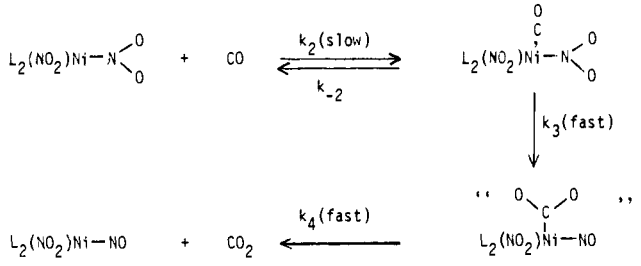
Scheme I



has a zero intercept (Figure 2). Addition of the free-radical inhibitor, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, had no effect on the rate of the reaction. Thus, the rate law, $-d[Ni(NO_2)_2(DPPE)]/dt = k_2[Ni(NO_2)_2(DPPE)][CO]$, is applicable with a value of 2.1×10^{-1} dm^3 mol^{-1} s^{-1} for k_2 at 20 °C.

It was concluded that this reaction is associative, which is typical for square planar complexes of nickel(II).[9] The proposed mechanism for this reaction, based on these results and other chemical properties of square planar NiX_2L_2 complexes discussed below, is outlined in Scheme I. In this mechanism, the rate-determining step is the formation of the five-coordinate monocarbonyl complex, $Ni(NO_2)_2(CO)(DPPE)$ (reaction 2), followed by the transfer of an oxygen atom to CO (reaction 3), and terminated by the loss of CO_2 (reaction 4). The isolation and characterization of $NiBr_2(CO)(PMe_3)_2$ reported recently by Saint-Joly et al.[10] show that square planar nickel complexes of the type NiX_2L_2 will indeed add one CO molecule. However, in the absence of an oxidizing NO_2 ligand, no further reaction of CO takes place and the five-coordinate monocarbonyl complex can then be isolated. When the NO_2 ligand is present, an intramolecular attack on the CO ligand analogous to that found for the reaction between the isoelectronic NO^+ ligand and the nitro group of *cis*-$[Fe(NO)(NO_2)(S_2CNMe_2)_2]$ which we reported earlier[1] can take place. The oxygen atom transfer from NO_2 to CO would then produce an unstable intermediate or transition state similar to the C-bonded CO_2 complex of Co(I), whose structure was recently reported.[11]

An alternative mechanism in which CO attacks the oxygen atom of the coordinated NO_2 group is also consistent with the observed rate law.[12] However, this mechanism provides a less than satisfactory explanation of the lack of reaction between NO_2^- and CO in the absence of transition metals and of the dependence of the rate of reaction 1 on L.[13] In contrast, Scheme I requires the rate of formation of $Ni(NO_2)_2(CO)L_2$ to be dependent upon the electronic and steric requirements imposed by L.[14] Experiments in progress are designed to detect the five-coordinate intermediate required by Scheme I. It is also worth noting that these nickel complexes are potential homogeneous catalysts for the reaction between O_2 and CO at subatmospheric pressure, since we have found that O_2 will oxidize $Ni(NO)(NO_2)(DPPE)$ to $Ni(NO_2)_2(DPPE)$.[15]

Another oxidation of carbon monoxide catalyzed by transition metals (reaction 5) has been extensively studied:[16]

$$2NO + CO \rightarrow CO_2 + N_2O \qquad (5)$$

Although reaction 5 is complicated and consists of several steps, the transfer of at least one oxygen atom is required. One of the possible mechanisms proposed for this reaction involves the transfer of an oxygen atom from a coordinated nitro group as one of the key reactions.[17] The present study shows that the nitro group can transfer an oxygen atom directly to carbon monoxide, a step which may also play a role in the catalysis of the CO/NO reaction.

Note Added in Proof. A recent study using ^{18}O-labeled *trans*-$[Ni(NO_2)_2(PEt_3)_2]$ has shown that $-NO_2$ is the oxygen source for CO_2 production. The observed ^{18}O enrichment of product CO_2 is consistent with Scheme I, and a similar mechanism was independently proposed by Doughty et al.[18]

Acknowledgments. We thank the National Science Foundation for its support of this research and Drs. J. V. Rund and J. H. Enemark for their many helpful discussions. We especially thank Drs. M. and Y. Dartiguenave for copies of their papers prior to publication.

