylate.—s-Triazolo[4,3-a]pyridine (0.6 g.) was dissolved in dry benzene (40 ml.) and, after 10 ml. of benzene was distilled off, dimethyl acetylenedicarboxylate (0.7 g.) was added and the reaction mixture was heated under reflux for 14 hr. After removal of the solvent, the dark residue was dissolved in benzene–chloroform (20 ml., 1:1) and absorbed onto a column of alumina (activity II, 30 g.); elution with benzene (200 ml.) and chloroform (120 ml.) yielded a yellow solid (0.4 g.). 3-(3-Methoxycarbonyl-1-oxopropynyl)-s-triazolo[4,3-a]pyridine (**9**) crystallized from chloroform–methanol as yellow needles: m.p. 242–243° dec.; infrared (KBr), cm.$^{-1}$, main bands 3115, 3090, 2223, 1725, 1703, 1626, 1565, 1490, 1455, 1337, 1296, 1272, 1253, 1222, 1135, 1035; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 312 (3.60), 268 (3.95).

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.6; H, 3.1; N, 18.3. Found: C, 57.8; H, 3.0; N, 18.45.

Reaction of s-Triazolo[4,3-a]pyridine with Tetracyanoethylene.—s-Triazolo[4,3-a]pyridine (0.6 g.) in dry benzene (30 ml.) was heated under reflux with tetracyanoethylene (0.7 g.) for 6 hr. The dark solution was poured onto a column of alumina (activity II, 25 g.) and eluted with chloroform–methanol (200 ml., 1:1). Evaporation of the solvent left a brown oil which crystallized from methanol–ether (charcoal) as colorless needles, 0.15 g., m.p. 156–157°, and was identified as 3-(1,1-dimethoxy-2,2-dicyanoethyl)-s-triazolo[4,3-a]pyridine (**10**): infrared (KBr), cm.$^{-1}$, main bands at 3110, 2970, 2186, 2160, 1635, 1544, 1434, 1320, 1116, 775, 752; $\lambda_{max}^{CH_3OH}$, mμ (log ε), 295 (sh) (3.61), 283 (3.83), 275 (sh) (3.82), 236 (4.23); n.m.r. [0.04 g./0.5 ml. of $(CD_3)_2SO$], τ 5.73, 6.57 (OCH_3), 0.27 (5-H), 1.05 (8-H), 1.69–1.79 (7-H), 2.40 (6-H).

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.0; H, 4.3; N, 27.4. Found: C, 55.9; H, 4.4; N, 27.4.

Under analogous reaction conditions, no reaction occurred with phenylacetylene and diphenylacetylene.

Bromination of the s-Triazolo[4,3-a]pyridine Nucleus. A. 3-Bromo-s-triazolo[4,3-a]pyridine.—s-Triazolo[4,3-a]pyridine (1.0 g., 0.008 mole) was dissolved in methanol (15 ml.), excess bromine (8 ml.) was added, and the reaction mixture was kept overnight at room temperature. Water (10 ml.) was added and the contents were heated on a steam bath to remove the excess bromine. After cooling to room temperature, the solid product was collected by filtration and treated with a 10% sodium hydroxide solution. The free base (1.0 g., 60%) was collected, and it crystallized from benzene as colorless plates, m.p. 165°. This product was identical in all respects with 3-bromo-s-triazolo[4,3-a]pyridine obtained by diazotization of 3-amino-s-triazolo[4,3-a]pyridine described below.

B.—3,8-Dibromo-5,7-dimethyl-s-triazolo[4,3-a]pyridine (0.5 g., 48%) was prepared in the same way by direct bromination of 5,7-dimethyl-s-triazolo[4,3-a]pyridine (0.5 g.). It crystallized from benzene as colorless needles, m.p. 212–213° dec.

Anal. Calcd. for $C_8H_7Br_2N_3$: C, 31.5; H, 2.3; N, 13.8. Found: C, 31.6; H, 2.3; N, 13.9.

3-Methyl-s-triazolo[4,3-a]pyridine Hydrobromide. A.—3-Methyl-s-triazolo[4,3-a]pyridine (1.0 g., 0.008 mole) was dissolved in acetic acid (15 ml.), and bromine (4 g.) was added dropwise. After 15 min. at room temperature, the reaction mixture was then poured onto ice. The crude product was collected, and it crystallized from ethanol as colorless needles, 0.9 g. (56%), m.p. 333°.

