

Diels-Alder Addition of Benzyne to 1-Methyl-2-pyridones

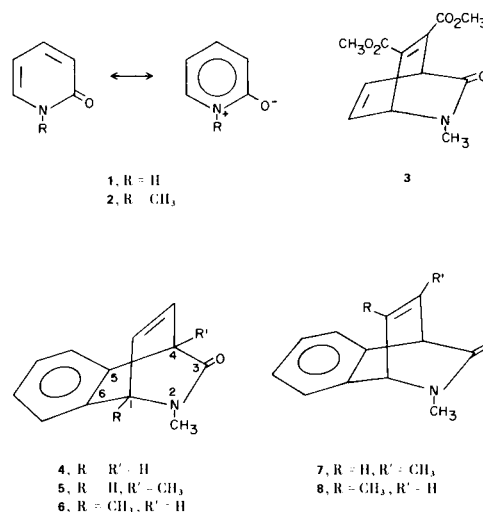
Eric B. Sheinin (1), George E. Wright (2), Charles L. Bell, and Ludwig Bauer

Department of Chemistry, College of Pharmacy, University of Illinois
at the Medical Center, P.O. Box 6998

The unique structure of 2-pyridone (1) presents a challenge in predicting in what type of aliphatic and aromatic reactions this molecule will participate. The inability of either acids or bases to hydrolyze the inherent amide function in 2-pyridones and their ready submission to electrophilic substitution reactions attests to their aromatic character. Yet, it is quite evident from infrared studies of 2-pyridone (3,4) and proton magnetic resonance (PMR) investigations of a number of 2-pyridones (5,6), that a certain amount of aliphatic character is associated with this type of molecule. In such a light, it would seem natural that the backbone of 2-pyridones, C-3 to C-6, represents a potential 1,3-diene system which should be capable of connecting with suitable dienophiles in typical Diels-Alder reactions. In the event of sufficient electron density at C-3 and C-6, it would still require a relatively nucleophilic dienophile to effect 1,4-addition. Previous attempts to bring about Diels-Alder additions of maleic anhydride to 1-methyl-2-pyridone (7), tetracyanoethylene to a number of 1-alkyl-2-pyridones (8), and hexafluoro-2-butyne to 1-methyl-2-pyridone (9) proved abortive. These particular dienophiles possessed a relatively electrophilic unsaturated linkage and this might account for the failure to participate in Diels-Alder reactions with 1-alkyl-2-pyridones (10). Under forcing conditions (195°, 4 days), methyl acetylenedicarboxylate reacted with 1-methyl-2-pyridone (2) to afford *N*-methylphthalimide (5%), which can be explained if an initial Diels-Alder adduct (3) decomposes to give this imide (11). Recently, irradiation of a methanolic solution of 4,5-tetramethylene-2-pyridone and diphenylacetylene furnished a product which can be explained if the pyridone first underwent a *photo*-Diels-Alder to give an adduct which underwent *photo*cyclization (12).

The present work utilized the relatively nucleophilic dienophile, benzyne, (13) as a probe for Diels-Alder additions to 2-pyridones. With 2-pyridone itself, only *N*- and *O*-arylation took place with benzyne to yield 1-phenyl-2-pyridone and 2-phenoxy pyridine (14). This is not unexpected, since the addition of 2-pyridone to benzyne

is bound to be faster than a Diels-Alder reaction. However, benzyne attached itself to 1-methyl-2-pyridone (2) in Diels-Alder fashion to furnish 4 (14). The structure of 4 was established by means of the elemental analysis and spectra. Diels-Alder reactions were successful between 1,3-, 1,4-, 1,5- and 1,6-dimethyl-2-pyridones and benzyne. In each instance, the requisite adducts (5-8) were obtained and characterized as discussed below. It is evident that the ring methyl group in either 1,3- or 1,6-dimethyl-2-pyridone offered little steric inhibition to the reaction.



PMR Spectra of Adducts.

