# Electrochemistry of natural products. 7. Oxidative decarboxylation of some tetrahydro-ƀ-carboxylic acids

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(relative intensity) 224 ($M^+$, 100), 223 (M - H, 30), 196 (M - CO, 12), 168 (M - 2 CO, 20), 139 (M - 2 CO - HCO, 35); metastable peak observed at $m/e$ 171.5, assigned to $M^+ \rightarrow (M - CO)^+ + CO$ ($m^*_{obsd}$ $m/e$ 171.5; $m^*_{calcd}$ $m/e$ 171.5); metastable peak observed at $m/e$ 144, assigned to $(M - CO)^+ \rightarrow (M - 2\,CO)^+ + CO$ ($m^*_{obsd}$ $m/e$ 144; $m^*_{calcd}$ $m/e$ 144); $^1H$ NMR ($CDCl_3$) $\delta$ 11.4 (s, 1 H), 8.4-7.3 (m, 7 H). The sample was identified (mass spectrum) by comparison with an authentic sample of 1-hydroxyanthraquinone.

Compound **14** was recovered (91%) from treatment with potassamide in ammonia.

**Reaction of 1 with Sodium Hydrosulfide.** The quinone **1** (8.28 g), sodium hydrosulfide (1.68 g), and benzyl alcohol (100 mL) were refluxed for 9 h. When the mixture was cool, the solid (7 g, impure starting material) was filtered off and discarded. The filtrate was concentrated to ca. 10 mL, acetone (30 mL) was added, and the solid was collected. Chromatography (silica gel, benzene) gave **15** (780 mg, 10%) as small orange cubes: mp 326-327 °C, mass spectrum, $m/e$ (relative intensity) 514 ($M^+$, 17), 275 (33), 273 ($C_{14}H_6ClO_2S^+$, 100), 240 (14), 218 (10), 206 (12), 185 (11), 173 (13), 150 (46), 105 (38).

(17) With G. J. Chen.

Anal. Calcd for $C_{28}H_{12}Cl_2O_4S$: C, 65.4; H, 2.3; Cl, 13.6; S, 6.2. Found: C, 65.3; H, 2.4; Cl, 13.5; S, 6.3.

**Acknowledgment.** We thank Mr. G. J. Chen and Mrs. M. M. Kayser for preliminary experiments, the National Research Council of Canada for financial support, and the Government of Ontario for graduate scholarships (to E. H.R.).

**Registry No.** **1**, 82-46-2; **2**, 117-11-3; **3**, 3098-20-2; **4**, 82-20-2; **5**, 73192-96-8; **6**, 73178-73-1; **7**, 73178-74-2; **8**, 2987-66-8; **9**, 18084-38-3; **10**, 18084-37-2; **11**, 71502-46-0; **12**, 73178-75-3; **13**, 73178-76-4; **14**, 73178-77-5; **15**, 73178-78-6; sodium azide, 26628-22-8; ammonia, 7664-41-7; 1-chloroanthraquinone, 82-44-0; potassamide, 17242-52-3; 1-aminoanthraquinone, 82-45-1; 2-aminoanthraquinone, 117-79-3; 1-chlorofluorenone, 36804-56-5; 1-aminofluorenone, 6344-62-3; 3-chlorobiphenyl-2'-carboxylic acid, 73178-79-7; 4-toluidine, 106-49-0; hexamethylphosphoric triamide, 680-31-9; 1-(methylamino)anthraquinone, 82-38-2; 1-(dimethylamino)anthraquinone, 5960-55-4; *N*-methylformamide, 123-39-7; potassium *tert*-butoxide, 865-47-4; potassium hydroxide, 1310-58-3; 1,5-dihydroxyanthraquinone, 117-12-4; 2-ethoxyethanol, 110-80-5; 1-hydroxyanthraquinone, 129-43-1; sodium hydrosulfide, 16721-80-5.