Anal. Calcd. for $C_7H_8BrN_3$: C, 39.3; H, 3.8; N, 19.6. Found: C, 39.4; H, 3.5; N, 19.5.

B.—Aqueous hydrobromic acid (2 ml., 48%) was added to 3-methyl-s-triazolo[4,3-a]pyridine (1.0 g.) in methanol (12 ml.). Ether was added to the solution and the resulting solid was collected by filtration. The hydrobromide crystallized from methanol as colorless needles, 0.8 g. (44%), m.p. 333°. This product was identical in all respects to the compound that was prepared by method A.

When 3,6-dimethyl-s-triazolo[4,3-a]pyridine was treated with bromine under analogous conditions, only its hydrobromide was isolated from the reaction mixture. It crystallized from methanol–ether (charcoal) as colorless needles, m.p. 288–300° dec. The mixture melting point determination and infrared spectral comparison showed the product to be identical with 3,6-dimethyl-s-triazolo[4,3-a]pyridine hydrobromide, prepared in the same way as above.

Anal. Calcd. for $C_8H_{10}BrN_3$: C, 42.1; H, 4.4; N, 18.4. Found: C, 41.9; H, 4.3; N, 17.9.

3-Benzamido-s-triazolo[4,3-a]pyridine was prepared from the 3-amino compound and benzoyl chloride using standard procedures. It was isolated by evaporation of the aqueous solution to dryness, and it crystallized from ethanol as colorless needles, m.p. 206–207°.

Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.4; H, 4.1; N, 23.5.

3-Benzalamino-s-triazolo[4,3-a]pyridine was prepared from the 3-amino compound, an equivalent amount of benzaldehyde, and a catalytic amount of zinc chloride in boiling ethanol for 2 hr. After removal of the zinc chloride by filtration, the addition of petroleum ether and chloroform induced crystallization of unreacted 3-amino compound. The mother liquor was concentrated, and the residue was crystallized from benzene–petroleum ether whence 3-benzalamino-s-triazolo[4,3-a]pyridine separated as yellow needles (18%), m.p. 134–135°.

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.3; H, 4.5; N, 25.2. Found: C, 70.5; H, 4.7; N, 25.1.

The Diazotization of 3-Amino-s-triazolo[4,3-a]pyridine. A. The Preparation of 3-Chloro-s-triazolo[4,3-a]pyridine.—The 3-amino compound (12.0 g.) in hydrochloric acid (120 ml. of acid and 60 ml. of water) at 0° was treated with sodium nitrite solution (13.8 g. in 50 ml. of water) in the presence of a small amount (*ca.* 200 mg.) of copper powder over 1 hr. After an additional 30 min. the temperature of the reaction mixture was slowly raised to room temperature and the diazonium salt was then decomposed by controlled heating on the steam bath. After a further 30 min. heating, the solution was basified with concentrated sodium hydroxide solution and then extracted with ether in a continuous ether extractor for 96 hr. The yield of 3-chloro-s-triazolo[4,3-a]pyridine, m.p. 125°, was 12.1 g. (87%) and it was identical in all respects with the product prepared from 3-hydroxy-s-triazolo[4,3-a]pyridine and phosphoryl chloride described below.

3-Bromo-s-triazolo[4,3-a]pyridine was prepared in a similar manner, using hydrobromic acid, except that the bromo product separated from the alkaline solution. It crystallized from benzene as pale yellow needles (37%), m.p. 165°.

Anal. Calcd. for $C_6H_4BrN_3$: C, 36.4; H, 2.0; N, 21.2. Found: C, 36.5; H, 2.1; N, 21.3.

B. The Formation of s-Triazolo[4,3-a]pyrid-3-ylazo-2-naphthol.—The 3-amino compound (1.0 g.) was dissolved in aqueous nitric acid (40 ml., 10%) and then cooled to −5°, when the nitrate separated. An aqueous solution of sodium nitrite (0.8 g. in 3 ml. of water) was added dropwise with vigorous stirring so that the temperature did not rise above −5°. After the addition, the reaction mixture was added to a cold solution of 2-naphthol (1.0 g.) in ethanol (20 ml.) when immediately a gummy material separated which, on trituration with methanol, gave a deep brown solid (0.12 g.). It was crystallized three times from methanol–chloroform (charcoal) and twice from methanol–petroleum ether when it separated as deep, reddish brown plates, m.p. 219–220° dec.