References and Notes

(1) For the previous paper in this series, see O. A. Ileperuma and R. D. Feltham, *Inorg. Chem.*, **16**, 1876 (1977).
(2) The calculated value of δH° for the reaction of CO with NO_2^- in aqueous solution, $2CO_{(g)} + 2NO_2^-{}_{(aq)} + H_2O_{(l)} \rightarrow 2HCO_3^-{}_{(aq)} + N_2O_{(g)}$, is -585.8 kJ.
(3) No reaction was observed between $NaNO_2$ (0.11 M) and CO (1 atm) in water or between $(Et_4N)(NO_2)$ (2.2×10^{-1} M) and CO (1 atm) in dichloromethane over a 2-h period. A modest search of the literature disclosed no reference to this reaction.
(4) (a) G. Booth and J. Chatt, *J. Chem. Soc.*, 2099; (b) K. R. Grundy, K. R. Laing, and W. R. Roper, *Chem. Commun.*, 1500 (1970); (c) W. Manchot and A. Waldmuller, *Chem. Ber.*, **59**, 2363 (1926); (d) W. Hieber and J. S. Anderson, *Z. Anorg. Allgem. Chem.*, **208**, 238 (1932); (e) W. Hieber and H. Beutner, *Z. Naturforsch., B*, **15**, 323 (1960); (f) W. Hieber and J. S. Anderson, *Z. Anorg. Allgem. Chem.*, **221**, 132 (1933).
(5) The $\{MNO\}^n$ notation is that of J. H. Enemark and R. D. Feltham, *Coord. Chem. Rev.*, **13**, 339 (1974).
(6) The nickel compounds $Ni(NO_2)_2L_2$ were prepared and their reactions with CO noted: L is $\frac{1}{2}$(DPPE), PMe_2Ph, and $\frac{1}{2}(Ph_2PCHCHPPh_2)$. Each of the compounds has been characterized by satisfactory elemental analyses and by IR and visible–UV spectroscopy.
(7) DPPE is 1,2-bisdiphenylphosphinoethane.
(8) Elemental analyses. Found (calcd) for $Ni(NO_2)_2(DPPE)$: C, 56.71 (56.86); H, 4.24 (4.37); N, 4.88 (5.10); O, 11.41 (11.66). Found (calcd) for $Ni(NO)(NO_2)(DPPE)$: C, 58.37 (58.58); H, 4.58 (4.50); N, 5.06 (5.26); O, 9.59 (9.01). The evolved gases were collected at −198 °C and fractionated, and the amount of CO_2 was determined by PV measurements at room temperature. The mole ratio found for CO_2 and Ni was 0.94:1.00.
