Electrochemistry of Natural Products. II. Electrolytic Oxidation of Some Simple 1,2,3,4-Tetrahydroisoquinoline Phenols[1]

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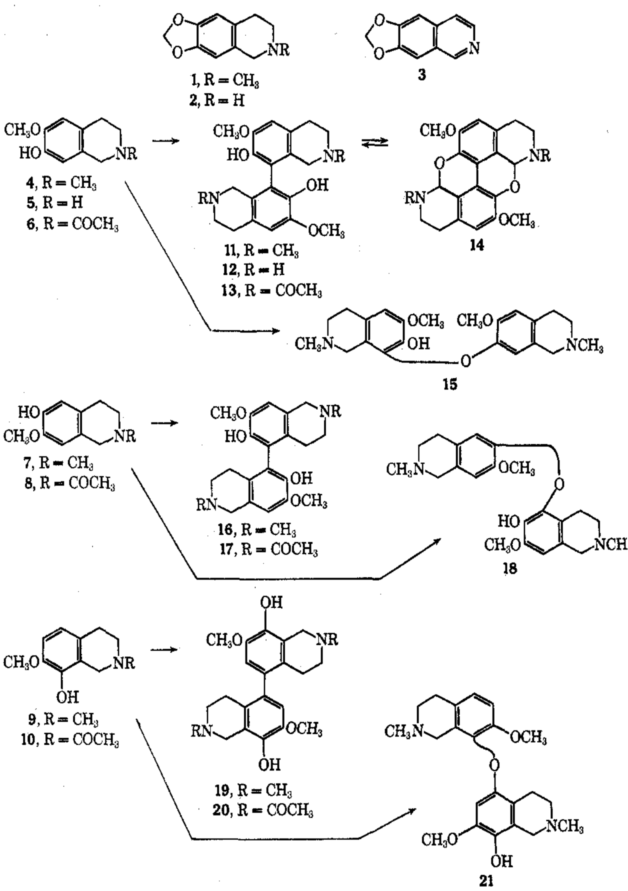
A series of derivatives of 1,2,3,4-tetrahydroisoquinoline has been oxidized electrolytically. Those containing phenol groups were dimerized to yield carbon–carbon dimers and carbon–oxygen–carbon dimers. Some of the variables such as the nature of the anode, the cell design, the solvent, the pH, and the reaction time were considered. The optimum conditions for the coupling of these phenols would seem to be oxidation of their sodium salts in CH_3CN using tetraethylammonium perchlorate as supporting electrolyte and a graphite felt anode. The results of a number of experiments are presented. The products of the reactions depend strongly upon the relative location of the phenol group in the aromatic ring and the nitrogen in the heterocyclic ring. An explanation for this phenomenon is proposed.

We have been interested in the electrolytic oxidations of phenolic tetrahydroisoquinolines[3] as model compounds for some of the more important biosynthetic oxidation reactions. In the previous paper of this series,[1] we studied the ratio of C–C dimers to C–O–C dimers as a function of the steric hindrance around the incipient bond between the isoquinolines. In this paper, we would like to present a more general and random study of some simple compounds.

The compounds oxidized fell into several groups. Compounds **1–3** were nonphenolic and were examined to see how easily the various forms of the nitrogen ring were oxidized. Three oxygenation patterns were examined for the phenols themselves. The pattern in **4–6** is the most common one in nature.[4] The isomeric patterns in **7** and **8** and in **9** and **10** were chosen for comparison. Three possible nitrogen functions, **4–6**, were studied for the natural system, and two were studied for the others. Compound **4**, the alkaloid, corypalline,[5] has been the starting point of several of our investigations[6] (Scheme I).

SCHEME I



Reaction Conditions. The Working Electrode.—The oxidation of **4** was studied in a two-compartment cell in aqueous systems with five different working electrodes. The results are given in Table I. The best yields at the lowest voltages were given on the Hg pool and graphite anodes. However, Hg failed to yield *any* product with the other phenols and was, itself, attacked in CH_3CN solutions. Graphite felt was chosen as the anode for most of our work because of its high surface area and its low cost.

Cell Design.—Two different cell designs were used. One was a two-compartment system and has been described.[6b] The other was a simple one-compartment system as described in the Experimental Section. Both worked well. However, when limited amounts of base were used, the base tended to concentrate in the cathode chamber of a two-compartment system and change the nature of the oxidation. This was avoided in the one-compartment system. These particular oxidations could be carried out in such a system because they seem to be irreversible.