Anal. Calcd. for $C_{16}H_{11}N_5O$: C, 66.4; H, 3.8; N, 24.2. Found: C, 66.35; H, 3.9; N, 24.3.

3-Chloro-s-triazolo[4,3-a]pyridine from s-Triazolo[4,3-a]pyridin-3-ol.—The 3-hydroxy compound (4.0 g.), phosphoryl chloride (30 ml.), and dimethylaniline (8 ml.) were heated together under reflux for 36 hr. After pouring the reaction mixture onto cracked ice, the resultant solution was concentrated to small bulk under reduced pressure on the steam bath and then made alkaline with 10% sodium hydroxide solution. The alkaline solution was extracted with ether (four 50-ml. portions); the ether extract was dried (Na_2SO_4) and then concentrated to small bulk and cooled to *ca.* −60°, whence 3-chloro-s-triazolo-[4,3-a]pyridine separated, 0.7 g. (15%), m.p. 125°. It crystallized from benzene–petroleum ether as lemon yellow needles, m.p. 125°.

Anal. Calcd. for $C_6H_4ClN_3$: C, 46.9; H, 2.6; N, 27.4. Found: C, 47.0; H, 2.7; N, 27.1.

Reaction of s-Triazolo[4,3-a]pyridin-3-ol with Methyl Sulfate.—The 3-hydroxy compound (2.7 g.) was dissolved in aqueous sodium hydroxide solution (20 ml., 10%), and to it was added dropwise methyl sulfate (2 ml.) while the mixture was thoroughly stirred. After 15 min., more sodium hydroxide (5 ml., 50%) was added, and after a further 30 min., methyl sulfate (1 ml.) was added and the mixture was then stirred for an additional 30 min. The brown solution was extracted with

chloroform (five 30-ml. portions) and, after drying (Na_2SO_4) and concentration of the extract, an oily residue was obtained (1.5 g.) which solidified. It was dissolved in methanol (charcoal) and dilution with ether yielded yellow needles (70 mg.) which were repeatedly recrystallized from methanol–ether and obtained as yellow needles: m.p. 217–219° dec.; infrared (KBr), cm.$^{-1}$, main bands at 3400, 3070, 3040, 1676, 1655, 1628, 1540, 1530, 1230, 750, 655.

Anal. Calcd. for $C_{14}H_{16}N_6O_3$: C, 53.2; H, 5.1; N, 26.6. Found: C, 53.2; H, 5.2; N, 26.3.

The mother liquor was concentrated to a small volume and ether was added. The yellow solid (0.9 g.) which separated crystallized from methanol and also from ether as pale yellow needles, m.p. 112–113°.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.4; H, 4.7; N, 28.2. Found: C, 56.2; H, 4.7; N, 28.0.

The same product was obtained from *s*-triazolo[4,3-*a*]pyridin-3-ol (0.5 g.) in methanol (50 ml.) and ethereal diazomethane (2 g.) and has been identified as 2-methyl-*s*-triazolo[4,3-*a*]-pyrid-3-one: infrared (KBr), cm.$^{-1}$, main bands at 1700, 1635, 1528, 1354, 882, 745; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 329 (3.44), 277 (3.37), 267 (3.50), 260 (sh) (3.46); n.m.r. (saturated solution in $CDCl_3$), τ 2.28 (5-H), 2.91 (7- and 8-H), 3.54 (6-H), 6.35 (N-CH_3).

Methyl-3-*s*-triazolo[4,3-*a*]pyridyl Sulfide. A.—*s*-Triazolo-[4,3-*a*]pyridine-3-thiol (1.6 g., 0.01 mole) was dissolved in aqueous sodium hydroxide solution (12 ml., 1 *N*) and was shaken with excess methyl iodide (0.8 ml., 0.013 mole) for 15 min. The reaction was considered complete when the reaction mixture turned from the orange to a yellow color. The alkaline reaction mixture was extracted with chloroform (two 15-ml. portions) and dried (Na_2SO_4). After removal of the chloroform, the residue was recrystallized twice from benzene–petroleum ether from which the sulfide separated as pale yellow plates, 1.2 g. (68%), m.p. 92–94°.