(9) (a) M. Cusmano and V. Ricevuto, *J. Chem. Soc., Dalton Trans.*, 1682 (1978); (b) R. K. Murmann, *Inorg. Chem.*, **2**, 116 (1963); (c) E. J. Billo, *ibid.*, **12**, 2783 (1973); (d) F. Basolo, J. Chatt, H. B. Gray, R. G. Pearson, and B. L. Shaw, *J. Chem. Soc.*, 2207 (1961); L. Cattalini, M. Martelli, and P. Rigo, *Inorg. Chim. Acta*, **1**, 149 (1967).
(10) S. Saint-Joly, M. Dartiguenave, and Y. Dartiguenave, *Adv. Chem. Ser.*, **No. 173**, in press.
(11) G. Fachinetti, C. Floriani, and P. F. Zanazzi, *J. Am. Chem. Soc.*, **100**, 7405 (1978).
(12) B. S. Tovrog, S. E. Diamond, and F. Mares, *J. Am. Chem. Soc.*, **101**, 270 (1979).
(13) The rates of reaction of CO with the nickel complexes listed in ref 6 show considerable variation based on qualitative observations.
(14) See, for example, C. A. Tolman, W. C. Seidel, and L. W. Gosser, *J. Am. Chem. Soc.*, **96**, 53 (1974); Y. Nakamura, K. I. Maruya and T. Mizoroki, *J. Organomet. Chem.*, **104**, C5 (1976).
(15) Several cycles of the reduction of $Ni(NO_2)_2(DPPE)$ in CH_2Cl_2 to $Ni(NO)(NO_2)(DPPE)$ followed by reoxidation to the starting material by atmospheric oxygen have been carried out. Atmospheric oxygen has also been observed to oxidize Ni(NO)Cl(DPPE) by R. Ugo, S. Bhaduri, B. F. G. Johnson, A. Khair, and A. Pickard, *J. Chem. Soc., Chem. Commun.*, 694 (1976).
(16) (a) B. F. G. Johnson and S. Bhaduri, *J. Chem. Soc., Chem. Commun.*, 650 (1973); (b) B. L. Haymore and J. A. Ibers, *J. Am. Chem. Soc.*, **96**, 3325 (1974); (c) C. D. Meyer and R. Eisenberg, *ibid.*, **98**, 1364 (1976); (d) D. E. Hendricksen and R. Eisenberg, *ibid.*, **98**, 4662 (1976); (e) D. E. Hendricksen, C. D. Meyer, and R. Eisenberg, *Inorg. Chem.*, **16**, 970 (1977); (f) S. Bhaduri and B. F. G. Johnson, *Trans. Met. Chem. (Weinheim, Ger.)*, **3**, 156 (1978); (g) M. Kubota, K. J. Evans, C. A. Koerntgen, and J. C. Marsters, *J. Am. Chem. Soc.*, **100**, 342 (1978); (h) R. Eisenberg and C. D. Meyer, *Acc. Chem. Resch.*, **8**, 26 (1975)
(17) See Scheme II, ref 16h.
(18) D. T. Doughty, G. Gordon, and R. P. Stewart, *J. Am. Chem. Soc.*, **101**, 2645 (1979).

