Mesoionic Compounds. XIII. 1,4-Dipolar-Type Cycloaddition Reactions of *anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium Hydroxide[1]

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Received June 24, 1970

The title six-membered mesoionic compound (1) undergoes cycloaddition reactions with acetylenic dipolarophiles to yield 1,2-disubstituted 4*H*-quinolizin-4-ones (3), with extrusion of methyl isocyanate. With tetracyanoethylene and diethyl azodicarboxylate, no cycloadducts were obtained; rather, substitution occurred at the 3 position of the nucleus. Reaction of 2-*N*-methylaminopyridine with carbon suboxide provided an extremely facile synthesis of the mesoionic compound 1.

In recent years numerous examples of the use of mesoionic compounds in cycloaddition reactions have been described.[2] These involved predominantly five-membered ring systems[3] and the ambident nature of the 1,3 dipole has been clearly shown.[4] Several six-membered mesoionic type ring systems have also been found[5] to undergo cycloadditions involving a 1,3-dipolar type intermediate and, in all cases, these cycloadditions have provided new and facile routes to new products. Our interest in mesoionic ring systems has led us to study a mesoionic type compound which would be capable of undergoing a 1,4-dipolar type cycloaddition reaction, and these results are described in this communication.

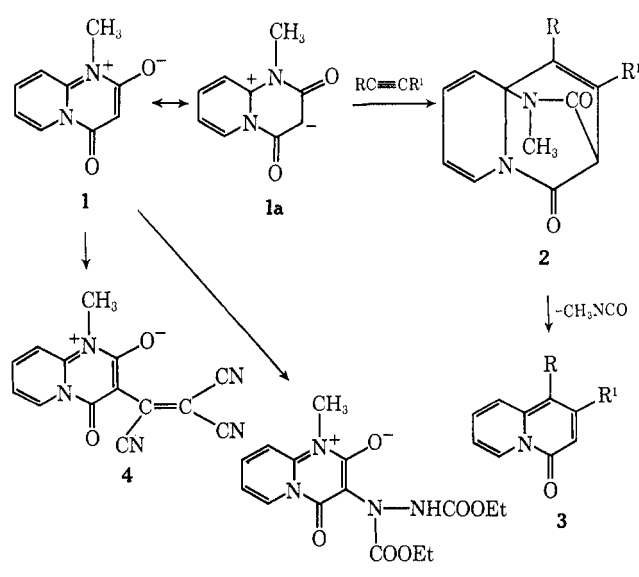
Cycloadditions[6] of the type [4 + 2 → 6] include the Diels–Alder reaction which has been the most extensively studied[7] of all cycloadditions. It has recently been shown that the reaction of isoquinoline and phenyl isocyanate is a cycloaddition of this general type. A two-step process involving a 1,4-dipolar intermediate is involved and this then undergoes reaction with additional phenyl isocyanate acting as a dipolarophile.[8] The considerable scope of the principle of 1,4-dipolar cycloadditions has recently been pointed out and our present results, with an endocyclic 1,4 dipole, are thus of particular interest.

Condensation of 2-aminopyridine with malonic ester has been shown to yield "malonyl α-aminopyridine" (pyrido[1,2-*a*]pyrimidine-2,4-dione) which has been shown to have considerable polar character.[9] Methylation occurred predominantly at N-1 and the resultant product 1 appeared to be a very good candidate for participation in 1,4-dipolar type cycloaddition reactions. *anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide (1) may be regarded as a six-membered mesoionic type compound and the 1,4-dipolar form represented by 1a is consistent with the octet–sextet representation of a 1,4 dipole employed earlier.[10]

Methylation of pyrido[1,2-*a*]pyrimidine-2,4-dione yields 1 in a moderate degree of purity only, and vacuum sublimation has to be used to obtain a pure product. We have now found that 1 can be prepared in excellent yield in a pure state from the reaction of 2-*N*-methylaminopyridine and carbon suboxide.