Anode Potential.—In all of the experiments presented, the anode potential was the minimum (as measured against sce and controlled with a potentiostat) which would produce a current flow of 20–30 mA (in solutions about 10^{-2} M in substrate and $10^{-1}M$ in supporting electrolyte). In a preliminary study of the potentials necessary to cause reactions in the various media, we were able to make some generalizations. The various phenols (**4** through **10**) were oxidizable at potentials of about +0.35 V in aqueous $Na_2B_4O_7$ solutions, at +0.7 to 0.8 V in aqueous HCl solutions and at −0.1 to +0.2 V in basic CH_3CN systems. A more detailed study of the voltammetric curves of some of the

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(1) (a) Paper I: J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.*, **35**, 2884 (1970). Paper I was numbered as part of another series but should now be considered as beginning a new one. (b) This work was sponsored, in part, by Grants CA-10494 from the National Cancer Institute of the National Institutes of Health and GP-7601 from the National Science Foundation.

(2) On leave from Tohoku University, Sendai, Japan.

(3) See paper I for pertinent background references and history.

(4) A. R. Battersby, "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1967, p 119.

(5) R. H. F. Manske, *Can. J. Res.*, *Sect. B*, **15**, 159 (1937).

(6) (a) J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (*London*), 2127 (1966); (b) G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, *J. Electrochem. Soc.*, **116**, 219 (1969); (c) paper I of this series.

TABLE I

OXIDATION OF 4 TO 11 USING VARIOUS WORKING ELECTRODES

	Anodes[a] and yields, %				
Medium	Pt gauze	Hg pool	Pt fuel cell[b]	Graphite cloth[c]	Graphite felt[c]
0.1 M $Na_2B_4O_7$	50–55[d] (0.35 V)	70 (0.3 V)	50 (0.4 V)	82 (0.35 V)	85 (0.35 V)
0.1 N HCl	10–20 (0.78 V)	e	10–15 (0.78 V)	40 (0.8 V)	35–40 (0.8 V)

[a] The cathode was platinum. The anode potentials were measured against a standard calomel electrode (sce). [b] Fuel-cell electrode (Pt powder on tantalum backing), type LAA-25, Commercial Developments Dept., American Cyanamide Co., Wayne, N. J. [c] WCB graphite cloth and WDF graphite felt, Carbon Products Division, Union Carbide Corp., New York, N. Y. [d] Reference 6b. [e] Mercury electrodes are unstable in the presence of chloride.

phenols has been published[6b] or will appear elsewhere.[7,8]

Solvent Systems.—Two solvent systems were studied, water and CH_3CN. In water, the supporting electrolytes were $Na_2B_4O_7$ for basic experiments and HCl for the acid reactions. In CH_3CN, the electrolyte was tetraethylammonium perchlorate. Aqueous systems were used exclusively in the initial phases of this work. While they give excellent results with **4** and some of its derivatives,[1] poor results were obtained with other compounds due to electrode coating and appreciable decomposition. Acetonitrile, frequently used in partially aqueous solutions but never especially dried, alleviated the coating problem and is now the solvent of choice.

pH.—Both acidic and basic systems were investigated. However, oxidations took place at lower potentials in base. This should minimize side reactions and was generally used. This is in agreement with Vermillion and Pearl.[9] In fact, the most satisfactory reactions were carried out on the sodium salts of the phenols in an essentially neutral medium.

Reaction Times.—These were especially difficult to determine since most of the products of the oxidations undergo further reaction to polymeric products. The current was highest at the beginning of the reaction and dropped slowly. However, it rarely returned to zero. Two general conditions were used. The first was the reaction time in which the theoretical electricity was passed to achieve a one-electron oxidation (coulometric control). This was estimated from the current and time but was not precisely measured. Alternatively, electrolysis was carried out until no starting material could be seen in the reaction mixture by tlc (tlc control). In general, the first condition produced the best results.

Oxidation Products.—The starting materials were prepared by methods previously reported from this laboratory[10,11] except for the amides (**6**, **8**, and **10**) which were prepared from the appropriate secondary amines by selective acetylation. Compound **3** was prepared by dehydrogenation of **2** over Pd on carbon.