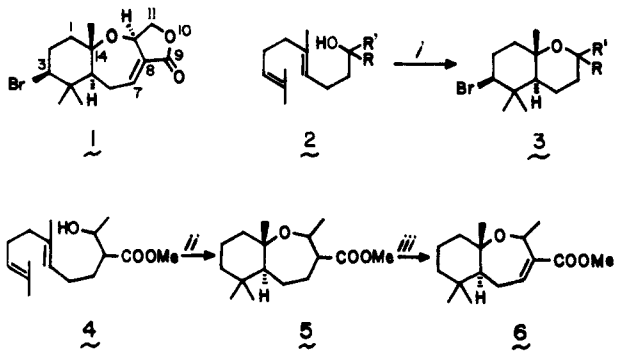
Robert D. Feltham,* Jeanne C. Kriege
Department of Chemistry, University of Arizona
Tucson, Arizona 85721
Received March 21, 1979

Total Synthesis of *dl*-Aplysistatin

Sir:

Aplysistatin (**1**) is a brominated sesquiterpene recently extracted from the South Pacific Ocean sea hare, *Aplysia ang-*

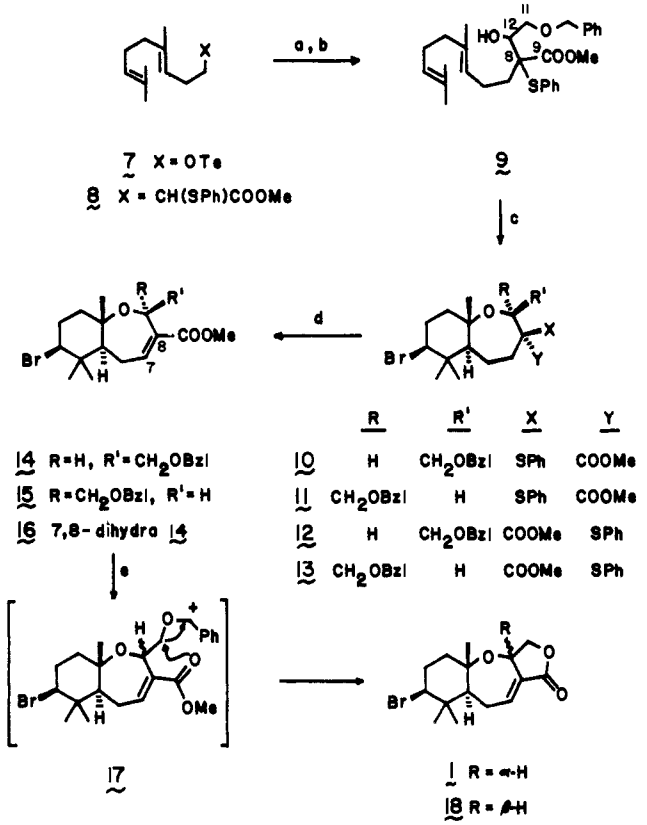
0002-7863/79/1501-5065$01.00/0



asi.[1] The compound possesses both a structurally unique heterocyclic skeleton and significant inhibitory activity against murine lymphocytic leukemia P-388 progression. This communication describes the first total synthesis of the molecule.

Our synthetic strategy was guided by three early experimental observations. (i) Mercuric trifluoroacetate mediated brominative cyclization of a variety of diene alcohols of type **2** ($Hg(TFA)_2$, CH_3NO_2; saturated KBr, H_2O; Br_2, LiBr, O_2, py) led to the bromoperhydro[1]benzopyrans **3** in 25-45% overall yield.[2] (ii) A diastereomeric mixture of alcohols **4**[3,4] was successfully cyclized by mercuric ion to the perhydro[1]-benzoxepins **5**[4] in somewhat lower yield ($Hg(TFA)_2$, CH_3NO_2; $NaBH_4$, NaOH, H_2O) thus confirming that seven-membered cyclic ethers could be prepared in this fashion.

Scheme I[a]

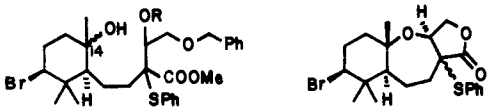


[a] (a) $PhSCH_2CO_2CH_3$, (LDA, THF, −78 °C, 40 min) added to **7** (Me_2SO, room temperature, 18 h); (b) **8** (LDA (1.4 equiv), THF, HMPA (2 equiv), −78 °C, 40 min) added to $ZnCl_2$ (1.4 equiv) (THF, 0 °C, 5 min), then add $PhCH_2OCH_2CHO$ (1.8 equiv) (THF, 0 °C, 2 min, NH_4Cl quench); (c) $Hg(TFA)_2$ (1.1 equiv) (CH_3NO_2, room temperature, ~1 h), saturated KBr (excess) (H_2O, room temperature, 16 h), Br_2 (1.5 equiv) (LiBr (2 equiv), O_2, py, room temperature 3 h); (d) *m*-CPBA (1 equiv) ($CDCl_3$, 0 °C), Δ (60-80 °C, $CDCl_3$, 15-30 min); (e) $Ph_3C^+BF_4^-$ (3 equiv) ($CDCl_3$, room temperature, 16 h).

(iii) One of the stereoisomers of **5** was selectively oxidized to the $\Delta^{7,8}$ olefin **6**[4,5] by α-phenylselenylation and oxidative elimination.[16] In light of these experiments, diene **9** was identified as an ideal acyclic precursor to test the validity of this general approach to aplysistatin (**1**) since positions 8, 9, 11, and 12[5] are appropriately oxidized.