Dimethyl acetylenedicarboxylate was found to undergo reaction with 1 over 24 hr in boiling xylene with the formation of dimethyl 4*H*-quinolizin-4-one-1,2-dicarboxylate (3, R = R[1] = COOMe) in 64% yield. Nmr spectral data clearly showed (Table I) that cycloaddition had occurred and that methyl isocyanate had been extruded during the course of the reaction. The spectral characteristics (Experimental Section) of this product were consistent with those reported for an earlier preparation of 3 from methyl 2-pyridylacetate and dimethyl acetylenedicarboxylate.[11]

Reaction of 1 with ethyl propiolate gave an analogous product, ethyl 4*H*-quinolizin-4-one-1-carboxylate (3, R = COOEt; R[1] = H) whose structure was immediately apparent from its nmr spectral characteristics (Table I). Two AX doublets at τ 3.45 and 1.65 (the 3 H and 2 H, respectively), were particularly important in



establishing structure 3 (R = COOEt; R[1] = H) and in eliminating alternate modes of addition. This product was found to be identical with one reported to have

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(1) Support of this work by U. S. Public Health Service Research Grant CA 08495-04, National Cancer Institute, is gratefully acknowledged.

(2) Recent reviews which discuss this aspect follow: M. Ohta and H. Kato in "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, Chapter 4; R. Huisgen in "Aromaticity," Chemical Society Special Publication No. 21, London, 1967, p 51.

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(11) E. Wintersfeld, *Chem. Ber.*, **98**, 3537 (1965).

Table I
Nmr Data of Products Derived from 1 and Dipolarophiles

Compd	Chemical shifts (ppm) τ_1	τ_2	τ_3	τ_6[a]	τ_7[b]	τ_8[c]	τ_9[a]	Coupling constants (Hz) $J_{6,7}$	$J_{6,8}$	$J_{7,8}$	$J_{7,9}$	$J_{8,9}$
1[d]	*6.47*, s		5.12, s	0.87	2.55	1.7	2.22	7.0	1.5	7.0	1.5	9.0
3, R = R[1] = $COOCH_3$[e,f]	*6.10*, s	*6.17*, s	3.32, s	0.80	2.87	2.42	2.20	7.0	1.5	7.0	1.5	9.0
3, R = $COOC_2H_5$; R = H[f,g]	*8.6*, t 5.5, qt	1.65, d	3.54, d	0.75	2.87	2.39	0.75	6.5	1.5	6.5	1.5	9.0
3, R = R[1] = CN[d]			2.94, s	0.75	1.90	2.37	2.00	6.0	2.0	6.0	2.0	8.0
4[d]	*6.40*, s			0.80	2.42	1.52	2.2	7.0	1.5	7.0	1.5	9.0
5[f]	*6.33*, s		*8.76*,[h] t 5.90,[h] qt 2.50,[i] s	0.69	2.64	1.77	2.42	7.0	1.5	7.0	1.5	9.0

[a] Quartets. [b] Singlets. [c] Octets. [d] Spectra determined in DMSO-d_6. [e] Methyl resonances italicized. [f] Spectra determined in $CDCl_3$. [g] $J_{2,3}$ = 9.5 Hz. [h] J_{CH_2,CH_3} = 7.0 Hz. [i] NH, exchanged with D_2O.

this structure formed from ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate, followed by hydrolysis and decarboxylation of the resulting diester.[12]

Dicyanoacetylene also underwent reaction with **1** forming in good yield 1,2-dicyano-4*H*-quinolizin-4-one (**3**, R = R[1] = CN). Analytical data and nmr spectral characteristics (Table I) showed that addition of the dipolarophile had occurred and that methyl isocyanate had been lost during the course of the reaction. As with all other acetylenic dipolarophiles in cycloadditions of this type, the driving force in the reaction may be attributed in part to the aromatization of the primary cycloadduct by the elimination of a stable species. In cases where aromatization cannot occur, as in the cycloadduct from dimethyl acetylenedicarboxylate and *anhydro*-4-hydroxy-2-methylcinnolinium hydroxide, a stable 1:1 adduct was formed.[13]