The PMR parameters for the adducts are listed in Table I. Whenever possible, first order analysis was applied to obtain chemical shifts and coupling constants. The chemical shifts for the various types of protons agreed with the proposed structures (4-8). The alkene protons of 5 and 6 are part of an allylic system and this 3-spin system was analyzed for an ABX type. In each instance, allylic coupling constants were negative, as had been reported previously (15). The spectrum of 4 did not lend itself to simple analysis, and exact chemical shift and coupling constant data are not available at present.

TABLE I
PMR Parameters for Adducts

Compound	Chemical Shifts, (a) δ , in CDCl_3 , from TMS							Coupling Constants, (b) in Hz						
	H-1	H-4	H-7	H-8	C- CH_3	N- CH_3	Aromatic	$J_{1,7}$	$J_{1,8}$	$J_{4,7}$	$J_{4,8}$	$J_{7,8}$	$J_{\text{x}, \text{CH}_3}$	
4	4.59													
	or 5.00 dd		--(c)		--	2.82	6.8- 7.4 m	--	--	--	--	--	--	--
5	4.92	--	6.80	6.48	1.82	2.82	6.93- 7.68 m	6.1	-2.6	--	--	6.9	--	
	dd		dd	dd	s	s								
6	--	4.42	6.39	6.88	1.97	2.73	6.95- 7.47 m	--	--	-1.9	6.2	7.1	--	
		dd	dd	dd	s	s								
7	4.85	4.30	6.22- 6.47	--	1.90	2.77	6.90- 7.42 m	5.2	--	-1.8	--	--	J_{7, CH_3} -1.7	
	d	d	ddq		d	s								
8	4.54	4.34	--	6.20- 6.43	1.85	2.75	6.71- 7.35 m	--	-1.6	--	5.0	--	J_{8, CH_3} -1.6	
	d	d		ddq	d	s								

(a) Multiplicities are indicated as follows: d = doublet, m = multiplet, q = quartet, s = singlet. (b) Coupling constants were not determined for 4. (c) Signals buried in multiplet due to aromatic protons.

Mass Spectra.

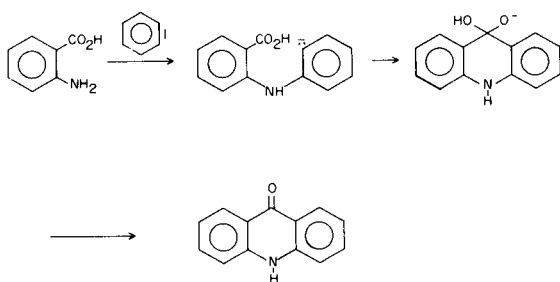
The parent ion of 4 proved to be its base peak, m/e 128, and corresponded to the molecular ion of naphthalene. Indeed, the rest of the mass spectrum of 4 was identical to that obtained from naphthalene. This raises the question of whether or not 4 decomposes thermally prior to electron-bombardment. This idea may be discounted, in part, since the compound is purified most conveniently by vacuum sublimation. Admittedly, pyrolysis of 4 at 200° did furnish some naphthalene. The mass spectra of 5-8 furnished somewhat better evidence that the loss of methyl isocyanate from these adducts to form a methylnaphthalene is more likely to be induced upon electron impact, although the possibility of some thermal decomposition on the filament cannot be totally excluded. In each of the mass spectra of 5-8, a small peak due to the molecular ion, m/e 199, was visible, although the base peak was

again that of methylnaphthalene, m/e 142. Furthermore, in each of the mass-spectra of adducts 6, 7 and 8, a weak metastable peak was observed [m/e 199 \rightarrow m/e 142, calcd. 101.3, found (in each instance) at 101.5] which would support the fact that the loss of methyl isocyanate is a transition from the molecular ion.

Acridone.

In this study, benzyne was conveniently generated from anthranilic acid and isoamyl nitrite (16). An interesting by-product of each of these reactions was acridone. As expected, this product resulted from the initial addition of anthranilic acid to benzyne to form an aryl anion, which then cyclized to give acridone as shown in Scheme 1. When anthranilic acid was reacted with benzyne, in the absence of pyridones, there was isolated *N*-phenylanthranilic acid and acridone.

SCHEME 1



EXPERIMENTAL (17)

Starting Materials.

