Preparation of 3-Hydroxypyrazolines (Table I). Hydrolysis Procedure.—A mixture of 10.0 g (0.059 mol) of 3-acetoxy-3,5,5-trimethylpyrazoline-1[6] and 30 ml of 5% methanolic sodium hydroxide was stirred at room temperature for 10 hr. It was diluted with water and carefully neutralized with 5% HCl. After extraction with ether, drying ($MgSO_4$), and concentration, distillation yielded 6.1 g (81%) of **3-hydroxy-3,5,5-trimethyl-1-pyrazoline**: ir (neat) 3378 (OH), 1560 cm^{-1} (N=N); nmr (neat) δ 1.32, 1.42, 1.58 (s, 3, CCH_3), 1.53 (m, 2, CH_2), 5.88 (s, 1, OH).

Hydrogenolysis Procedure.—A solution of 17.0 g (0.1 mol) of 3-acetoxy-3,5,5-trimethyl-1-pyrazoline in 100 ml of CH_3OH was added, dropwise and with stirring, to a solution of 37.85 g (1 mol) of sodium borohydride in 450 ml of CH_3OH. This mixture was heated under reflux for 1 hr, cooled, diluted with water, concentrated to half its volume, and extracted with five 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$), concentrated, and distilled to yield 11.0 g (86%) of 3-hydroxy-3,5,5-trimethyl-1-pyrazoline.

3-(3,5-Dinitrobenzoyloxy)-3,5,5-trimethyl-1-pyrazoline.—To a cold mixture of 1.65 g (0.0078 mol) of 3,5-dinitrobenzoic acid and 2.8 g (0.016 mol) of benzenesulfonyl chloride in 15 ml of pyridine was added 1.0 g (0.0078 mol) of 3-hydroxy-3,5,5-trimethylpyrazoline (**6a**). The mixture was stirred for 4 hr, poured into water, and filtered, and the residue was recrystallized from C_2H_5OH–C_6H_6 to give 0.7 g (28%) of the title compound, mp 162–163°.

3-Methoxy-3,5,5-trimethyl-1-pyrazoline. Procedure A.—An ether suspension of the sodium salt of **6a** was prepared by adding 12.3 g (0.096 mol) of **6a** to a suspension of 2.2 g of sodium in ether. This mixture was stirred at room temperature for several days to ensure complete reaction. Methyl iodide (28.4 g, 0.2 mol) was added dropwise and the mixture was heated under reflux for 24 hr. It was filtered, dried, and distilled to give 9.9 g (73%) of 3-methoxy-3,5,5-trimethylpyrazoline-1: bp 22° (0.25 mm); ir (neat) 1655 (N=N), 1201 cm^{-1} (COC); nmr ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 1.40 (m, 2, CH_2), 1.46, 1.35, 1.27 (s, 3, CCH_3 groups).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.14; H, 9.95; N, 18.31.

Procedure B.—A 1.7-g (0.013 mol) sample of **6a** was slowly added to 1.1 ml of cold, concentrated H_2SO_4. This solution in turn was added immediately to 5 ml of cold methanol. This solution was stirred for 15 min, diluted with water, and extracted with ether. The ether extracts were dried and distilled to yield 0.98 g (54%) of the methyl ether.

Procedure C.—A solution of 11.2 g (0.1 mol) of 3,3,5-trimethylpyrazoline in 100 ml of CH_3OH was added over a 2-hr period to a solution of 25.4 g (0.1 mol) of iodine and 27.2 g (0.2 mol) of sodium acetate in 600 ml of CH_3OH. The mixture was stirred at 25° for 2 hr, concentrated *in vacuo*, diluted with ether, and washed with water, $NaHSO_3$ solution, and saturated NaCl solution. The dried ether extracts were distilled to yield 4 g (28%) of the methyl ether. Mesityl oxide and pinacolone were also present in the product mixture.

1,1,2-Trimethylcyclopropyl Methyl Ether.—3-Methoxy-3,5,5-trimethyl-1-pyrazoline (1.75 g, 0.012 mol) was heated under reflux (~200°) until N_2 evolution ceased (6 hr). The residue was distilled to yield 0.58 g (42.5%) of the title compound, identical in all respects with an authentic sample:[16] bp 48–50° (150 mm); nmr (neat) δ 3.16 (s, 3, OCH_3), 1.30, 1.13, 1.05 (s, 3, CCH_3), 0.23 (m, 2, CH_2).

Ring-Opening Reaction of Hydroxypyrazolines. Acid Catalyzed.—The general procedure was to mix methanol solutions of the hydroxypyrazoline and methanolic HCl at room temperature and then to stir the mixture for various times at various temperatures. After the reaction period the mixtures were diluted with water, washed with base, and extracted with ether. The ether extracts were dried and distilled to remove the solvent; the residue was then subjected to gas chromatographic analysis. Silicone columns operating between 50 and 100° proved to be adequate for resolving the ketones and starting material. In all cases the columns were calibrated using authentic samples (Table II).

Base Catalyzed.—The general procedure was the same except that methanolic NaOH was employed (Table III).

Registry No.—**6a**, 22883-54-1; **6a** 3,5-DNB, 34277-62-8; **6b**, 34277-63-9; **6b** 3,5-DNB, 34277-64-0; **6c**, 34277-81-1; **6c** 3,5-DNB, 34281-09-9; **6d**, 34281-10-2; **6e**, 34281-11-3; **6f**, 34281-12-4; 3-acetoxy-3-methyl-5,5-pentamethylene-1-pyrazoline, 34281-13-5; 3-acetoxy-3-isobutenyl-5,5-dimethyl-1-pyrazoline, 34281-14-6; 3-methoxy-3,5,5-trimethyl-1-pyrazoline, 23019-13-8.

(16) C. H. DePuy and A. DeBoer, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, ORGN 62.

The Direct Alkylation of Pyridine 1-Oxides

R. A. ABRAMOVITCH,*[1] ELIZABETH M. SMITH, E. E. KNAUS, AND M. SAHA

Departments of Chemistry, University of Alabama, University, Alabama 35486, and University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Received November 18, 1971

n-Butyllithium in inert nonprotic solvents abstracts a ring proton from the α position of pyridine 1-oxides to give a carbanion which can be trapped with aldehydes and ketones to give 2-(α-hydroxyalkyl)- and 2,6-di(α-hydroxyalkyl)pyridine 1-oxides. A chloro, ethoxyl, or methyl group at the 4 position is unaffected under these conditions, but a 2-methyl substituent undergoes proton abstraction morer eadily than does the C_6H. When a 3-methyl group is present it directs the entering hydroxyalkyl group to the 6 position, but 2,6-disubstituted derivatives are also formed. This orientation is discussed. The use of some bases other than butyllithium is described.