Of the products of these reactions, only three, **11**,[1] **15**,[1] and **14**,[12] have been reported. The compounds were mostly crystalline and fall into two classes, the carbon–carbon dimers (**11–13**, **16**, **17**, **19**, and **20**) and the carbon–oxygen dimers (**15**, **18**, and **21**). Both classes are completely characterized by their nmr[1a,13,14] and mass spectra. The carbon–carbon dimers show a sharp singlet at about δ 6.6 in their nmr spectra, and the carbon–oxygen dimers, **15** and **18**, show three aromatic singlets in the region δ 6.3–6.7. The dimer **21** shows a singlet at δ 6.39 and an AB pattern, $J = 9$ Hz, at δ 6.6 and 6.25.

None of the dimers contain any open ortho or para positions in respect to the phenol, and all should give negative tests with diazotized sulfanilic acid.[15] All gave negative tests except **17** and **18** which were questionable and **16** which gave a positive test. However, when these three compounds were investigated for ortho, meta, and para protons (to the phenol) by the nmr procedure of Highet and Highet,[16] the shifts observed in the aromatic protons between the free bases and the sodium salts, as measured in dimethyl sulfoxide-d_6, were well within the range for meta protons. Specifically, the shifts for **16**, **17**, and **18** were 0.24 for **16**, 0.16 for **17**, and 0.08 ppm (one proton only) for **18**. The ranges quoted[16] are 0.42–0.59, ortho; 0.19–0.38, meta; and 0.71–0.79, para.

Discussion of Results

Compounds **1–3** were unchanged after attempted electrolysis at +1.0 V in H_2O or CH_3CN solutions for 2 hr. This potential is well above that necessary for phenol coupling reactions in any system we have investigated and makes possible the desired, selective coupling reaction in isoquinoline alkaloids. This is in accord with our earlier work[1a] and the literature concerning the oxidizability of amine functions.[17] One exception to this has been noted, the facile oxidation of **11** to **14**. This does involve the oxidation of the nitrogen ring and takes place under normal coupling reaction conditions. It is probably best explained by the proximity of a radical generated from the phenol of **11** and the 1 position of the neighboring ring system. In fact, **11** was frequently isolated as **14** and regenerated from it with $NaBH_4$.

The results of the oxidations in aqueous systems are given in Table II, and those in CH_3CN are given in Table III. The most remarkable aspect of the data in-

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(7) J. T. Stock, *Microchem. J.*, **15**, 564 (1970).

(8) When the preparative reactions were correlated with voltammetric data, the oxidations were carried out at potentials slightly more positive than the foot of the wave.

(9) F. J. Vermillion, Jr., and I. A. Pearl, *J. Electrochem. Soc.*, **111**, 1392 (1964).

(10) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(11) J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *ibid.*, **32**, 2225 (1967).

(12) T. Kametani and H. Yagi, *J. Chem. Soc. C*, 2182 (1967).

(13) M. Tomita, K. Fujitani, Y. Masaki, and K.-H. Lee, *Chem. Pharm. Bull.*, **16**, 251 (1968).

(14) M. Tomita, Y. Masaki, and K. Fujitani, *ibid.*, **16**, 257 (1968).

(15) E. Müler, Ed., "Methoden der Organischen Chemie, Houben-Weyl," Vol. II, 4th ed, Georg Thieme Verlag, Stuttgart, 1953, p 368.

(16) R. J. Highet and P. F. Highet, *J. Org. Chem.*, **30**, 902 (1965).

(17) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 449 (1968).

TABLE II

OXIDATIONS IN AQUEOUS SYSTEMS ON A PLATINUM ANODE

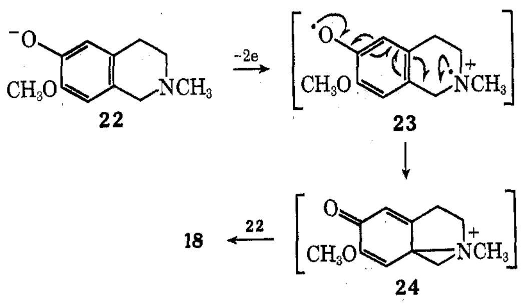
Compd	Products (%)	
	0.1 *N* HCl, +0.7–0.8 V	0.1 *M* $Na_2B_4O_7$, +0.3–0.4 V
4	**11** (20)	**11** (50–55), **15**[a] (3–5)
5	**12**[b] (48)	**12**[c] (39)
7	**16**[d] (15)	No products
9	**19**[e] (24)	No products
10		**20**[f] (56)
		20 (40)