Preparation of **9** (see Scheme I) commenced with the alkylation of the enolate anion from methyl 2-phenylthioacetate[6] with the *p*-toluenesulfonate ester of homogeraniol (**7**)[7] which gave ester **8** (64%).[4] Aldol condensation of the enolate anion derived from **8** with 2-benzyloxyacetaldehyde[8] required the presence of anhydrous zinc chloride,[9] presumably to drive the equilibrium to favor the alkoxide precursors of **9** (84%, 2:1 ratio of separable diastereomers).[4,10]

With **9** in hand we turned our attention to the crucial brominative cyclization. Each diastereomer of **9** led to a 1:1 mixture of diastereomeric bromoperhydro[1]benzoxepins **10** (11%) and **13** (11%) or **11** (11%) and **12** (11%).[4,10] The major and only other identifiable product in this reaction was the partially cyclized diol **19**[4,10] (1:1 ratio of C-14[5] epimers in 30% yield from the major diastereomer of **9**). This structural assignment was supported by conversion of the pair of epimers **19** into the separable monoacetates **20**.[4,10]



19 R = H
20 R = Ac

21

Initial attempts at reductive removal of the benzyl ether in preparation for lactonization of compounds **10–13** (H_2, 10% Pd/C, EtOH; H_2, 10% Pd/C, BF_3·OEt_2, MeOH[11]) or of the corresponding sulfoxides were unsuccessful. Furthermore, olefin **14**,[4] arising from pyrolysis (80 °C) of the sulfoxides derived from **10** and **12** was selectively saturated to **16**[4] rather than deprotected upon catalytic reduction (H_2, 10% Pd/C, EtOH). However, *oxidative* debenzylation of **10** or **12** with triphenylcarbenium tetrafluoroborate[12] ($Ph_3C^+BF_4^-$ (4 equiv) $CDCl_3$, room temperature, 22 h) not only induced loss of the benzyl ether moiety but proceeded with concomitant lactonization, presumably via direct nucleophilic participation of the adjacent methoxycarbonyl group.[13] The α-phenylthiolactone **21**[4,10] was the sole product originating from **10** or **12** that could be observed by direct NMR analysis of the reaction mixture. Oxidative elimination of **21** then afforded the first synthetic sample of aplysistatin (**1**).[14]

In practice it was more expedient to first convert each of the diastereomeric sulfides **10–13** into the epimeric unsaturated benzyl ethers **14** (from **10** and **12**) and **15** (from **11** and **13**) by oxidative elimination (~70%). In turn, each of these epimers obligingly suffered simultaneous debenzylation and lactonization (see **17**) under the influence of trityl fluoroborate to provide both aplysistatin (**1**, 51% from **14**)[14] and 12-epiaplysistatin (**18**, 60% from **15**).[4,15,17]

Acknowledgment. This research was supported by funds from the University of Minnesota Graduate School, the Research Corporation, a Du Pont Young Faculty Award, and the National Cancer Institute of the National Institutes of Health.

References and Notes

(1) Pettit G. R.; Herald, C. L.; Allen, M. S.; Von Dreele, R. B.; Vanell, L. D.; Kao, J. P. Y.; Blake, W. *J. Am. Chem. Soc.* **1977**, *99*, 262.
(2) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.*, in press.
(3) Prepared by alkylation of methyl acetoacetate with homogeranyl bromide ($CH_3COCH_2CO_2CH_3$, LiH, DMF, RBr, 80 °C) followed by reduction ($NaBH_4$, EtOH, 0 °C) of the purified β-keto ester.