Diazotization of 2-amino-3-, 4-, 5-, and 6-picolines (18) by the method of Seide (19) produced the corresponding pyridones, which were methylated by the procedure of Bradlow and Vanderwerf (20), to yield the known 1,*n*-dimethyl-2-pyridone. 1-Methyl-2-pyridone and acridone were purchased from Aldrich Chemical Co. Inc., Milwaukee, Wisconsin.

2-Methyl-5,6-benzo-2-azobicyclo(2.2.2)oct-7-en-3-one (4).

A solution of anthranilic acid (7.54 g., 0.055 mole) in acetone (40 ml.) was added dropwise to a boiling solution of 1-methyl-2-pyridone (5.45 g., 0.05 mole) and isoamyl nitrite (21) (7.03 g., 0.06 mole) in methylene chloride (150 ml.). The addition took 1.5 hours and the solution was boiled under reflux for an additional 0.5 hour. The dark brown solution was washed with 10% hydrochloric acid (two 50-ml. portions) and water (two 50 ml. portions). Evaporation of the organic solution furnished a black oil which was dissolved in benzene and chromatographed on alumina (Alcoa, grade F-20, 100 g.). Elution with benzene (200 ml.) gave 0.93 g. (10%) of 4, which was sublimed twice at 100° (7 mm.), m.p. 98-100°, infrared (chloroform) 1680 cm⁻¹ (C=O); mass spectrum (70 eV) base peak, m/e 128.

Anal. Calcd. for C₁₂H₁₁NO: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.80; H, 6.03; N, 7.69.

Further elution with ethanol-chloroform (1:9, 250 ml.) gave acridone as a yellow solid (0.06 g., 1.2%) m.p. 360-363°, undepressed on admixture with an authentic sample, lit. (22) m.p. 350°. It gave a blue fluorescent solution in ethanol and its ultraviolet spectrum was identical to that in the literature (22).

2,4-Dimethyl-5,6-benzo-2-azobicyclo(2.2.2)oct-7-en-3-one (5).

A solution of anthranilic acid (3.77 g., 0.0275 mole) in acetone (40 ml.) was added dropwise to a boiling solution of 1,3-dimethyl-2-pyridone (3.10 g., 0.0250 mole) and isoamyl nitrite (3.52 g., 0.030 mole) in methylene chloride (90 ml.). The addition took 1.5 hours and the solution was boiled under reflux for an additional 1.0 hour. The solvents were removed *in vacuo* and the residue was dissolved in benzene (50 ml.). The solution was concentrated to 25 ml. over a steam bath and was chromatographed on alumina (Alcoa, grade F-20, 200 g.). Elution with benzene (700 ml.) gave 0.59 g. (12%) of 5, which was sublimed twice at 85° (0.6 mm.), m.p. 92.5-95°; infrared (chloroform) 1680 cm⁻¹ (C=O), mass spectrum (70 eV), m/e (relative intensity) 199 (1), 144 (2), 143 (12), 142 (100), 141 (36), 140 (3), 139 (4), 128 (2), 116 (2),

115 (4), 89 (2), 63 (3), 51 (2), 42 (2).

Anal. Calcd. for C₁₃H₁₃NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.25; H, 6.62; N, 6.91.

1,2-Dimethyl-5,6-benzo-2-azobicyclo(2.2.2)oct-7-en-3-one (6).

A solution of anthranilic acid (3.77 g., 0.0275 mole) in acetone (40 ml.) was added dropwise to a boiling solution of 1,6-dimethyl-2-pyridone (3.10 g., 0.025 mole) and isoamyl nitrite (3.52 g., 0.030 mole) in methylene chloride (90 ml.). The addition took 1.5 hours and the solution was boiled under reflux for an additional 0.5 hour. The solvents were removed *in vacuo* and the residue was dissolved in benzene (50 ml.). The solution was concentrated to 25 ml. over a steam bath and was chromatographed on alumina (Alcoa, grade F-20, 200 g.). Elution with benzene (850 ml.) gave 0.20 g. (4%) of 6, which was sublimed twice at 60° (0.05 mm.), m.p. 79-83°; infrared (chloroform) 1675 cm⁻¹ (C=O), mass spectrum (70 eV), m/e (relative intensity) 199 (3), 144 (2), 143 (12), 142 (100), 141 (37), 140 (3), 139 (5), 128 (2), 116 (2), 115 (16), 89 (3), 63 (3), 51 (2).