[a] Reference 1a. [b] Oxidation on graphite felt; **12** isolated by methylation to **11**. [c] Oxidation on graphite felt; **12** isolated as **13**. [d] Isolated as the hydrochloride. [e] Isolated as the acetate. [f] In 0.05 *M* $Na_2B_4O_7$–CH_3CN (2:1) using a graphite felt electrode.

volves the different types of products obtained when the sodium salts of **4**, **5**, **7**, and **9** were oxidized in CH_3CN. Compounds **4** and **5** yielded mainly the carbon–carbon dimers **11** and **12**, but **7** and **9** yielded the carbon–oxygen dimers **18** and **21**. When the electron pair of the nitrogen is less available as in acid reactions (Table II) or in the *N*-acetyl compounds **6**, **8**, and **10**, the products were all carbon–carbon dimers. From these results and the literature,[9,18] it would appear that carbon–carbon dimers are normal for this oxygenation system (without serious steric effects[1a]) and that compounds **7** and **9** are unique.

The reasons for the unique behavior of **7** and **9** are not clear. Since the *N*-acetyl derivatives yield normal carbon–carbon dimers, the electron pair of the nitrogen would seem to be involved. In **7** and **9**, the phenol is ortho-para to the benzylamine portion while, in **4** and **5**, it is meta. If these reactions take place by a radical-coupling mechanism[18a] this relationship in **7** and **9** must give rise to an enhanced stability of the oxygen radical. This is understandable, assuming that the CH_2N group is an electron-feeding group.[18a] However, the sharp differences in behavior between the phenols do not seem explainable by such a subtle effect.

An alternate argument could be made involving a two-electron oxidation of one molecule followed by an addition of phenolate ion. This type of mechanism is an alternate to radical coupling.[18a] It could be visualized as shown in **22**–**24**.



The simultaneous oxidation of nitrogen and oxygen has been observed in the enzymatic oxidation[19] and electrolytic[20] oxidation of 1-(*p*-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinolines. This mechanism is impossible in acid or when the nitrogens are acetylated.

From a synthetic viewpoint, all of the skeletal types except **15** are now available selectively. Compound **15** can be isolated in small quantity only.

Experimental Section[21]

Oxidations in Aqueous Media.—These were carried out in a two-compartment system[6b] using a platinum gauze working anode (50 × 75 mm) separated from the platinum cathode by a porous glass disk. The tip of the sce was placed just over the top of the anode. The cell was covered with a piece of rubber dental dam, and a stream of N_2 was passed in through a capillary.

The acidic oxidations were carried out in 150 ml of 0.1 *N* HCl on samples of base hydrochlorides ranging from 300 to 500 mg. The reactions were carried out in an ice bath at temperatures between 5 and 10°. In general, the cell was set up; the anode potential was set at the estimated value; the circuit was opened and the system was allowed to equilibrate for a few minutes; and the sample was added in one portion. The potential was adjusted if necessary to give a current of about 20–40 mA. After the reaction was finished, the electrodes were removed and the anode was washed with CH_3OH. The reaction mixture was basified with NH_4OH and extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4), combined with the CH_3OH wash, and evaporated to a residue which was treated as described for the specific compounds.

The basic oxidations were carried out in 150 ml of 0.1 *M* $Na_2B_4O_7$ (pH 9) using essentially the same set of operations. The reaction mixture, however, was not treated with NH_4OH before extraction.

Oxidations in CH_3CN.—These were carried out on a graphite felt anode (60 × 60 mm) in a two-compartment system as described above and in a one-compartment system. In the one-compartment cell, the sce tip[22] was adjacent to the anode, and the platinum gauze cathode was located approximately 2 cm from the anode.

The oxidations were carried out in media consisting of 150 ml of CH_3CN, 5 ml of H_2O, and 3.45 g of tetraethylammonium perchlorate. The sodium salts were prepared by treating 300–500-mg samples of the phenols with 1 molar equiv of $NaOCH_3$ in CH_3OH. The solutions were warmed for 30 min and evaporated to dryness. The sample was dissolved in 10 ml of H_2O and added to the cell after the circuit had been opened and the system had been allowed to equilibrate. After reaction, the electrodes were removed and the anode was washed several times with CH_3OH. The combined CH_3OH and reaction mixture were evaporated to a residue which was further processed.