In contrast to the above acetylenic dipolarophiles, tetracyanoethylene and ethyl azodicarboxylate did not undergo cycloaddition but gave instead "ene-type" reaction products. Thus, tetracyanoethylene and **1** in refluxing chlorobenzene gave a 42% yield of a yellow product of molecular formula $C_{14}H_7N_5O_2$, indicating that HCN had been lost from a simple 1:1 condensation product. The infrared spectrum of **4**, besides a strong CN absorption at 2255 cm^{-1}, showed the presence of two amide groups (ν_{CO} 1715, 1665 cm^{-1}) which were very similar to those of **1**. The nmr spectrum (Table I) indicated that all the components of **1**, other than the 3 H, were present. These data can be readily accommodated in terms of structure **4**, *anhydro*-2-hydroxy-1-methyl-4-oxo-3-(tricyanoethenyl)pyrido[1,2-*a*]pyrimidinium hydroxide. This may be regarded as an "ene-type" reaction[14] in which the initial product lost HCN under the reaction conditions. Examples of this type of reaction have been observed with other mesoionic systems.[15]

Ethyl azodicarboxylate also underwent an analogous type reaction[16] with **1**. Analytical data and spectral characteristics (Table I and Experimental Section) indicated that the product formed was a 1:1 adduct which is best represented as *anhydro*-3-(1,2-dicarbethoxyhydrazino)-2-hydroxy-1-methyl-4-oxopyrido[1,2-*a*]-pyrimidinium hydroxide (**5**). Infrared absorptions at 3315 and 3225 cm^{-1}, a low melting point, and good solubility in nonpolar solvents indicate the presence of H bonding[16] in **5**, most likely between the NH group and the carbonyl group at the 2 position. The absorption of this carbonyl group has shifted from 1665 cm^{-1} in the original mesoionic system to 1640 cm^{-1}, indicating some degree of interaction with a neighboring group.

The formation of these substitution products is most likely the result of steric influences. In attempts to prepare cycloadducts from dipolarophiles such as diphenylacetylene, phenyl isocyanate and phenyl isothiocyanate, maleic anhydride, and dimethyl maleate, no well-defined products were obtained.

Experimental Section[17]

***anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium Hydroxide** (1).—2-*N*-Methylaminopyridine (0.108 g, 1.0 mmol) dissolved in anhydrous ether (5 ml) with a catalytic amount of anhydrous $AlCl_3$ was added slowly to a stirred ethereal solution of a slight excess of carbon suboxide.[18] Crystals started to form toward the end of this addition and the reaction mixture was then refluxed for 12 hr. The crude product (100%) crystallized from methanol as yellow prisms: mp 243–245° (lit.[10] mp 245–252°); ir (KBr) 3100, 2950 (CH), 1720, 1665 (CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 322 (3.67), 257 (4.07), 230 (4.50); mass spectrum (70 eV) *m/e* (rel intensity) 176 (20), 148 (5), 107 (3), 80 (12), 79 (38), 78 (20), 69 (20), 32 (70), 31 (100). This product was identical with that obtained by methylation of "malonyl-α-aminopyridine."

Dimethyl 4*H*-Quinolizin-4-one-1,2-dicarboxylate (**3**, **R = R[1] = COOMe**).—*anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]-pyrimidinium hydroxide (0.528 g, 3.0 mmol), dimethyl acetylenedicarboxylate (0.852 g, 6.0 mmol), and dry xylene (500 ml) were heated under reflux for 24 hr. The dark, insoluble matter was filtered, the hot filtrate concentrated *in vacuo*, and the crude residue chromatographed on silica gel (Florosil F-100) using ether as eluent. The product crystallized from cyclohexane and then from methanol as yellow prisms: 0.5 g (64%); mp 113–115° (lit.[11] mp 115°); ir (KBr) 3145, 2980 (CH), 1740, 1720 (COOMe), 1670 (amide CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 385 (3.98), 275 (3.67), 258 (3.86), 250 (3.88), 220 (4.06); mass spectrum, M^+, *m/e* 261 (15).

Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.81; H, 4.24; N, 5.36. Found: C, 59.79; H, 4.22; N, 5.22.