There are few methods available for the direct alkylation of pyridines and related systems, particularly since Friedel–Crafts alkylation is not possible with such π-deficient molecules. Other than high-temperature reactions, the most common modes of nuclear alkylation involve nucleophilic addition–eliminations with organometallic, and in particular organolithium, compounds and by the use of aldehydes and ketones in the Emmert reaction.[2a] More recently, the novel enamine-type alkylation of *N*-lithio-1,2-dihydropyridines has resulted in a useful route to 3-alkylpyridine derivatives.[2b] We now report a convenient method of effecting alkylations of pyridine 1-oxides which promises to have wide utility and to lead to compounds which would be otherwise tedious to prepare.[3]

Nuclear proton abstraction from substituted pyridines has only found sporadic application, this usually involving the formation of pyridyne intermediates.[4]

(1) University of Alabama.

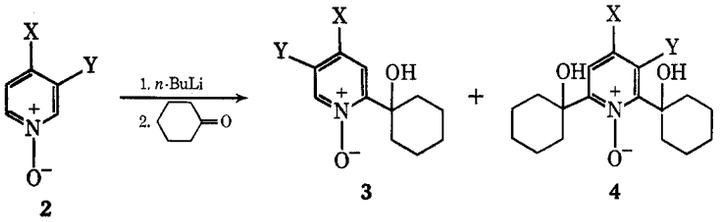
(2) (a) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966); (b) C. S. Giam and J. L. Stout, *J. Amer. Chem. Soc.*, **93**, 1294 (1971).

(3) For preliminary communication, see R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Amer. Chem. Soc.*, **89**, 1537 (1967).

(4) (a) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, **4**, 121 (1965); (b) T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965); T. Kauffmann and R. Wirthwein, *ibid.*, **10**, 20 (1971).

TABLE I

REACTION OF 2-LITHIOPYRIDINE 1-OXIDES WITH CYCLOHEXANONE

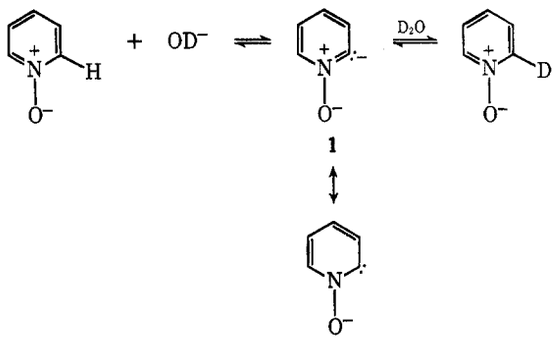


2 3 4

N-Oxide (2)	Conditions	Products, % 3	4
X = Y = H	n-BuLi, Et_2O, −65°	7.4	
X = Y = H	n-BuLi, THF–Et_2O (2:1 v/v), −65°	4.6	14.8
X = Y = H	n-BuLi, Et_2O, *a*	12.5	35.5
X = Y = H	LiOEt–EtOH		
X = Y = H	TlOEt–Et_2O or EtOH		
X = Y = H	$(Me_3Si)_2NNa$, C_6H_6, Δ	0.85	
X = Me; Y = H	n-BuLi, THF, −65°	21.1	27.3
X = Me; Y = H	n-BuLi, Et_2O, *a*	19.8	24.9
X = Cl; Y = H	n-BuLi, Et_2O, −100°		10.9
X = Cl; Y = H	n-BuLi, Et_2O, −65°	35.6	20.7
X = Cl; Y = H	n-BuLi, THF, −65°		10.5
X = Cl; Y = H	n-BuLi, Et_2O, −15°		13.2
X = Cl; Y = H	n-BuLi, Et_2O, 0°		7.3
X = OEt; Y = H	n-BuLi, Et_2O, −65°	3.7	12.5
X = OEt; Y = H	n-BuLi, THF, −65°	19.9	20.7
X = OEt; Y = H	NaH, THF, bp	7.5	
X = H; Y = Me	n-BuLi, THF–Et_2O (1:4 v/v), −65°	25.1	7.7
X = Y = Me	n-BuLi, THF, −65°	38.7	12.1
X = Y = Me	n-BuLi–TMEDA, THF, −65°	28.5	6.7
X = Y = Me	MeLi, THF, −65°	47.3	8.9
X = Y = Me	n-BuLi, Et_2O, −65°	56.3	15.6
X = Y = Me	$(Me_3Si)_2NNa$, C_6H_6, Δ	1.68	
X = Y = Me	$(Me_3Si)_2NNa$, THF, *a*	1.41	
X = Y = Me	$(Me_3Si)_2NNa$, THF, Δ	1.4	
X = Y = Me	$(Me_3Si)_2NLi$, Et_2O, *a*	4.0	(2.6)[b]
X = Y = Me	$(Me_3Si)_2NLi$, Et_2O, Δ	4.5	(3.3)[b]
X = Cl; Y = Me	n-BuLi, Et_2O, −65°	43.8	4.7
5	n-BuLi, −78°	6 (4.3%)	7 (19.6%)

[a] Room temperature. [b] 3-Methyl-4-(1-hydroxycyclohexylmethyl)pyridine 1-oxide.

It was expected[5] that base-catalyzed deprotonation of pyridine 1-oxides and pyridinium salts should occur much more readily than in pyridine themselves,[6] and that the C_2 H would be the most acidic proton; this prediction has been verified quantitatively.[5,7] If, indeed, base-catalyzed H–D exchange in pyridine 1-oxide did involve formation of an intermediate carbanion **1**; it might be possible to trap such a carbanion with appropriate electrophiles if it were generated in a nonprotic solvent. This has indeed been found to be the case, and we report here the use of aldehydes and ketones as the electrophiles, leading to α-hydroxy alkylated pyridine 1-oxides. In subsequent papers we shall consider reactions with other electrophiles.