Preparation of 6, 8, and 10.—To an ice-cooled mixture of 2.5 g (0.014 mol) of the appropriate secondary amines,[10] 5 g of triethylamine and 100 ml of $CHCl_3$ was added, in portions, 2.5 g (0.032 mol) of acetyl chloride (within 30 min). The mixture was stirred for 2 hr at room temperature, washed with H_2O (two 20-ml portions), dried ($MgSO_4$), and evaporated to give the crude *O*,*N*-diacetyl compound as an oil. This oil was heated at 80–90° with 50 ml of 10% KOH to hydrolyze the *O*-acetyl group. The mixture was acidified with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to give a crystalline product which was recrystallized from benzene.

Compound **6** was obtained in 71% yield and melted at 159–160°. Compound **8** was obtained in 68% yield and melted at 149–150°. Compound **10** was obtained in 68% yield and melted at 160–161°.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found for **6**: C, 65.07; H, 6.76; N, 6.08. Found for **8**: C, 65.12; H, 6.98; N, 6.24. Found for **10**: C, 65.14; H, 6.67; N, 6.36.

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(18) (a) H. Musso in ref 4, p 1; (b) reference 15, p 486.

(19) Y. Inubushi, Y. Aoyagi, and M. Matsuo, *Tetrahedrom Lett.*, 2363 (1969).

(20) Unpublished work from this laboratory.

(21) The melting points were taken on a Kofler hot-stage apparatus and are corrected. The nmr spectra were measured on a Varian A-60 instrument in $CDCl_3$ using tetramethylsilane as an internal standard unless noted. Mass spectra were measured on an AEI MS-12 instrument. Microanalyses were carried out by Baron Consulting Co., Orange, Conn. Tlc was carried out on silica gel GF layers, and column chromatography was carried out on silica gel M (Hermann Brothers, Cologne, Germany). All of the voltages were measured against sce and were controlled with a Wenking potentiostat No. 61TR (Brinkmann Instrument Co., Westbury, N. Y.). The tetraethylammonium perchlorate and CH_3CN were commercial materials and were used without purification. The evaporations were all carried out on a rotary vacuum evaporator.

(22) The sce was placed directly in the CH_3CN, thus casting some doubt on the meaning, but not the reproducibility, of the potentials.

TABLE III

OXIDATIONS IN BASIC CH_3CN SYSTEMS WITH A GRAPHITE ANODE

	Products, %[b]		
	One compartment		Two compartments
Compd[a]	Coulometric control	Tlc control	Coulometric control
4[c]	**11**, 40 (62.5), 2.3 hr at 0[e] V	**11**, 86, 3.5 hr at 0[e] V	**11**, 60.4 (60.4), 3.5 hr at 0[e] V
5	**12**,[d] 24 (37.5), 2.4 hr at 0[e] V		
6	**13**, 59.4 (68), 2 hr at +0.02–0.1 V	**13**, 43.4, 5 hr at +0.02–0.1 V	
7	**18**, 50.4 (62.1), 2.3 hr at −0.06–0.03 V	**18**, 43, 3.5 hr at −0.06–0.03 V	**18**, 39 (80), 3 hr at +0.1 V
8	**17**, 57.8 (84), 2 hr at +0.04–0.1 V	**17**, 44, 5 hr at +0.04–0.1 V	
9	**21**, 31 (51.7), 2.3 hr at +0.16 V	**21**, 34, 3.5 hr at +0.16 V	**21**, 25.8 (71), 3.5 hr at 0 V
10	**20**, 36 (41), 2 hr at +0.16–0.2 V	**20**, 31, 5 hr at +0.16–0.2 V	

[a] The phenols were oxidized as their sodium salts. [b] The figures in parentheses represent the conversion after correction for recovered starting material. [c] Traces of the C–O–C dimer **15** were seen in the reaction products by tlc. [d] Isolated as its *O,O′,N,N′*-tetracetyl derivative. [e] A potential of 0 V does not mean that there is no potential. It only means that the potential used is the same as that of the standard calomel electrode.

Oxidation of Corypalline, 4.—The oxidation of **4** in aqueous base has been described.[1a]

Corypalline hydrochloride (300 mg) was oxidized in aqueous acid at 0.72 V for 3 hr. The chloroform extract was treated as described[1a] to obtain 50 mg of **11**. The small amount of **15** observable on tlc was not isolated.