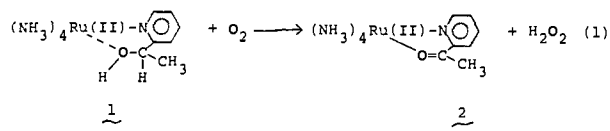
(4) All new compounds were characterized by complete (NMR, IR, mass spectrum (electron and/or chemical ionization)) spectroscopic analysis. Yields refer to isolated and chromatographically purified products.
(5) Aplysistatin numbering (see **1**) is used throughout the text.
(6) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318. Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *Ibid.* **1973**, *95*, 6137.
(7) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 2539.
(8) Rigby, W. *J. Chem. Soc.* **1950**, 1907.
(9) (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. Auerbach, R. A.; Crumrine, D. S.; Ellison, D. L.; House, H. O. *Org. Synth.* **54**, 49. It is interesting to note that enolates of the analogous α-alkoxy[9b,c] and α-dialkylamino[9c] esters and α-aryloxy-[9d] and α-phenylthio[9e] carboxylates do add efficiently to aldehydes and ketones in the absence of strongly chelating metals: (b) Glass, R. S.; Deardorff, D. R. Abstracts of Papers, 175th National Meeting of the American Chemical Society, Anaheim, Calif., March 1978; American Chemical Society: Washington, D.C., 1978; ORGN 81. (c) Touzin, A. M. *Tetrahedron Lett.* **1975**, 1477. (d) Adam, W.; Fick, H.-H. *J. Org. Chem.* **1978**, *43*, 772, 4574. (e) Kosugi, H.; Uda, H.; Yamagiwa, S. *J. Chem. Soc., Chem. Commun.* **1975**, 192.
(10) The stereochemical assignments for the two diastereomers of **9** (and therefore for **10** vs. **12**, **11** vs. **13**, **19**, **20**, and **21**) are not yet firm. Experiments are in progress to establish them conclusively and will be reported soon.
(11) Yajima, H.; Kawasaki, K.; Kinomura, Y.; Oshima, T.; Kimoto, S.; Okamoto, M. *Chem. Pharm. Bull.* **1968**, *16*, 1342.
(12) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans 1* **1972**, 542.
(13) We are currently in the process of assessing the synthetic generality of this type of cyclization reaction.
(14) The racemic synthetic material (mp 179–181 °C from hexanes–acetone (lit.[1] mp 173–175 °C)) gave identical NMR and mass spectra and a nearly identical IR (KBr) spectrum with those of a natural sample kindly provided by Professor Pettit.
(15) A second, more or less independent synthetic approach to aplysistatin (**1**) which focuses upon the formation of the C_{12}–O^5 ether linkage to complete the oxepane construction has led to a synthesis of 3-norbromo-4,4-nordimethylaplysistatin.[16] This work is currently being extended to aplysistatin itself and the details will be reported in due course.
(16) Experimental work of A. J. Caruso.
(17) This crystalline (mp 138–140 °C) epimer gave a satisfactory combustion analysis for C, H, Br.

Thomas R. Hoye,* Mark J. Kurth
Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455
Received March 21, 1979

Oxidation of Ruthenium Coordinated Alcohols by Molecular Oxygen to Ketones and Hydrogen Peroxide

Sir:

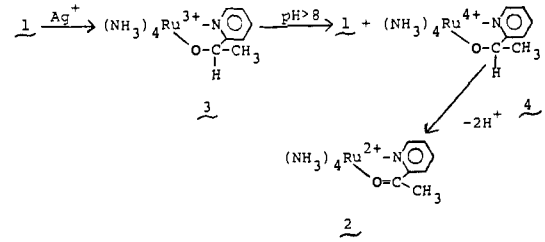
Selective oxidations of organic substrates mediated by metal complexes which would allow the formation of H_2O_2 instead of water (the usual final product of oxygen reduction) would be of great importance. This concept is demonstrated in the work described herein using ruthenium(II) complexes. Previously, ruthenium(II) complexes have been utilized to facilitate oxidation of coordinated imines and primary or secondary amines by molecular oxygen.[1-6] However, the mechanism of these oxidations and the fate of the molecular oxygen have only been speculated upon. We have observed that Ru(II)-alcohol complexes can be oxidized by O_2 to H_2O_2 and the corresponding Ru(IV)-alcohol complexes which then undergo metal-ligand redox leading to a Ru(II)-ketone complex (eq 1). Hydrogen peroxide has been identified as a reduction product of molecular oxygen.