Anal. Calcd. for $C_7H_7N_3S$: C, 50.9; H, 4.3; N, 25.5. Found: C, 51.1; H, 4.5; N, 25.3.

B.—A solution of the 3-thiol (0.5 g.) in methanol (50 ml.) was added to ethereal diazomethane (2 g.) and left at room temperature for 12 hr. The solvent was removed, the oily residue was taken up in benzene (charcoal), and the product separated on the addition of petroleum ether. It crystallized from benzene–petroleum ether as pale yellow plates, 0.42 g., m.p. 93–95°, identical in all respects with the product obtained above: infrared (Nujol), cm.$^{-1}$, main bands at 1630, 1460, 1380, 1300, 1048, 1000, 982, 918, 773, 754, 746, 680; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 291 (sh) (3.60), 272 (3.70), 267 (sh) (3.69); n.m.r. (0.035 g./0.3 ml. of $CDCl_3$), τ 1.93 (5-H), 2.28 (8-H), 2.72 (7-H), 3.10 (8-H), 7.29 (S-CH_3).

3,3′-Dithiodi-*s*-triazolo[4,3-*a*]pyridine.—*s*-Triazolo[4,3-*a*]pyridine-3-thiol (4.0 g., 0.027 mole) was dissolved in aqueous sodium hydroxide solution (35 ml., 1 *N* solution) and titrated with potassium ferricyanide (47 ml., 1 *N* solution) until no further yellow precipitate formed. The precipitated material crystallized from ethanol as yellow needles, 3.9 g. (99%), m.p. 240° dec.

Anal. Calcd. for $C_{12}H_8N_6S_2$: C, 48.0; H, 2.7; N, 28.0. Found: C, 48.4; H, 2.7; N, 27.6.

Similarly, **3,3′-dithiodi(5-methyl-*s*-triazolo[4,3-*a*]pyridine)** was prepared from 5-methyl-*s*-triazolo[4,3-*a*]pyridine-3-thiol (6.7 g., 0.4 mole) in aqueous sodium hydroxide solution (55 ml., 1 *N*) and potassium ferricyanide solution (50 ml., 1 *N*). It crystallized from dimethylformamide as yellow, irregular prisms, 3.6 g. (47%), m.p. 255° dec.

Anal. Calcd. for $C_{14}H_{12}N_6S_2$: C, 51.1; H, 3.7; N, 25.6. Found: C, 51.4; H, 4.0; N, 25.4.

1-Methyl-3-methylthio-*s*-triazolo[4,3-*a*]pyridinium Iodide. A.—Methyl-3-*s*-triazolo[4,3-*a*]pyridyl sulfide (0.5 g.) in methanol (5 ml.) was treated with methyl iodide (1.0 ml.) and left at room temperature for 4 hr. and then warmed on the steam bath for 15 min. Dilution with ether yielded a pale yellow solid (0.6 g.). It crystallized from methanol–ether as colorless needles, m.p. 215–217° dec., with sintering at 210°. The mixture melting point determination and infrared spectral comparison showed it to be identical with a sample of 1-methyl-3-methylthio-*s*-triazolo[4,3-*a*]pyridinium iodide prepared below.

B.—Anhydro-1-methyl-3-mercapto-*s*-triazolo[4,3-*a*]pyridinium hydroxide (0.5 g.), suspended in methanol (20 ml.), was treated with methyl iodide (5 ml.) and heated on the steam bath for 10 min. Dry ether was added to the clear solution and 1-methyl-3-methylthio-*s*-triazolo[4,3-*a*]pyridinium iodide crystallized as shiny, cream plates: 0.70 g. (75%); m.p. 215–217°; infrared (Nujol), cm.$^{-1}$, main bands at 1634, 1520, 1445, 1370, 1308, 1272, 1240, 1163, 1134, 1040, 980, 772, 742; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 300 (3.64), 276 (3.70), 269 (3.70), 221 (4.44). The melting point was not raised on recrystallization from methanol from which it separated as colorless plates.

Anal. Calcd. for $C_8H_{10}IN_3S$: C, 31.3; H, 3.3; N, 13.7. Found: C, 31.5; H, 3.3; N, 13.7.