The sodium salt of **4** (from 500 mg of **4**) was oxidized in a one-compartment system at 0.0 V for 2.3 hr (coulometric control for **15**) and 3.5 hr (tlc control). The initial current was 27 mA which fell off to 24 mA after 3.5 hr. The residue was dissolved in 25 ml of H_2O and treated with 1 g of $NaBH_4$ to reduce **14** back to **11**. The mixture was kept cold for 30 min and stirred at room temperature for 3 hr. The mixture was acidified (10% HCl), basified (10% NH_4OH), and extracted with $CHCl_3$. This $CHCl_3$ extract was processed as described[1a] to yield starting material **4** (180 mg for 2.3 hr, and 0 mg for 3.5 hr) and **11** (200 mg for 2 hr and 430 mg for 3.5 hr), mp 235–237° (lit.[1a] 235–237°). A small amount of **15** observable on tlc was not isolated.

The sodium salt of 500 mg of **4** was oxidized in a two-compartment system at 0.0 V for 3.5 hr (coulometric control). The initial current was 50 mA which dropped off to 4 mA. The product was isolated as previously described[1a] to yield no **4** and 251 mg of **11**, mp 235–237°. Preparative tlc of the mother liquors yielded an additional 51 mg.

Oxidation of 5.—Oxidation of **5** in aqueous systems using a platinum anode was unsuccessful. The current at the beginning of the experiments was 20–30 mA but dropped off to 0 in a few minutes.

Compound **5** (500 mg) was oxidized in 0.1 *N* HCl on a graphite felt anode at +0.78 V for 3.5 hr. The $CHCl_3$ extract obtained as described above was evaporated to give 200 mg of syrup (crude **12**) which was heated at 50° for 1 hr with 2 ml of 37% HCHO and 20 ml of CH_3OH. The mixture was cooled, treated with 0.5 g of $NaBH_4$, neutralized with NH_4Cl, evaporated to dryness, and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract and crystallization from ethanol gave 203 mg of **11**, mp 235–237°.

Compound **5** (500 mg) was oxidized in 225 ml of 0.1 *M* $Na_2B_4O_7$–CH_3CN, 1:2, on a graphite felt anode at +0.2 V for 3.5 hr. The CH_3CN was evaporated and the aqueous residue was extracted with $CHCl_3$. Evaporation of the solvent gave 450 mg of brownish solid (crude **12**) which was acetylated with 3 g of triethylamine, 50 ml of $CHCl_3$, and 1 g of acetyl chloride, to yield, after crystallization from CH_3OH, 353 mg of **13** acetate: mp 293–294°; nmr δ 6.88 (s, 2, aromatic), 3.88 (s, 6, OCH_3), 2.00 (s, 6, $OCOCH_3$), 2.10 and 1.97 (each s, 6, $NCOCH_3$);[23] mass spectrum M^+ 524, calcd 524; ir (KBr) 1740 ($OCOCH_3$) and 1630 cm^{-1} ($NHCOCH_3$).

Anal. Calcd for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34. Found: C, 63.75; H, 6.19; N, 5.14.

The sodium salt from 500 mg of **5** was oxidized at 0.0 V in a one-compartment system. The initial current was 30 mA and the time for coulometric control was 2.4 hr. The residue after evaporation of CH_3CN was dissolved in 25 ml of H_2O and reduced with 1 g of $NaBH_4$. The reduction mixture was kept cool in ice for 30 min and stirred for 3 hr. The mixture was treated with 5 g of NH_4Cl and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated under vacuum to a small volume, and 180 mg of starting material was removed by filtration. Acetylation of the residue from the mother liquor (200 mg) as described above for **13** gave 120 mg of **13** acetate, mp 294–295°.

Oxidation of 6.—The sodium salt of **6** (500 mg) was oxidized in a one-compartment system at +0.02 to 0.1 V for 2 hr (coulometric control) and for 5 hr (tlc control). The initial current was 30 mA at +0.02 V. The potential was raised to 0.1 V to keep the current at about 30 mA. The residue obtained as described above was dissolved in 40 ml of H_2O, washed with $CHCl_3$,[24] acidified with NH_4Cl, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to a pale yellow syrup which was triturated with $CHCl_3$–ether to give crystals of **13**, 257 mg for the 2-hr experiment and 180 mg for the 5-hr experiment. Preparative tlc ($CHCl_3$–acetone, 1:1) of the mother liquors yielded 60 mg of **6** and an additional 40 mg of **13** from the 2.2-hr experiment and 37 mg of **13** from the 5-hr experiment. Compound **13** was recrystallized from methanol to give colorless prisms: mp 256–257°; nmr ($CDCl_3$) δ 6.72 (s, 2, aromatic), 5.70 (s broad, 2, OH), 3.90 (s, 6, OCH_3), 2.11 and 1.91 (each s, 6, $NHCOCH_3$)[23]; mass spectrum, M^+ 440, calcd 440.