Similarly, **ethyl 4*H*-quinolizin-4-one-1-carboxylate** (**3**, **R = COOEt**; **R[1] = H**) was obtained in 47% yield from 1 and ethyl propiolate on refluxing in chlorobenzene for 5 days. It crystallized from cyclohexane as yellow prisms: mp 113–114° (lit.[12] mp 117–118°); ir (KBr) 3120, 3080, 3000 (CH), 1730 (COOEt), 1690 (amide CO) cm^{-1}; $\lambda_{max}^{CH_3OH}$, nm (log ϵ), 370 (4.09), 274 (3.96),

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(15) K. T. Potts and S. Husain, *J. Org. Chem.*, **35**, 3451 (1970).
(16) R. K. Murray, Jr., and H. Hart, *Tetrahedron Lett.*, **54**, 4781 (1969).
(17) Spectral characterization of products was carried out on the following instrumentation: ir, Perkin-Elmer Model 337 spectrophotometer; uv, Cary Model 14 spectrophotometer; nmr, Varian A-60 nmr spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer, 70 eV, using the direct inlet probe at a source temperature of *ca.* 100°. All evaporations were done under reduced pressure using a rotatory evaporator and melting points were taken in capillaries. Chromatographic columns utilized a length:width ratio of *ca.* 10:1. Microanalyses were by Instranal Laboratories, Rensselaer, N. Y.
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255 (3.89), 248 sh (3.85), 207 (4.20); mass spectrum, M+, *m/e* 217 (100).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.45; H, 5.11; N, 6.46. Found: C, 66.18; H, 5.02; N, 6.14.

In a similar fashion, **1,2-dicyano-4*H*-quinolizin-4-one** (**3**, **R = R¹ = CN**) was obtained from **1** and dicyanoacetylene on refluxing in chlorobenzene overnight. It crystallized from benzene as yellow prisms: mp 263–265° (33%); ir (KBr) 3150, 3140 (CH), 2225 (CN), 1710 (amide CO) cm⁻¹; $\lambda_{max}^{CH_3OH}$, nm (log ε), 415 (4.20), 394 (4.12), 278 (3.69), 261 (4.02), 235 (4.31), 212 (4.23); mass spectrum, M+, *m/e* 195 (45).

Anal. Calcd for $C_{11}H_5N_3O$: C, 67.65; H, 2.58; N, 21.53. Found: C, 67.69; H, 2.55; N, 21.49.

***anhydro*-2-Hydroxy-1-methyl-4-oxo-3-(tricyanoethenyl)pyrido[1,2-*a*]pyrimidinium Hydroxide** (**4**).—*anhydro*-2-Hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide (0.528 g, 3.0 mmol), tetracyanoethylene (0.561 g, 4.5 mmol), and chlorobenzene (750 ml) were heated under reflux for 15 hr. After removal of the dark, insoluble matter the hot filtrate was evaporated to dryness under reduced pressure. Trituration of the residue with a small amount of cold acetone caused it to crystallize, and it was recrystallized from acetone and then from acetonitrile–ether (1:1) from which it separated as yellow prisms: mp 301–302° (42%); ir (KBr) 3140, 2920 (CH), 2255 (CN), 1715, 1665 (CO) cm⁻¹; $\lambda_{max}^{CH_3OH}$, nm (log ε), 416 (3.20), 250 (3.98), 218 (4.36); mass spectrum, M+, *m/e* 277 (60).

Anal. Calcd for $C_{14}H_7N_5O_2$: C, 60.65; H, 2.54; N, 25.21. Found: C, 60.56; H, 2.39; N, 25.32.

Similarly, ***anhydro*-3-(1,2-dicarbethoxyhydrazino)-2-hydroxy-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide** (**5**) was obtained from the mesoionic compound **1** and ethyl azodicarboxylate in refluxing chlorobenzene over 24 hr. In this case the crude residue was dissolved in acetone and purified[19] by chromatography on silica gel. It crystallized from benzene–*n*-heptane (2:1) as yellow, irregular prisms: mp 106–109° (24%); ir (KBr) 3315, 3225 (NH), 3100, 2998 (CH), 1770, 1750 (COOEt), 1720, 1640 (amide CO) cm⁻¹; $\lambda_{max}^{CH_3OH}$, nm (log ε), 340 sh (3.02), 330 (3.14), 265 (3.54), 230 (4.23); mass spectrum (70 eV) *m/e* (rel intensity), M+, 350 (1), 277 (5), 276 (10), 217 (15), 203 (10), 189 (15), 135 (20), 133 (15), 108 (15), 79 (32), 78 (100), 77 (15).