The 2-pyridyl 1-oxide anions were conveniently generated by the addition of *n*-butyllithium to a solution of the *N*-oxide in ether or tetrahydrofuran at −65°, followed by the addition of the aldehyde or ketone. A number of other conditions were investigated and the results are summarized in Table I, but no attempt was made to optimize yields. When pyridine 1-oxide itself in a mixture of ether and tetrahydrofuran was treated

(5) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967); R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. B*, 131 (1971).

(6) J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **88**, 4766 (1966).

(7) Base-catalyzed nuclear proton abstraction may be of importance in biological systems and could be involved in the appearance of an absorption maximum at 290 mμ when NAD^+ is treated with 0.17 *N* KOH or the rapid formation of a species absorbing at 282 mμ when 1-methylnicotinamide iodide is treated with 0.3 *N* KOH solution.[8] This had previously been attributed[8] to the formation of a charge-transfer intermediate between the pyridinium salt and OH^-. In preliminary studies we have shown that the change in the uv spectrum observed when nicotinonitrile methiodide is treated with aqueous base parallels the rate of H–D exchange with NaOD in D_2O.

(8) R. M. Burton and N. O. Kaplan, *Arch. Biochem. Biophys.*, **101**, 139 (1969). For an alternate explanation, see R. B. Martin and J. G. Hull, *J. Biol. Chem.*, **239**, 1237 (1964).

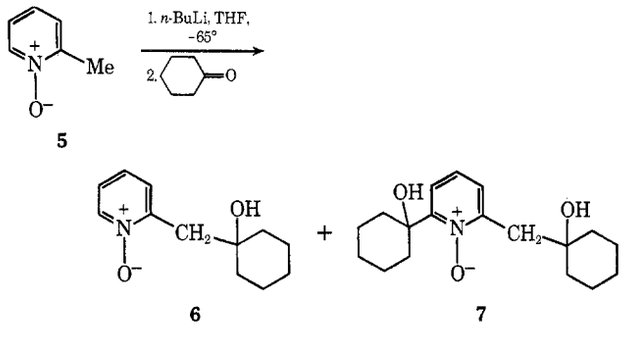
with *n*-BuLi at −65°, two products were obtained: 2-(1-hydroxycyclohexyl)pyridine 1-oxide (**3**, X = Y = H) (4.6%) and 2,6-di(1-hydroxycyclohexyl)pyridine 1-oxide (**4**, X = Y = H) (14.8%). The structures of the products were established mainly on the basis of microanalysis and infrared and nmr spectroscopy. **3** (X = Y = H) was found to be identical with an authentic sample prepared from 2-(1-hydroxycyclohexyl)-pyridine *via* 2-pyridyllithium and cyclohexanone. When this reaction was carried out in ether alone only **3** (X = H) was obtained in low yield.

The reaction of 4-picoline 1-oxide (**2**, X = Me; Y = H) with *n*-BuLi and then cyclohexanone gave both **3** (X = Me; Y = H) and **4** (X = Me; Y = H). No exchange of the otherwise active side-chain protons took place under these conditions, or even at room temperature, since no product derived from a 4-pyridylmethyl anion was observed (see below, however, for conditions under which such a product *was* formed from 3,4-lutidine 1-oxide). This is to be contrasted with the ready formation of 4-picolyllithium from 4-picoline and phenyllithium and indicates that under the present conditions the C_2 H proton is more acidic than the 4-methyl protons in 4-picoline 1-oxide. In all cases, some 2-*n*-butylpyridines and 1-butylcyclohexanol were detected but not analyzed further.

The case of C_2 H proton abstraction is further emphasized by the fact that the 2-pyridyl 1-oxide carbanion is formed preferentially even in the presence of substituents in **2** which normally undergo nucleophilic substitution or halogen–metal interconversion very readily, *e.g.*, X = Cl or OEt. Thus, the reaction of 4-chloropyridine 1-oxide with *n*-BuLi in ether and then with cyclohexanone gave **3** (X = Cl, Y = H) (35.6%), and **4** (X = Cl, Y = H) (20.7%). No evidence for the formation of any 1-oxido-4-pyridyllithium was found in any of the reactions studied in which a 4-chloro substituent was present in the *N*-oxide. A 4-ethoxyl group was similarly inert. The retention of both a 4-chloro substituent and of the *N*-oxide function in these products should make this reaction quite useful, since such a 4-chloro group is known to undergo nucleophilic aromatic substitution readily.

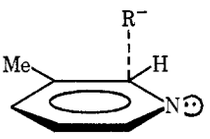
The physical constants of **3** and **4** are given in Table II.

The alkylation of 2-picoline 1-oxide (**5**) was investigated briefly. In contrast to the behavior of a 4-methyl group, the 2-methyl substituent was found to be more reactive than C_6–H toward proton abstraction by BuLi; thus, both 1-(1-oxido-2-pyridylmethyl)cyclohexanol (**6**) (4.3%) and α,6-di-(1-hydroxycyclohexyl)-2-methylpyridine 1-oxide (**7**) (19.6%) were obtained. **6** was identical with an authentic sample prepared from 2-picolyllithium and cyclohexanone followed by peracid N oxidation. As expected,[9] it was observed that in cases as those above where no substituents are present at the β and γ positions of the pyridine 1-oxide ring the C_3 H and C_4 H protons are not well resolved when the nmr spectra of the compounds in nonprotic solvents are determined.

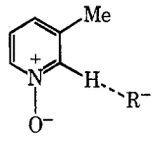


5 **6** **7**

The reaction with a number of 3-methylpyridine 1-oxides with cyclohexanone was studied with a view of determining the effect of a 3-methyl group upon the orientation of the entering group. It has been established that in the addition–elimination of an organolithium compound to 3-picoline the main product formed is the 2,3 isomer. For example, with phenyllithium the ratio of 3-methyl-2-phenyl- to 5-methyl-2-phenylpyridine is 19:1,[10] and, indeed, the 3-methyl group *activates* C_2 toward nucleophilic attack. It was expected that this situation would not obtain in the present case since the transition states for the two reactions should be quite different. In the SNAr process, the highly reactive nucleophile attacks the α carbon atom in a direction perpendicular to the plane of the ring and the transition state is reached quite soon, before too much rehybridization has taken place (**8**) (*i.e.*, the transition state looks more like the ground state than the intermediate σ complex),[1,10] so that a 3-methyl group exerts very little, if any, steric hindrance to attack at C_2. On the other hand, proton abstraction from C_2 by base involves the approach of the base in line with the C_2–H bond and in the same plane as the *N*-oxide and 3-methyl group (**9**), so that the latter



8



9

might be expected to exert an appreciable steric effect in this case. It should be noted that there is no marked preference for C_2 H over C_6 H proton abstraction in the H–D exchange of 3-picoline methiodide with 0.1 *N* NaOD in D_2O at 26° ($k_{H\text{-}2}^{26°}/k_{H\text{-}6}^{26°}$ = 1.2)[5] and with 3-picoline 1-oxide the rates are almost identical.[11] On the other hand, *n*-butyllithium (tetramer or hexamer) is much bulkier than OD^-, and, even if the 2-lithio derivative is formed, its approach to the carbonyl group in cyclohexanone in the subsequent reaction will be sterically hindered by the groups flanking the carbanionic site.