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.53; H, 6.64; N, 6.23.

Acetylation of **13** yielded the same *O,O′,N,N′*-tetracetyl derivative of **12** obtained in the oxidation of **5**.

Oxidation of 7.—The hydrochloride of **7** (300 mg) was oxidized at +0.72 V in 0.1 *N* HCl at room temperature for 3 hr. The $CHCl_3$ extract obtained as previously described was evaporated to a small volume and triturated with ethanol to give a slightly colored powder. This powder was collected, dissolved in ethanol, and treated with concentrated HCl to prepare the hydrochloride of **16**. The hydrochloride, 47 mg, mp 284–285°, was crystallized from ethanol–ether: nmr (D_2O) δ 6.85 (s, 2, aromatic), 3.85 (s, 6, OCH_3), 3.0 (s, 6, NCH_3); mass spectrum, M^+ 384, calcd 384.

Anal. Calcd for $C_{22}H_{28}N_2O_4 \cdot 2HCl \cdot H_2O$: C, 55.58; H, 6.72; N, 5.89. Found: C, 55.84; H, 6.76; N, 5.79.

Oxidation of **7** in base at +0.35 V led to no products. The

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[23] Two explanations are possible for these two acetylmethyl peaks. One involves the conformation of the nitrogen ring as described by G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, **89**, 329 (1967). The other involves the different forms of the acetyl group itself as brought about by restricted rotation of the carbon–nitrogen bond; see H. Paulsen and K. Todt, *Angew. Chem.*, **78**, 943 (1966).

[24] This $CHCl_3$ extract was evaporated to leave a noncrystalline powder (17 mg from 2-hr experiment and 45 mg from 5-hr experiment) of a still unknown structure.

current rapidly dropped off to 0 and only starting material could be seen by tlc.

The sodium salt from 500 mg of **7** was oxidized in a one-compartment system at −0.03 to +0.06 V for 2.3 hr (coulometric control) and 3.5 hr (tlc control). The current was maintained at about 30 mA by slowly raising the voltage over the range stated. The $CHCl_3$ extract obtained as described above was washed (saturated NaCl), dried ($MgSO_4$), and concentrated under vacuum to a small volume. Cooling yielded starting material, 80 mg, from the 2.2-hr experiment. Preparative tlc ($CHCl_3$–acetone–methanol–NH_4OH, 100:100:50:2.5) of the mother liquor yielded 13 mg of **7** and 252 mg of **18** from the 2.2-hr experiment and 215 mg of **18** from the 3.5-hr experiment. Compound **18**, mp 152–153°, was recrystallized from ether–hexane: nmr ($CDCl_3$) δ 6.63, 6.45, and 6.36 (each s, each 1, aromatic), 4.95–5.2 (s broad, 1, OH), 3.90 and 3.77 (each s, each 3, OCH_3), 2.52 and 2.48 (each s, each 3, NCH_3); mass spectrum M^+ 384, calcd 384.

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.45; H, 7.46; N, 7.11.

The sodium salt from 500 mg of **7** was oxidized in a two-compartment system at +0.1 V for 3 hr. The initial current of 25 mA dropped off to 3 mA. The products were isolated as described above to yield 254 mg of starting material and 197 mg of **18**.

Oxidation of 8.—The sodium salt from 500 mg of **8** was oxidized in a one-compartment system at +0.04–0.1 V for 2 hr (coulometric control) and 5 hr (tlc control). The current was maintained at about 30 mA by slowly raising the voltage over the range stated. The $CHCl_3$ extract, obtained as previously described, was washed (saturated NaCl), dried ($MgSO_4$), and evaporated to a residue. The residue was chromatographed over a column of 35 g of silica gel, eluted with $CHCl_3$–methanol, 99:1, to yield 155 mg and 0 mg of starting material and 289 and 220 mg of **17** from the 2-hr experiment and the 5-hr experiment, respectively. Compound **17** was recrystallized from benzene to give pale yellow prisms: mp 233–235°; nmr δ 6.70 (s, 2, aromatic), 5.74 (s broad, 2, OH), 3.90 (s, 6, OCH_3), 2.17 and 2.10 (each s, 6, $NCOCH_3$);[23] mass spectrum M^+ 440, calcd 440; ir (KBr) 1620 cm^{-1} ($NCOCH_3$).