Anal. Calcd for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18; N, 15.99. Found: C, 52.72; H, 5.15; N, 15.72.

Registry No.—**1**, 26460-93-5; **3** (R = R¹ = $COOCH_3$), 4627-24-1; **3** (R = $COOC_2H_5$; R¹ = H), 24403-35-8; **3** (R = R¹ = CN), 26460-96-8; **4**, 26460-97-9; **5**, 26460-98-0.

Acknowledgments.—The award of a grant from the National Science Foundation (NSF GP 6905) for the purchase of the mass spectrometer used in this study is gratefully acknowledged.

(19) This product always separated with fractional amounts of solvent of crystallization and several determinations of carbon contents gave results of this order.

1,2,4-Triazoles. XXVII. Synthesis of the Thiazolo[2,3-*c*]-*s*-triazole and the Thiazolo[3,2-*b*]-*s*-triazole Systems[1]

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2-Triazolylhydrazines underwent ring closure with aliphatic acids or ortho esters to thiazolo[2,3-*c*]-*s*-triazoles, cyanogen bromide, and carbon disulfide readily giving the corresponding 3-amino and 3-mercapto derivatives. The isomeric thiazolo[3,2-*b*]-*s*-triazole system was readily obtained from *s*-triazole-3-thiols and α-halo ketones. Spectral characteristics of these ring systems are described.

Fusion of the thiazole and the *s*-triazole nuclei can be effected in two ways, represented by thiazolo[2,3-*c*]-*s*-triazole (**2**) and thiazolo[3,2-*b*]-*s*-triazole (**4**). The only hitherto reported[2] examples of these ring systems are relatively complex. We now describe the synthesis and properties of alkyl- and aryl-substituted derivatives of both systems, as well as some amino and mercapto derivatives. Though the isomerization of *s*-triazolo[4,3-*a*]pyridines to *s*-triazolo[1,5-*a*]pyridines has been reported[3] as well as isomerizations in related [5,6] ring-fused systems,[4] no such isomerizations have been found in [5,5] ring-fused systems. Thiazolo-[2,3-*c*]-*s*-triazole (**2**) is particularly suitable for studying such isomerizations.

Cyclization of 2-thiazolylhydrazines[5] (**1**), a synthetic approach well documented for the preparation of ring-fused *s*-triazoles,[6] has provided a simple synthesis of the fused-ring system **2** (Table I). Cyclization of 4-methyl-2-thiazolylhydrazine (**1**, R = CH_3) with formic, acetic, or propionic acids under reflux for 6–8 hr led directly to **2**. However, 4-phenyl-2-thiazolylhydrazine (**1**, R = Ph) gave the intermediate hydrazides (**3**, R = Ph; R¹ = CH_3, Et) with acetic and propionic acids and these hydrazides underwent a smooth cyclization to the fused system **2** with phosphoryl chloride. Ortho esters were equally effective as cyclization agents but slightly longer reaction periods were required. Attempts to prepare the fused system **2** with 3-phenyl substituents by the cyclization of the 2-thiazolylhydrazines (**1**) with benzoic acid were unsuccessful. However, phosphoryl chloride cyclization of 2-[4-methyl(phenyl)thiazol-2-yl]benzhydrazide [**3**, R = CH_3(Ph); R¹ = Ph], prepared from 1-benzoylthiosemicarbazide and chloroacetone, or phenacyl bromide, respectively, gave **2**. The ease of these cyclizations are particularly interesting in view of the formation of 2-azidothiazole on attempted ring closure of 2-amino or 2-hydrazinothiazole to thiazolo[3,2-*d*]-tetrazole.[7]

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(1) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged.

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