1-Methyl-*s*-triazolo[4,3-*a*]pyridinium Iodide.—*s*-Triazolo[4,3-*a*]pyridine (0.5 g.) in methanol (5 ml.) was treated with methyl iodide (1 ml.) and left overnight. Dilution of the reaction mixture with ether gave a pale yellow solid (0.7 g.) which crystallized from methanol–ether (charcoal) as colorless needles: m.p. 198–200°; infrared (Nujol), cm.$^{-1}$, main bands at 1640, 1500–1560, 1450, 1370, 1336, 1290, 1258, 1242, 1190, 1165, 1145, 1020, 927, 870, 830, 794, 762, 740–730; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 278 (3.74), 270 (sh) (3.69).

Anal. Calcd. for $C_7H_8IN_3$: C, 32.2; H, 3.1; N, 16.1. Found: C, 32.5; H, 3.3; N, 16.3.

3-Amino-2-methyl-*s*-triazolo[4,3-*a*]pyridinium Iodide.—The 3-amino compound (2.0 g.) in methanol (25 ml.) was treated with methyl iodide (3 ml.) and left overnight. The solution upon concentration gave a white solid (1.8 g.). It crystallized from methanol (charcoal) as colorless needles, m.p. 273–275° dec.

Anal. Calcd. for $C_7H_9IN_4$: C, 30.4; H, 3.3; N, 20.3. Found: C, 30.5; H, 3.5; N, 20.5.

The methiodide (0.5 g.) was refluxed in aqueous methanol with silver bromide (4.0 g.) for 16 hr. The corresponding bromide crystallized from methanol–ether and finally from methanol as colorless needles: m.p. 288–289° dec.; infrared (KBr), cm.$^{-1}$, main bands at 3335, 3280, 3200, 3035, 1668, 1552, 1400, 1240, 1150, 872, 754, 674; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 309 (3.51), 275 (3.48), 264 (3.52), 254 (infl.) (3.44).

Anal. Calcd. for $C_7H_9BrN_4$: C, 36.7; H, 3.9; N, 24.45. Found: C, 37.0; H, 4.05; N, 24.4.

3-Amino-1-methyl-*s*-triazolo[4,3-*a*]pyridinium Bromide.—1-Methyl-1-(2-pyridyl)hydrazine[30] (12.3 g., 0.1 mole) and cyanogen bromide (10.6 g., 0.1 mole) in methanol (150 ml.) were mixed together. An exothermic reaction immediately set in. After 1 hr. reflux, the methanol was removed from the reaction mix- under reduced pressure and the crystalline residue then was recrystallized from methanol–ether (charcoal) from which the bromide separated as shiny, cream plates: 14.5 g. (63%); m.p. 247°; infrared (KBr), cm.$^{-1}$, main bands at 3400, 3260, 3100, 1670, 1652, 1530, 1420, 1150, 1065, 765, 745; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 321 (4.0), 267 (3.86), 229 (4.21).

Anal. Calcd. for $C_7H_9BrN_4$: C, 37.6; H, 4.0; N, 24.45. Found: C, 36.6; H, 4.0; N, 24.3.

3-Amino-2-phenacyl-*s*-triazolo[4,3-*a*]pyridinium Bromide.—3-Amino-*s*-triazolo[4,3-*a*]pyridine (0.67 g., 0.005 mole) was dissolved in ethanol (15 ml.). Phenacyl bromide (1.0 g., 0.005 mole) was added to the solution and the reaction was heated on a steam bath for 30 min. The product which formed was collected by filtration; it crystallized from aqueous methanol as colorless plates: 1.1 g. (65%); m.p. 298° dec.; $\lambda_{max}^{CH_3OH}$, mμ (log ϵ), 275 (3.66), 245 (4.29).

Anal. Calcd. for $C_{14}H_{13}N_4O$: C, 50.5; H, 3.9; N, 16.8. Found: C, 50.5; H, 3.7; N, 17.0.