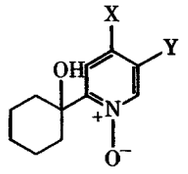
When 3-picoline 1-oxide in ether–tetrahydrofuran solution was treated with *n*-butyllithium followed by cyclohexanone, the main product formed was the 2-(1-hydroxycyclohexyl)-5-methyl derivative (**10**), and the 2,6-disubstituted compound (**11**) was the minor product. No 2-substituted compound unsubstituted at C_6 (**12**) was obtained in any of the alkylations studied here. An authentic sample of **10** was prepared from 2-bromo-5-methylpyridine.

The 3,4-disubstituted pyridine 1-oxides (**2**) studied behaved similarly on treatment with BuLi and then with an aldehyde or a ketone, giving either the 2α-

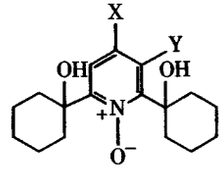
(9) R. A. Abramovitch and J. B. Davis, *J. Chem. Soc., B*, 1137 (1966).
(10) R. A. Abramovitch and C. S. Giam, *Can. J. Chem.*, **40**, 213 (1962).
(11) R. A. Abramovitch and G. M. Singer, unpublished results.

TABLE II

PHYSICAL CONSTANTS FOR 2-(1-HYDROXYCYCLOHEXYL)PYRIDINE 1-OXIDES (3) AND 2,6-DI(1-HYDROXYLCYCLOHEXYL)PYRIDINE 1-OXIDES (4)[f]



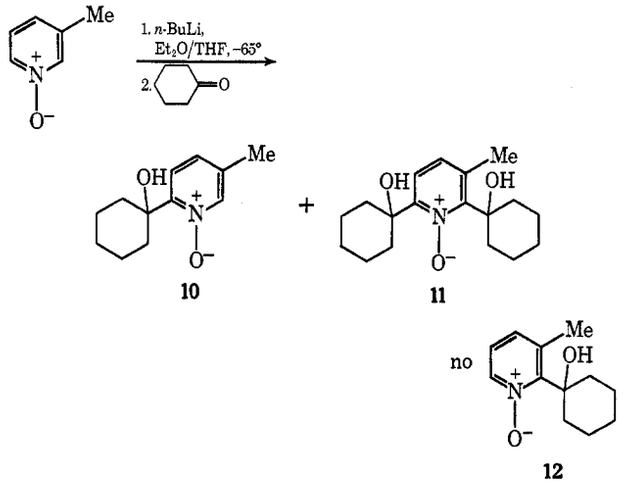
3



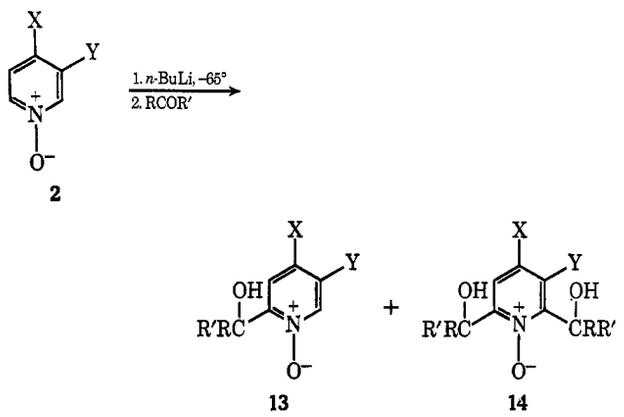
4

Registry no.	N-Oxide	Mp,[a] °C	Infrared spectrum, cm^{-1}	Nmr spectrum, τ: H_3	H_4	H_5	H_6	OH[e]	Aliphatic protons
34277-33-3	**3**, X = Y = H	93–94	3100 (s), 1296 (s), 1276 (w), 1237 (s), 1192 (s)	2.46–2.90[c]	2.46–2.90	2.46–2.90	1.82	2.44	7.40–9.00 (cyclohexyl)
17117-10-1	**4**, X = Y = H	158	3275 (s), 3180 (s), 1258 (m)	2.67[d]	2.67	2.67		2.74	7.50–8.65 (cyclohexyl)
17117-08-7	**3**, X = Me; Y = H	115	3130 (m), 1200 (s)	2.85[c]		2.96 ($J_{5,6}$ = 6 Hz)	1.93	2.17	7.68–8.85 (cyclohexyl), 7.66 ($ArCH_3$)
17117-09-8	**4**, X = Me; Y = H	198–199	3220 (s), 1125 (s)	2.90[c]		2.90		2.55	7.70–8.65 (cyclohexyl), 7.68 ($ArCH_3$)
34277-37-7	**3**, X = Cl; Y = H	113–114	3220 (w), 1276 (s)	2.70[c]		2.70	1.87	2.70	7.50–8.80 (cyclohexyl)
34277-38-8	**4**, X = Cl; Y = H	195	3260 (s), 1250 (s)	2.70[c]		2.70		3.01	7.50–8.65 (cyclohexyl)
17117-03-2	**3**, X = OEt; Y = H	128	3150 (m), 3040 (m), 1270 (m), 1220 (m), 1200 (w), 1155 (s)	3.10[c]		3.10	1.89	1.70	7.55–8.80 (cyclohexyl, $-CH_2CH_3$), 5.66–6.01 ($-OCH_2CH_3$)
17117-07-6	**4**, X = OEt; Y = H	166	3190 (s), 1270 (s), 1155 (s)	3.16[c]		3.16		2.18	7.55–8.70 (cyclohexyl, $-CH_2CH_3$), 5.68–6.03 ($-OCH_2CH_3$)
34277-41-3	**3**, X = H; Y = Me	123–125	3080 (m), 1265 (s), 1233 (s), 1193 (m), 1164 (s)	2.82[c]	2.82		1.96	2.40	7.50–8.90 (cyclohexyl, $ArCH_3$)
34277-42-4	**4**, X = H; Y = Me	138–139[b]	3600–3100 (s), 1260 (m), 1230 (w), 1208 (w), 1182 (m)		2.86[c]	2.86		1.40, 2.80	7.30–8.80 (cyclohexyl), 7.48 ($ArCH_3$)
17117-06-5	**3**, X = Y = Me	148–149	3140 (m), 1250 (s)	2.95[c]			2.10	2.18	8.10–8.87 (cyclohexyl), 7.87, 7.78 ($ArCH_3$)
34277-44-6	**4**, X = Y = Me	189–190	3320–3100 (m), 1260 (m), 1190 (s)			2.98[d]		1.57, 3.15	7.65–8.80 (cyclohexyl), 7.58, 7.48 ($ArCH_3$)
17117-04-3	**3**, X = Cl; Y = Me	164–165	3120 (m), 3015 (m), 1240 (m), 1160 (s)	2.83[d]			2.03	3.28	7.80–8.70 (cyclohexyl), 7.73 ($ArCH_3$)
34277-45-7	**4**, X = Cl; Y = Me	168–169	3340–3110 (m), 1263 (s), 1241 (s), 1215 (w), 1185 (s)			2.75[d]		2.01, 3.58	7.50–8.80 (cyclohexyl), 7.47 ($ArCH_3$)