1 2

Our initial study has centered on the oxidation of 2-(1′-hydroxyethyl)pyridine coordinated to Ru(II) as a bidentate ligand (eq 1). The complex **1** is prepared by substitution of the aquo ligands in *cis*-$(NH_3)_4Ru^{II}(OH_2)_2$ by 2-(1′-hydroxyethyl)pyridine in deoxygenated aqueous solution at 25 °C and pH 5. In analogy to other pyridine-Ru(II) complexes the absorption of **1** at 4100 Å (ϵ 3900) confirms coordination of the pyridine ring. Coordination of the alcohol group can be verified by the observed chemical shift in the ^1H NMR from δ_{CH_3} 1.51 in free 2-(1′-hydroxyethyl)pyridine to δ_{CH_3} 1.54 in $(NH_3)_5Ru^{II}$[2-(1′-hydroxyethyl)pyridine][7] where only the pyridine nitrogen is coordinated, to δ_{CH_3} 1.63 in **1**. The oxidation of the hydroxyethyl group in **1** to the acetyl group in **2** has been achieved via the Ru(IV) analogue of **1** which was generated by two independent routes as discussed below.

Disproportionation of Ru(III) Complex. Rudd and Taube have shown that $(NH_3)_5Ru^{III}py$ ($E°_{Ru(III)/Ru(II)} = +0.30$ V) disproportionates in solutions of pH >8 to $(NH_3)_5Ru^{II}py$ and the Ru(IV) analogue.[8] To determine if Ru(IV) could function as an oxidant, we performed an analogous disproportionation reaction with **3** (eq 2). Complex **3** was prepared in deoxygen-



ated acidic solution by oxidation of **1** with AgTFA. The pale yellow solution obtained after filtration of Ag^0 is stable indefinitely toward conversion into **2.** Upon raising the pH above 8, **3** disproportionates to **1** and **4.** The deep blue color characteristic of **2** (λ_{max} 6220 Å)[6] forms slowly, reaching a value of 72% of theoretical after 24 h at pH 11. Concurrently, formation of **1** can be verified by its absorption at 4100 Å. Similarly, the NMR of the reaction solution shows the presence of **1** and **2** in roughly similar amounts as observed in the visible spectra.[9]

The chemical shift in **2**,[10] δ_{CH_3} 2.92, relative to that in free 2-acetylpyridine, δ_{CH_3} 2.72, reveals that the ketone group in **2** is coordinated.

The disproportionation of $(NH_3)_5Ru^{III}py$ can be reversed by lowering the pH.[8] However, disproportionation of **3** can only be partially reversed owing to the formation of **2** from **4** produced in the disproportionation. For example, in a solution of **3**, [**3**] = 3.08×10^{-2} M at pH 10, 30% **2** is produced after 1 h. Upon lowering the pH at this time, the visible spectrum due to **2** is unchanged and the presence of **1** is apparent. These facts demand that **3** is only partially recovered and indicate that **4** has undergone an irreversible reaction, the ligand oxidation indicated in eq 2. Thus it has been demonstrated that Ru(IV) can be efficiently generated by Ru(III) disproportionation and that Ru(IV) can function as an oxidant for coordinated alcohols.

Reaction of 1 with O_2. The product profile obtained in reactions of **1** with O_2 is pH dependent (Table I). At pH 1 (expt 1) 5% **2** is produced in 2 h, an amount which does not increase with time. The other product of the reaction is **3**,[11] which is formed in analogy to the reaction of many other ammine-Ru(II) complexes with O_2.[12]

Reaction of **1** with O_2 at pH >7, however, is much different. For example, at pH 10, in an initial rapid reaction **1** is converted into **3** or **4.** This result alone is in contrast to the reactivity of the similar complex, $(NH_3)_5Ru^{II}py$, which is completely oxidized to its Ru(III) analogue in ~30 min[13] at pH 1 but only extremely slowly (hours) at pH 10. We attribute this difference to deprotonation of the hydroxy group in **3** or **4** leading to formation of Ru(III) or Ru(IV) alkoxide. This alkoxide formation should stabilize these higher oxidation states and lower the $E°_{Ru(III)/Ru(II)}$ of **3** below that of $(NH_3)_5Ru^{III}py$ ($E°_{Ru(III)/Ru(II)} = 0.30$ V).[14] A lower $E°$ should facilitate a faster reaction of **1** with O_2.[15] A similar

0002-7863/79/1501-5067$01.00/0