Treatment of 3-Amino-2-phenacyl-*s*-triazolo[4,3-*a*]pyridinium Bromide with Base.—A suspension of the above bromide (3.0 g.) in ethanol (30 ml.) was treated with a saturated solution of potassium carbonate (10 ml.) and warmed on a steam bath for 20 min. when the initial yellow solution turned a final, reddish brown color. After removal of the alcohol under reduced pressure, the residue was diluted with water (10 ml.) and extracted with chloroform (90 ml.). After drying (K_2CO_3) and concentration of the yellow chloroform extract, a deep brown, oily residue (2.1 g.) was obtained which, after trituration with methanol–ether gave a yellow solid. Attempts to recrystallize this product resulted in extensive decomposition. It was finally dissolved in methanol, hydrobromic acid was added, and the cream solid (2.6 g.) which was obtained crystallized from aqueous methanol as colorless plates, m.p. 298° dec. The melting point was not depressed on admixture with 3-amino-2-phenacyl-*s*-triazolo[4,3-*a*]pyridinium bromide with which it had an identical infrared spectrum.

(30) G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 3202 (1959).

Reduction of 1-Methyl-*s*-triazolo[4,3-*a*]pyridinium Iodide with Sodium Borohydride.—The iodide (2.0 g.) in methanol (75 ml.) was treated with sodium borohydride (4.0 g.) at room temperature and the reaction mixture was left overnight. The solvent was removed and the residue was treated with water (20 ml.) and then extracted with chloroform (150 ml.). The chloroform solution was dried (Na_2SO_4) and concentrated to a light colored oil (0.8 g.) which rapidly darkened. A methanolic solution of the product was treated with picric acid and then diluted with ether, yielding a brown gum that eventually crystallized from methanol–ether (charcoal) as yellow needles, m.p. 186–187° dec.

Anal. Calcd. for $C_{13}H_{11}N_6O_7$: C, 42.8; H, 3.5; N, 22.9. Found: C, 42.9; H, 3.3; N, 23.1.

Reduction of 1-Methyl-3-amino-*s*-triazolo[4,3-*a*]pyridinium Bromide with Sodium Borohydride.—The bromide (0.5 g.) in methanol (30 ml.) was slowly treated with sodium borohydride (1.0 g.) at room temperature and then left for 1 hr. The solvent was removed on the steam bath, the residue was treated with water (10 ml.), and the aqueous solution was saturated with sodium sulfate and then extracted with chloroform (100 ml.). Evaporation of the chloroform solution gave an oil which was chromatographed on alumina (activity II, 25 g.) and eluted with chloroform (100 ml.) and a chloroform–methanol mixture (100 ml., 9:1). Removal of the combined solvents left an oily base which was converted into the hydrobromide. This crystallized from methanol–ether (charcoal) as colorless, irregular prisms: m.p. 191–193°, with previous sintering at 181°; infrared (Nujol), cm.$^{-1}$, 3100–2600, 1660, 1550, 1448, 1380, 1310, 1237, 1180, 1125, 1092, 1063, 1040, 982, 953, 910, 985–975, 692, 673; ultraviolet, strong end absorption only.

Anal. Calcd. for $C_7H_{11}BrN_4$: C, 36.4; H, 4.8; N, 24.2. Found: C, 36.5; H, 5.0; N, 24.5.

Reaction of 3-Methyl-*s*-triazolo[4,3-*a*]pyridine with Iodine and Pyridine.—3-Methyl-*s*-triazolo[4,3-*a*]pyridine (1.3 g.) in dry pyridine (10 ml.) was refluxed with iodine (1.3 g.) for 90 min. After removal of the pyridine under reduced pressure, the dark residue was dissolved in ethanol (charcoal) and treated with ether when a yellow solid (2.1 g.) separated. It crystallized from methanol–ether (charcoal) as colorless needles, m.p. 217–219° dec. The mixture melting point determination and infrared spectral comparison showed it to be identical with a sample of 3-methyl-*s*-triazolo[4,3-*a*]pyridine hydriodide prepared from the base and hydriodic acid by the method described above for the bromide.

Anal. Calcd. for $C_7H_8IN_3$: C, 32.2; H, 3.1; N, 16.1. Found: C, 32.3; H, 3.1; N, 15.7.

Deuteration of *s*-Triazolo[4,3-*a*]pyridine.—The base (0.1 g.) in deuterium oxide (3 ml.) was heated in a sealed tube in an atmosphere of nitrogen at 100° for 12 hr. The solvent was removed under reduced pressure, giving the 3-deuterio product as a low-melting solid: n.m.r. (infinite dilution, $CDCl_3$), τ 1.67 (5-H), 2.22 (8-H), 2.73 (7-H), 3.12 (6-H).