[a] Recrystallized from acetone. [b] Recrystallized from methanol. [c] $CDCl_3$. [d] CCl_4. [e] OH exchanges with D_2O. [f] Satisfactory analytical values (±0.4% for C, H, N) for all compounds were reported: Ed.

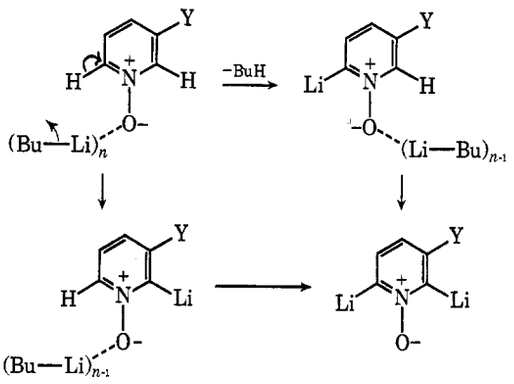


hydroxyalkyl 4,5-disubstituted compound (**13**) only or a mixture of the 2- and 2,6-di(α-hydroxyalkyl) derivatives (**14**). The question of the lack of formation of

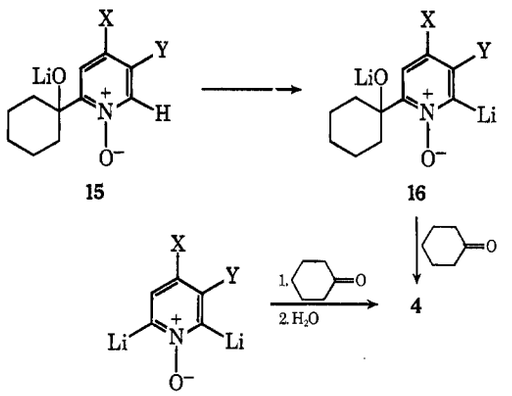


any 2-hydroxyalkyl 3-substituted derivatives in these reactions but the formation of 2,6-disubstitution product deserves discussion. Steric hindrance to approach in the plane of the ring of the bulky tetrameric or hexameric butyllithium, probably coordinated at the *N*-oxide oxygen, to the proton ortho to the methyl group would readily account for the preferential formation of **13**. The 2,6-disubstitution products **14** could then arise in a number of ways. The 2,6 dianion may first be formed (*cf.* *o*-dilithiobenzene[12]) and this then attacks the carbonyl compound. The question which comes to mind is why *no* 2-hydroxyalkyl derivative is formed if the 2,6 derivative is. If any 2-lithio 3-substituted 1-oxide were formed, one would expect some steric hindrance to its approach of the electrophilic carbonyl group, so that the latter might well be slower than that of the 6-lithio derivative, but not be forbidden as again the isolation of the 2,6 isomer testifies (proton abstraction leading to the cyclohexanone enolate anion and the pyridine 1-oxide may be favored over nucleophilic addition of the crowded anion to the carbonyl group). It is tempting to speculate that once the *N*-oxide-complexed butyllithium tetramer or hexamer has abstracted the proton from the 6 position the remaining complexed species may be less associated and hence less bulky, thus permitting an intramolecular approach to the C_2 H. This does not necessarily rule out the formation of some 2-lithio derivative initially, but the latter

(12) G. Wittig and F. Bickelhaupt, *Chem. Ber.*, **91**, 883 (1958).



would be expected to give the 2,6-dilithio derivative faster than would the 6-lithio compound, so that this fact, combined with the slower attack of the C_2 carbanion on the ketone when the latter is added, could account for the observation that no 2-monosubstituted derivative was formed in these cases. It is possible that with smaller electrophiles some 2 monosubstitution would be observed. Alternatively a dicarbanion may not be formed but the 6-monosubstituted anion **15** abstracts a proton from C_2 of another molecule to give **16**, this now reacting with more cyclohexanone to



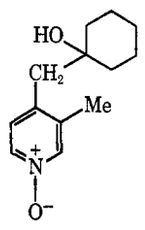
give **4**. An intramolecular proton abstraction can undoubtedly be ruled out on steric grounds. It is not clear why **15** might prefer to abstract a proton from the hindered 2 position rather than from a molecule of the unreacted *N*-oxide (some of which is always recovered). 1-Butylcyclohexyl oxide anion or cyclohexanone enolate anion could be the bases abstracting the C_2 H proton intermolecularly from **15** in the excess cyclohexanone present. None of these explanations appear to account for all the facts, but the evidence available from the use of halogens as electrophiles suggests that the dicarbanions are indeed formed, at least to some extent.[13] On the other hand, *both* possible 1-hydroxy-2-pyridinethiones were obtained on treatment of the lithio derivatives of 3,4-lutidine 1-oxide with sulfur, indicating that in this case both the 2- and the 6-lithio 3-substituted 1-oxides were formed,[13] which would be consistent with the first explanation proposed if sulfur is regarded as a smaller electrophile than cyclohexanone.