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.17; H, 6.37; N, 6.30.

Oxidation of 9.—The hydrochloride of **9** (500 mg) was oxidized at +0.72 V in 0.1 *N* HCl for 3.5 hr. The $CHCl_3$ extract obtained as described above was evaporated to dryness and acetylated by the procedure given above for the preparation of **6**, **8**, and **10** (without the base treatment). The resulting oil was chromatographed over 25 g of silica gel using benzene–ether as an eluent. The major fraction crystallized on evaporation to yield 122 mg of the diacetate of **19**, mp 185–186°, recrystallized from ether: nmr δ 6.72 (s, 2, aromatic), 3.8 (s, 6, OCH_3); mass spectrum M^+ 468, calcd 468.

Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.46; H, 6.89; N, 5.98.

Oxidation of **9**, like **7**, in aqueous base yielded no products.

The sodium salt from 500 mg of **9** was oxidized in a one-compartment system at +0.16 V for 2.3 hr (coulometric control) and 3.5 hr (tlc control). The initial current of 30 mA dropped off to 24 mA during the experiment. The dry residue obtained as described above was washed with 300 ml of dry CH_3CN (to remove starting material) and dissolved in 25 ml of H_2O. The H_2O was acidified (10% HCl), basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to dryness and separated by preparative tlc (methanol–NH_4OH, 98.5:1.5) to yield 155 mg of **21** from the 2.3-hr experiment and 170 mg from the 3.5-hr experiment. Compound **21**, as precipitated from ether with hexane, melted at 135–137°: nmr δ 6.60 (d, J = 9 Hz, 1, aromatic at C-5), 6.39 (s, 1, aromatic), 6.25 (d, J = 9 Hz, 1, aromatic at C-6), 6.18 (s broad, 1, OH), 3.77 and 3.63 (each s, each 3, OCH_3), 2.49 and 2.44 (each s, each 3, NCH_3); mass spectrum M^+ 384, calcd 384.

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.61; H, 7.59; N, 7.03.

Starting material, 201 mg from the 2.3-hr experiment and 0 mg from the 3.5-hr experiment, was obtained by evaporating the CH_3CN wash solution to dryness.

The sodium salt from 500 mg of **9** was oxidized in a two-compartment system at 0 V for 3.5 hr at room temperature. The initial current of 50 mA dropped off to about 3 mA. The products were isolated as described above to yield 130 mg of **21** and 311 mg of starting material.

Oxidation of 10.—The sodium salt derived from 500 mg of **10** was oxidized in CH_3CN in a one-compartment system at +0.16–0.2 V for 2 hr (coulometric control) and 5.5 hr (tlc control). The current was maintained at 30 mA by slowly raising the voltage over the range given. The residue was dissolved in 25 ml of H_2O, acidified (10% HCl), and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (saturated NaCl), evaporated to dryness and separated by preparative tlc ($CHCl_3$–acetone, 1:1). Starting material, 60 mg, and 180 mg of **20** were obtained from the 2.2-hr experiment, and 155 mg of **20** was obtained from the 5.5-hr experiment. Compound **20** was a noncrystalline glass: nmr δ 6.62 (s, 2, aromatic), 3.88 (s, 6, OCH_3), 2.26 and 2.18 (each s, 6, $NCOCH_3$).[23]

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.90; H, 6.96; N, 6.49.

Oxidation of 500 mg of **10** in a two-compartment system in 0.1 *M* aqueous $Na_2B_4O_7$ at +0.9 V (platinum anode) for 3.5 hr at room temperature yielded 200 mg of **20**. Oxidation of 500 mg of **10** in a two-compartment system in a medium of 100 ml of aqueous 0.05 *M* $Na_2B_4O_7$ and 50 ml of CH_3CN at +0.2 V using a felt anode yielded, after 3 hr, 280 mg of **21**.

Registry No.—**4**, 450-14-6; **6**, 30597-81-0; **8**, 30542-00-8; **10**, 30542-01-9; **11**, 14510-48-6; **13**, 30542-03-1; **13** diacetate, 30542-04-2; **16** 2HCl, 30546-01-1; **17**, 30597-82-1; **18**, 30546-02-2; **19** diacetate, 30546-03-3; **20**, 30546-04-4; **21**, 30546-05-5.

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