The following experiments illustrate reaction procedures which were unsuccessful when applied to this ring system.

Attempted Reaction of *s*-Triazolo[4,3-*a*]pyridine with Sodamide.—*s*-Triazolo[4,3-*a*]pyridine (1.0 g.) was dissolved in dry benzene (40 ml.), and after distillation of 15 ml. of solvent, sodamide (0.7 g.) was added and the mixture was refluxed for 7 hr. The benzene was decanted and the black tarry residue was washed with hot chloroform (two 15-ml. portions). The combined solution was concentrated and the oily residue (0.6 g.) was converted into the picrate, m.p. 235–237° dec. Mixture melting point determination showed the picrate to be identical with the picrate of *s*-triazolo[4,3-*a*]pyridine.

The dark tarry residue was decomposed with ice water (5 ml.); the solution was saturated with sodium sulfate and then extracted with chloroform (100 ml.). The chloroform solution, after drying (Na_2SO_4), was concentrated to a brown oil (0.34 g.) which was identified as impure starting material by conversion into its picrate.

When the reaction was carried out using dimethylaniline at 120° as solvent, only the starting material again was obtained.

Attempted Reaction of *s*-Triazolo[4,3-*a*]pyridine with Butyllithium.—*s*-Triazolo[4,3-*a*]pyridine (1.2 g.) in ether (300 ml.) was treated slowly with a solution of butyllithium (10 ml.) in dioxane in a nitrogen atmosphere, and the mixture was stirred for 3 hr. at room temperature. Dry carbon dioxide was bubbled through the dark brown reaction mixture for 45 min., and the black residue that was isolated immediately formed a gum. The untractable gummy residue in chloroform was poured through a column of alumina (activity II, 10 g.) and eluted with chloroform when only a very small amount of pungent oil was obtained.

Proton Magnetic Resonance Spectra of Isomeric N-Methyl-3(5)-H-pyrazoles

J. DONALD ALBRIGHT AND LEON GOLDMAN

Organic Chemical Research Section, Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York

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The p.m.r. spectra of isomeric N-methyl-3(5)-H-pyrazoles such as 1-methyl-4,5,6,7-tetrahydroindazole (**2**), 2-methyl-4,5,6,7-tetrahydroindazole (**3**), 1′-methylyohimbano[18,17-*d*]pyrazole (**5**), and 1′-methylyohimbano-[17,18-*c*]pyrazole (**6**) have been examined. The numerical differences in the chemical shifts between the N-methyl proton signal and the signal of the proton on the pyrazole nucleus are found to be characteristic for each isomer and can be used to assign structures to isomeric N-methyl-3(5)-H-pyrazoles.

A number of studies on the p.m.r. spectra of pyrazoles have been delineated recently. Williams[1] reported on the utility of p.m.r. for determining structures of isomers formed on acylation of unsymmetrically substituted pyrazoles while Moore and Habraken[2] described the use of p.m.r. for determining the tautomeric structures of 1-alkyl-3(5)-methylpyrazoles and 1-alkyl-3(5)-methyl-4-phenylpyrazoles, utilizing chemical shift differences between signals from the 3(5)-H and the 4-substituent and between signals from the 3(5)-H and the 5(3)-methyl. The chemical shifts of protons in the 3-, 4-, and 5-positions of the pyrazole nucleus and the chemical shifts of 3- and 5-methyl groups have been discussed by Finar and Mooney.[3] The characteristic ranges reported for the 3-, 4-, and 5-protons in various substituted pyrazoles and the characteristic shifts observed on protonation promise to be of use for an unambiguous assignment of structures.[3] We wish to report on some studies with isomeric N-methylpyrazoles such as **2** and **3**, for until now there has been no simple method for differentiating between isomeric pyrazoles of this type. Therefore a convenient method, such as p.m.r., for structural assignment of isomeric N-methylpyrazoles would be of considerable utility.

In connection with our alkaloid studies the pyrazoles **5** and **6** were prepared.[4] The p.m.r. spectra showed

(1) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).

(2) J. A. Moore and C. L. Habraken, *J. Am. Chem. Soc.*, **86**, 1456 (1964); C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30**, 1892 (1965).

(3) I. L. Finar and E. F. Mooney, *Spectrochim. Acta*, **20**, 1269 (1964).

(4) J. D. Albright and L. Goldman, to be published.