The effect of temperature upon the yields of products was studied briefly. In some cases, *e.g.*, pyridine 1-oxide in ether and cyclohexanone, it was found that warming the mixture to room temperature before the addition of cyclohexanone gave improved yields, while

(13) R. A. Abramovitch and E. E. Knaus, *J. Heterocycl. Chem.*, **6**, 989 (1969).

in others, *e.g.*, 4-chloropyyridine 1-oxide and cyclohexanone, the opposite was true. The addition of tetramethylethylenediamine (TMEDA) to the butyllithium solution did not improve the yields.

Sodium hydride and sodium bistrimethylsilylamide in benzene were not particularly effective as proton abstractors. Lithium bistrimethylsilylamide in ether was somewhat more effective, and in the reaction with 3,4-lutidine 1-oxide and cyclohexanone no 2,6-disubstitution product was formed. In addition to the 2-(1-hydroxycyclohexyl)-4,5-dimethyl derivative, however, there was obtained a small yield of 3-methyl-4-(1-hydroxycyclohexylmethyl)pyridine 1-oxide (**17**). Its



17

mass spectrum exhibited a parent ion peak at *m/e* 221 and an $(M - 18)^+$ ion at *m/e* 203 due to loss of water. The most important fragment arose from loss of the 3,4-dimethylpyridine 1-oxide ion ($C_7H_9NO^+$) to give a base peak at *m/e* 123. Interestingly, there was no $(M - 16)^+$ ion peak at *m/e* 205 which would have arisen from the loss of an oxygen atom from the molecular ion. The isolation of **17** provides the first example of a base-catalyzed proton abstraction of a 4-methyl proton in this study.

Lithium and thallous ethoxide, as well as potassium 2,6-di-*tert*-butylphenoxide, were completely ineffective as basic catalysts in this reaction.

Experimental Section

Melting points are uncorrected. In most cases only the main infrared bands are reported.

Starting Pyridine 1-Oxides.—3,4-Lutidine 1-oxide, prepared in 77.4% yield by the peracetic acid oxidation of 3,4-lutidine and purified by chromatography on alumina followed by recrystallization from acetone, had mp 138° (lit.[14] mp 128–130°).

Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.50; H, 7.44; N, 11.32.

4-Chloropyridine 1-oxide[15] (86%) had mp 181–182°, and 4-chloro-3-methylpyridine 1-oxide[16] (87%) had mp 119–120°.

2-(1-Hydroxycyclohexyl)pyridine 1-Oxide.—2-(1-Hydroxycyclohexyl)pyridine[17] (2.021 g) was oxidized with peracetic acid at 70–80° for 6 hr, with the addition of further amounts (2 ml) of 30% H_2O_2 every 12 hr. The product was purified by chromatography on a column of alumina and recrystallized from acetone, and was obtained as a solid (1.89 g, 86.4%).

2-(1-Hydroxycyclohexyl)-5-methylpyridine 1-Oxide.—2-(1-Hydroxycyclohexyl)-5-methylpyridine[18] (0.822 g) was oxidized with peracetic acid at 70° for 24 hr. The product was purified by chromatography on a column of alumina and recrystallized from acetone (0.513 g, 56.7%).

1-(1-Oxido-2-pyridylmethyl)cyclohexanol.—1-(2-Pyridylmethyl)cyclohexanol[19] (3.2 g) was oxidized with peracetic acid at 70° for 18 hr to give the ***N*-oxide** (3.1 g, 89.4%), mp 113–114° (acetone), ir (KBr) 3400–3200 (s, OH) and 1225 cm^{-1} (s, $^+NO^-$).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.25; N, 6.76. Found: C, 69.59; H, 8.16; N, 6.91.

Preparation of Pyridyl 1-Oxide Carbanions and Their Reactions with Aldehydes and Ketones. General Procedure.—To a stirred solution (or suspension) of the pyridine 1-oxide (0.007 mol) in anhydrous ether (or tetrahydrofuran) (40–60 ml) at −65° under dry N_2, *n*-butyllithium (0.96 g in hexane solution, 0.015 mol) was added dropwise. After stirring the solution for 15 min at that temperature, a solution of the aldehyde or ketone (0.015 mol) in anhydrous ether (or tetrahydrofuran) (10 ml) was added dropwise to give a dark red to brown solution. The reaction mixture was stirred for 1–3 hr at −65° and then allowed to warm to room temperature and decomposed with water (10 ml). The excess ether (or tetrahydrofuran) was evaporated *in vacuo*, and the products were isolated from the aqueous solution as described in individual cases.

Reaction of Pyridyl 1-Oxide Carbanion with Acetaldehyde.—Pyridine 1-oxide (1.90 g, 0.02 mol) in anhydrous tetrahydrofuran (70 ml) was treated with *n*-butyllithium (2.56 g in hexane, 0.04 mol) and then with acetaldehyde (1.76 g, 0.04 mol) at −65°. The orange viscous oil (2.6 g) obtained was chromatographed on a silica gel column (2.5 × 35 cm). Elution with benzene–ether (3:1, v/v) gave a brown aliphatic oil (0.198 g) which was not investigated further. Further elution with benzene–ether (3:1, v/v) and then ether gave **2,6-di(1-hydroxyethyl)pyridine 1-oxide** as a yellow oil (1.103 g, 30.1%), bp 127° (0.075 mm), which crystallized on standing to give a white solid: mp 70–72°; ir (neat) 3350 (s); nmr ($CDCl_3$) τ 8.47 (d, J = 6.5 Hz, 6, $-CHCH_3$), 4.76 (q, J = 6.5 Hz, 2, $-CHCH_3$), 4.18 (s, 2, OH, exchange with D_2O), 2.56 (s, 3, C_3H, C_4H, C_5H); mass spectrum no M^+ at *m/e* 183, *m/e* 165 (45, $M^+ - H_2O$).

Anal. Calcd for $C_9H_{13}NO_3$: C, 58.99; H, 7.15. Found: C, 58.45; H, 7.52.