Anal. Calcd. for C₁₃H₁₃NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.22; H, 6.57; N, 7.19.

2,8-Dimethyl-5,6-benzo-2-azobicyclo(2.2.2)oct-7-en-3-one (7).

A solution of anthranilic acid (3.77 g., 0.0275 mole) in acetone (40 ml.) was added dropwise to a boiling solution of 1,4-dimethyl-2-pyridone (3.10 g., 0.0250 mole) and isoamyl nitrite (3.52 g., 0.030 mole) in methylene chloride (90 ml.). The addition took 1.5 hours and the solution was boiled under reflux for an additional 0.5 hour. The solvents were removed *in vacuo* and the residue was dissolved in benzene (50 ml.). The solution was concentrated to 25 ml. over a steam bath and was chromatographed on alumina (Alcoa, grade F-20, 200 g.). Elution with benzene (850 ml.) gave 0.33 g. (7%) of 7, which was sublimed twice at 85° (0.10 mm.), m.p. 99-102°; infrared (chloroform) 1675 cm⁻¹ (C=O), mass spectrum (70 eV), m/e (relative intensity) 199 (5), 143 (13), 142 (100), 141 (40), 140 (3), 139 (4), 128 (3), 116 (3), 115 (15), 89 (3), 63 (3), 51 (2), 42 (3).

Anal. Calcd. for C₁₃H₁₃NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.52; H, 6.60; N, 7.10.

2,7-Dimethyl-5,6-benzo-2-azobicyclo(2.2.2)oct-7-en-3-one (8).

A solution of anthranilic acid (3.77 g., 0.0275 mole) in acetone (40 ml.) was added dropwise to a boiling solution of 1,5-dimethyl-2-pyridone (3.10 g., 0.0250 mole) and isoamyl nitrite (3.52 g., 0.030 mole) in methylene chloride (90 ml.). The addition took 2.0 hours and the solution was boiled under reflux for an additional 1.0 hour. The solution was washed with 10% hydrochloric acid (two 50 ml. portions) and water (two 50-ml. portions). The solvents were removed *in vacuo* and the residue was dissolved in benzene (50 ml.). The solution was concentrated to 25 ml. over a steam bath and chromatographed on alumina (Alcoa, grade F-20, 200 g.). Elution with benzene (550 ml.), chloroform-benzene (1:9, 200 ml., 1:1 250 ml.) and chloroform (650 ml.) gave 0.62 g. (13%) of 8, which was sublimed twice at 120° (0.5 mm.), m.p. 126-129°; infrared (chloroform) 1675 cm⁻¹ (C=O) mass spectrum (70 eV), m/e (relative intensity) 199 (2), 143 (12), 142 (100), 141 (43), 140 (3), 139 (4), 128 (2), 116 (2), 115 (15), 89 (3), 63 (3) 51 (2).

Anal. Calcd. for C₁₃H₁₃NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.47; H, 6.72; N, 7.03.

Reaction of Anthranilic acid and Isoamyl Nitrite.

A solution of isoamyl nitrite (4.16 g., 0.027 mole) in tetrahydrofuran (50 ml.) was added dropwise to a boiling solution of

anthranilic acid (6.85 g., 0.05 mole) in tetrahydrofuran (100 ml.). The addition took 1.0 hour and the solution was boiled under reflux for an additional 1.0 hour. After cooling, 10% hydrochloric acid (50 ml.) was added and the solvents removed on a steam bath. The residue was collected and mixed with 5% sodium hydroxide (220 ml.) and the mixture was filtered, giving, after recrystallization from acetic acid (40 ml.), 0.77 g. (15%) of acridone, m.p. 364-367°, lit. (22) m.p. 350°. Its infrared spectrum was identical to that reported in Satdler (23).