Further elution with ether–methanol (4:1, v/v), and then methanol gave 2-(1-hydroxyethyl)pyridine 1-oxide as a yellow oil (1.01 g, 36.3%), bp 110° (0.075 mm), which crystallized on standing: mp 97–98° (lit.[20] mp 97–99°); ir (KBr) 3350 (s) and 1225 cm^{-1} (s); nmr ($CDCl_3$) τ 8.47 (d, J = 6.5 Hz, 3, $-CHCH_3$), 4.76 (q, J = 6.5 Hz, 1, $-CHCH_3$), 4.02 (s, 1, OH exchanges with D_2O), 2.60–2.94 (m, 2, C_4H, C_5H), 2.46 (q, $J_{3,4}$ = 8 Hz, $J_{3,5}$ = 3 Hz, 1, C_3H), 1.85 ($J_{5,6}$ = 6 Hz, $J_{4,6}$ = 2 Hz, 1, C_6H); mass spectrum *m/e* 121 ($M^+ - H_2O$) (no M^+ ion at *m/e* 139 observed).

Reaction of 4-Chloro-3-methylpyridyl 1-Oxide Carbanion with Benzaldehyde.—4-Chloro-3-methylpyridine 1-oxide (1.00 g, 0.007 mol) was suspended in anhydrous ether (50 ml) and treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol) and then with freshly distilled benzaldehyde (1.59 g, 0.015 mol) at −65° for 1 hr. The aqueous solution was acidified with dilute hydrochloric acid and then extracted with ether to remove any unreacted benzaldehyde. The acidic solution was made alkaline with 10% NaOH solution, and then extracted with $CHCl_3$ (3 × 75 ml). The dried (K_2CO_3) $CHCl_3$ extract was evaporated *in vacuo* to give a yellow-oil (0.824 g) which was distilled at 140° (0.03 mm) to give a yellow oil (0.593 g), trituration of which gave **4-chloro-2-(1-hydroxy-2-benzyl)-5-methylpyridine 1-oxide** (0.163 g, 9.4%): mp 134–135° (from acetone); ir (KBr) 3300–3100 (s), 1235 (s), and 1155 cm^{-1} (s); nmr ($CDCl_3$) τ 7.70 (s, 3, $ArCH_3$), 3.82 (s, 2, Ar_2CH- and OH, the latter exchanges with D_2O), 2.53 (m, 6, $-C_6H_5$, C_3H), 1.93 (s, 1, C_6H).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.18; H, 4.89; N, 5.67.

Reaction of 3,4-Dimethylpyridine Carbanion with *n*-Butyraldehyde.—3,4-Dimethylpyridine 1-oxide (0.68 g, 0.007 mol) in anhydrous tetrahydrofuran (60 ml) was treated with *n*-butyllithium (0.96 g in hexane, 0.015 mol), and then with *n*-butyraldehyde (1.08 g, 0.015 mol) at −65° for 1 hr and worked up as above. The yellow oil obtained (0.988 g) was distilled at 122° (0.01 mm) to give a yellow oil (0.400 g) which, on trituration with ether, chromatography on alumina, and recrystallization from acetone, gave **(4,5-dimethyl-1-oxido-2-pyridyl)-*n*-propylcarbinol** (0.200 g, 14.7%): ir (KBr) 3250–3050 (s), 3000–2860 (s), 1260 (s), 1175

(14) R. A. Jones and R. P. Rao, *Aust. J. Chem.*, **18**, 583 (1965).

(15) N. N. Vereschchagina and I. Ya. Postovski, *Tr. Ural. Politekh. Inst. imeni S. M. Kirova*, **94**, 24 (1960); *Chem. Abstr.*, **56**, 8681e (1962).

(16) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

(17) H. I. Lochte, P. F. Kruse, and E. N. Wheeler, *J. Amer. Chem. Soc.*, **75**, 4477 (1953); R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. C*, 2104 (1969).

(18) C. F. H. Allen and J. R. Thirtle, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 136.

(19) T. Kato, H. Yamanaka, and T. Adachi, *Yakugaku Zasshi*, **85**, 611 (1965); *Chem. Abstr.*, **63**, 9911c (1965); M. J. Betts and B. R. Brown, *J. Chem. Soc.*, 1730 (1967).

(20) V. Bockelheide and W. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

(s), and 1135 cm^{-1} (w); nmr ($CDCl_3$) τ 7.90–9.30 (m, 7, C_3H_7), 7.83 (s, 3, $ArCH_3$), 7.75 (s, 3, $ArCH_3$), 5.08 [t, 1, $ArCH(CH_2)_2$], 4.00 (s, 1, OH, exchanges with D_2O), 2.88 (s, 1, C_3H), 1.99 (s, 1, C_6H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.75. Found: C, 67.63; H, 8.93.

Reaction of Pyridyl 1-Oxide Carbanion with Acetone.—Pyridine 1-oxide (1.35 g, 0.015 mol) in anhydrous tetrahydrofuran (70 ml) was treated with *n*-butyllithium (1.92 g in hexane, 0.03 mol) and the mixture was treated with acetone (1.74 g, 0.03 mol) for 3 hr. The product was a brown oil which crystallized to give **2,6-di(1-methyl-1-hydroxyethyl)pyridine 1-oxide** (0.534 g, 17.8%): mp 118° (chromatographed on alumina and recrystallized from acetone); ir (KBr) 3300–3200 (s), 1266 (w), 1195 (s), 1168 (s), and 1150 cm^{-1} (m); nmr ($CDCl_3$) τ 8.40 [s, 12, 2 $>C(CH_3)_2$], 2.60 (s, 3, C_3H, C_4H, C_5H), 2.50 (s, 2, OH, exchanges with D_2O).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11. Found: C, 62.40; H, 8.35.

4-(1-Hydroxycyclohexylmethyl)-3-methylpyridine 1-oxide had mp 217–219° (acetone); ir (KBr) 3240 (s), 1275 (s), 1185 (s), 1175 (s), and 1160 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.35; H, 8.79.

Dimethyl (1-oxido-4,5-dimethyl-2-pyridyl)carbinol had mp 129° (acetone); ir (KBr) 3150 (s), 1250 (s), 1180 (s), and 1150 cm^{-1} (s); nmr ($CDCl_3$) τ 8.35 [s, 6, $>C(CH_3)_2$], 7.77 (s, 3, $ArCH_3$), 7.68 (s, 3, $ArCH_3$), 2.82 (s, 1, C_3H), 1.98 (s, 1, C_6H), 1.93 (s, 1, OH, exchanges with D_2O).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.00; H, 8.47; N, 7.89.