The filtrate was acidified with 10% hydrochloric acid (100 ml.) and filtered, giving, after recrystallization from acetic acid (25 ml.), 0.67 g. (12%) of *N*-phenylanthranilic acid, m.p. 181-184°, lit. (24) m.p. 182°. Its infrared spectrum was identical to that reported in the literature (25).

Reaction of 2-Pyridone with Anthranilic Acid and Isoamyl Nitrite.

A solution of anthranilic acid (7.54 g., 0.055 mole) in acetone (40 ml.) was added dropwise to a boiling solution of 2-pyridone (4.75 g., 0.05 mole) and isoamyl nitrite (7.03 g., 0.06 mole) in methylene chloride (150 ml.). The addition took 0.5 hour and the solution was boiled under reflux for an additional 1.5 hours. The black solution was washed with 10% hydrochloric acid (50 ml.) and water (two 50 ml. portions). Evaporation of the organic solution furnished a black oil which was dissolved in benzene and chromatographed on alumina (Alcoa, grade F-20, 200 g.). Elution with benzene (150 ml.) gave 0.33 g. (4%) of 2-phenoxy pyridine, which was sublimed at 45° (20 mm.) and after recrystallization from petroleum ether (b.p. 30-60°) had m.p. 41-42°, lit. (26) m.p. 42-44°, undepressed on admixture with an authentic sample.

Elution with 1:5 benzene-chloroform (400 ml.) gave, after sublimation at 130° (20 mm.), 0.15 g. (2%) of 1-phenyl-2-pyridone, m.p. 124-126°, lit. (27) m.p. 128°, PMR (deuteriochloroform) δ 6.17 (t, H-5); 6.56 (d, H-3); 7.1-7.6 (m, H-4, H-6, aromatic); couplings (Hz) $J_{3,4} = 9.5$; $J_{4,5} = J_{5,6} = 6.5$; $J_{3,5} = 1.5$; mass spectrum (70 eV), m/e 171 (base peak).

Further elution with 1:5 benzene-chloroform (50 ml.) gave acridone, 0.1 g. (2%).

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- (2) Taken in part from the Ph.D. Dissertation of G.E.W., University of Illinois at the Medical Center, Chicago, Illinois, June, 1967.
- (3) An infrared spectral investigation of natural and 2-pyridone-¹⁸O indicates, without any doubt, that the molecule possesses a stretching vibration associated with C=O motion (lactam ν C=O at about 1660 cm^{-1}) indicative of a certain amount of aliphatic character in the 2-pyridone molecule [G. H. Keller, L. Bauer, and C. L. Bell, *Can. J. Chem.*, **46**, 2475 (1968)].
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- (6) That these compounds possessed a considerable amount of aliphatic character was demonstrated by the specific coupling of C-methyl to ring protons in C-methyl-2-pyridones which indicates a certain amount of localization of the π -electrons in the molecule [C. L. Bell, R. S. Egan, and L. Bauer, *J. Heterocyclic Chem.*, **2**, 420 (1965)].
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- (17) Melting-boiling points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Infrared spectra were obtained in chloroform solution with a Perkin-Elmer Model 337 recording spectrophotometer. PMR spectra were taken at 60 MHz with a Varian A-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal TMS. Each A-60 spectrum was calibrated by a sample of TMS ($\delta=0$) in chloroform ($\delta = 7.28$). Proton assignments were based on integral information, on chemical shifts anticipated for the particular protons, and, whenever possible, spin-spin coupling constants (J) were derived from a first-order analysis. Mass spectra were obtained by Mr. Richard Dvorak using a Hitachi Perkin-Elmer RMU-6D mass spectrometer equipped with a Honeywell Visicorder. Solids were introduced by the direct inlet system at the lowest possible temperatures for all parts of the system. Spectra were recorded at 10 and 70 eV. Relative abundances are reported, in general, for fragments over 2% of the base peak, except the molecular ion.
- (18) We acknowledge the generous gifts of the amino picolines from Reilly Tar and Chemical Corporation, Indianapolis, Indiana.
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Chicago, Illinois 60680