1-(1-Oxido-4,5-dimethyl-2-pyridyl)-1-phenylethanol had mp 141° (acetone); ir (KBr) 3200–3100 (w), 1245 (s), and 1155 cm^{-1} (s); nmr ($CDCl_3$) τ 8.17 (s, 3, $-CCH_3$), 7.82 (s, 3, $ArCH_3$), 7.70 (s, 3, $ArCH_3$), 2.70 (m, 6, C_3H, C_6H_5), 2.05 (s, 1, C_6H), 1.60 (s, 1, OH, exchanges with D_2O).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.97; H, 7.17.

α,6-Di(1-hydroxycyclohexyl)-2-methylpyridine 1-oxide had mp 111° (acetone); ir (KBr) 3300–3100 (s), 1275 (m), and 1200 cm^{-1} (s).

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91. Found: C, 70.83; H, 9.11.

Acknowledgments.—This work was carried out during the tenure of National and Medical Research Council of Canada Studentships by E. M. S. and E. E. K. Preliminary work was carried out with the financial support of the National Research Council and the balance with the support of a grant from the National Institutes of Health (Grant No. GM16626) whom we thank. We also wish to thank the Reilly Tar and Chemical Corporation for the gift of some pyridine 1-oxides.

Registry No.—1-(1-Oxido-2-pyridylmethyl)cyclohexanol, 34277-46-8; 2,6-di(1-hydroxyethyl)pyridine 1-oxide, 34277-47-9; 2-(1-hydroxyethyl)pyridine 1-oxide, 34277-48-0; 4-chloro-2-(1-hydroxy-2-benzyl)-5-methylpyridine 1-oxide, 34965-48-5; (4,5-dimethyl-1-oxido-2-pyridyl)-*n*-propylcarbinol, 34277-50-4; 2,6-di(1-methyl-1-hydroxyethyl)pyridine 1-oxide, 34277-51-5; 4-(1-hydroxycyclohexylmethyl)-3-methylpyridine 1-oxide, 34277-52-6; dimethyl (1-oxido-4,5-dimethyl-2-pyridyl)carbinol, 34277-58-2; 1-(1-oxido-4,5-dimethyl-2-pyridyl)-1-phenylethanol, 34277-59-3; 2,6-di(1-hydroxycyclohexyl)-2-methylpyridine 1-oxide, 34277-60-6.

Ring-Opening Reactions of the Pyrazolo[1,2-*a*]pyridazin-6-one System[1]

ROBERT J. WEINKAM[2] AND BERNARD T. GILLIS*[3]

Chemistry Department, Duquesne University, Pittsburgh, Pennsylvania 15219

Received December 28, 1971

The ring-opening reactions of 8-phenyl-1,4-methano-1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (**4**) and 1,4,8-triphenyl-1,4-dihydropyrazolo[1,2-*a*]pyridazin-6-one (**5**) in dilute hydrochloric acid and potassium hydroxide solutions were found to give 1- and 2-nitrogen-substituted pyrazol-3-one derivatives in high yield. The ring-opening reactions of **5** yielded 1-(1,4-diphenyl-1,3-butadienyl)-3-hydroxy-5-phenylpyrazole in potassium hydroxide solution, 1-(4-hydroxy-1,4-diphenyl-2-butenyl)-3-hydroxy-5-phenylpyrazole in hydrochloric acid, and the corresponding trichloroacetate in trichloroacetic acid. The ring opening of **4** in hydrochloric acid gave 1-(4-hydroxy-2-cyclopentenyl)-5-hydroxy-3-phenylpyrazole but no ring opening of **4** was observed in potassium hydroxide solution. The hydrogenated adduct, 8-phenyl-1,4-methano-1,2,3,4-tetrahydropyrazolo[1,2-*a*]-pyridazin-6-one, did not open under acidic or basic conditions.

The Diels–Alder reaction has been known to yield pyridazine derivatives since 1925.[4] The majority of work in this area from 1925 until 1960 has dealt with adducts of acyclic azodicarboxylates. Since 1960 a number of workers have reported adducts of cyclic acyl[5–7] and diacyl-cis-azo compounds.[8–11] Although the azodicarboxylate adducts have been shown to undergo a number of useful reactions,[12–15] investigations of the potentially more interesting adducts of cyclic azo compounds have not been pursued. The following is a report of some ring-opening reactions of pyrazol-3-one adducts to give N-substituted pyrazolin-3-ones.

The oxidation of a 3-substituted 2-pyrazolin-5-one (**1**) with lead tetraacetate gave the pyrazol-3-one ring system (**2**). When the oxidation was carried out in the presence of a diene the pyrazol-3-ones were trapped as Diels–Alder adducts (**3**).[6] The adducts **4** and **5** of cyclopentadiene and of 1,4-diphenylbutadiene, respectively, with 5-phenylpyrazol-3-one (**2**, R = C_6H_5)[6] were investigated in the course of this work.

(1) This investigation was supported in part by Grant GP-7680 from the National Science Foundation.

(2) National Aeronautics and Space Administration Fellow, 1965–1968.

(3) Indiana University of Pennsylvania, Indiana, Pa. 15701.

(4) O. Diels, J. H. Blom, and W. Koll, *Justus Liebigs Ann. Chem.*, **443**, 242 (1925).

(5) E. F. Ullman and E. A. Bartkus, *Chem. Ind. (London)*, 93 (1962).

(6) B. T. Gillis and R. J. Weinkam, *J. Org. Chem.*, **32**, 3321 (1967).

(7) B. T. Gillis and J. G. Dain, *ibid.*, **36**, 518 (1971).

(8) R. A. Clement, *ibid.*, **25**, 1724 (1960).

(9) R. A. Clement, *ibid.*, **27**, 1115 (1962).

(10) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, **No. 14**, 615 (1962).

(11) B. T. Gillis and R. A. Izydore, *J. Org. Chem.*, **34**, 3181 (1969).

(12) R. G. Criegee and A. Rimmelin, *Ber.*, **90**, 44 (1957).

(13) C. G. Overberger and J. R. Hall, *J. Org. Chem.*, **26**, 4359 (1961).

(14) H. R. Snyder and J. G. Michels, *ibid.*, **28**, 1144 (1963).

(15) E. L. Allred, C. L. Anderson, and R. L. Smith, *ibid.*, **31**, 3493 (1966).