# Electrochemistry of Natural Products. 7. Oxidative Decarboxylation of Some Tetrahydro-β-carbolinecarboxylic Acids[1]

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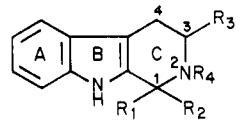
A series of 1,2,3,4-tetrahydro-β-carboline-1- and -3-carboxylic acids containing various substituents in positions 1, 2, and 3 were oxidized electrochemically. In general, the acids were decarboxylated, and unsaturation was introduced into the C ring. The oxidation appears to take place through the indole ring nitrogen, and possible mechanisms of the reactions are presented. Parallels between the observed reactions and early steps in indole alkaloid biosynthesis are discussed. The oxidative dimerization of tetrahydrocarbazole is reported.

In the previous paper of this series,[1a] we presented an argument in favor of the inclusion of an oxidative decarboxylation step in the early stages of isoquinoline alkaloid biosynthesis. The reaction was the decarboxylation of phenolic tetrahydroisoquinoline-1-carboxylic acids, and the oxidations were carried out electrochemically.[2] In this paper we have extended the work to the indole alkaloids, more specifically, to a study of tetrahydro-β-carboline-1- and -3-carboxylic acids.

As shown in Scheme I, several pathways may be visualized for the biosynthesis of the simple β-carboline alkaloids,[3] harman, **9**, for example.[4] There are essentially two points of variation in the possible pathways. The first depends upon whether tryptophan, **1**, or tryptamine, **2**, is involved in the ring-closure step. For many years, it was thought that only tryptamine was involved. However, the recent discovery of some alkaloids containing a 3-carboxyl group[5] means that at least some coupounds are derived directly from 1. Actually, this idea was suggested many

Table I. Tetrahydro-β-carboline Derivatives




| compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 3 | $CH_3$ | $CO_2H$ | $CO_2H$ | H |
| 4 | $CH_3$ | $CO_2H$ | H | H |
| 5 | $CH_3$ | H | $CO_2H$ | H |
| 6[a] | $CH_3$ | | $CO_2H$ | |
| 8 | $CH_3$ | H | H | H |
| 10 | $CH_3$ | $CH_2OH$ | $CO_2H$ | H |
| 11 | H | $CH_2OH$ | $CO_2H$ | H |
| 12 | H | H | $CO_2H$ | H |
| 13 | H | H | H | H |
| 14 | H | H | H | $COCH_3$ |
| 15 | $CH_3$ | H | H | $COCH_3$ |
| 16 | $CH_3$ | $CH_3$ | $CO_2H$ | H |
| 17 | H | $CH_2CH_2$[b] | $CO_2H$ | CO[b] |

[a] 1-Methyl-3,4-dihydro-β-carboline-3-carboxylic acid. [b] Contains a five-membered lactam ring between positions 1 and 2.

(1) (a) Part 6: J. M. Bobbitt and T. Y. Cheng, *J. Org. Chem.*, 41, 443 (1976). (b) Taken in part from the Ph.D. dissertation of J. P. W., The University of Connecticut, 1977. The work was sponsored in part by Research Grant No. CA-10494 from the Cancer Institute of the National Institutes of Health and by Grant No. GP-7601 from the National Science Foundation.

(2) J. M. Bobbitt, *Heterocycles*, 1, 181 (1973).

(3) R. H. F. Manske in "The Alkaloids", Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, 1965, p 47.

(4) (a) T. A. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolites", Freeman, Cooper and Co., San Francisco, 1969, p 473; (b) R. A. Abramovitch and I. D. Spencer, *Adv. Heterocycl. Chem.*, 3, 83 (1964); (c) M. Slayton and I. J. McFarlane, *Phytochemistry*, 7, 605 (1968); (d), I. A. Veliky, *ibid.*, 11, 1405 (1972).

(5) (a) R. T. Brown, C. L. Chapple, and G. K. Lee, *J. Chem. Soc., Chem. Commun.*, 1007 (1972); (b) K. L. Stuart and R. Woo-Ming, *Heterocycles*, 3, 223 (1975).

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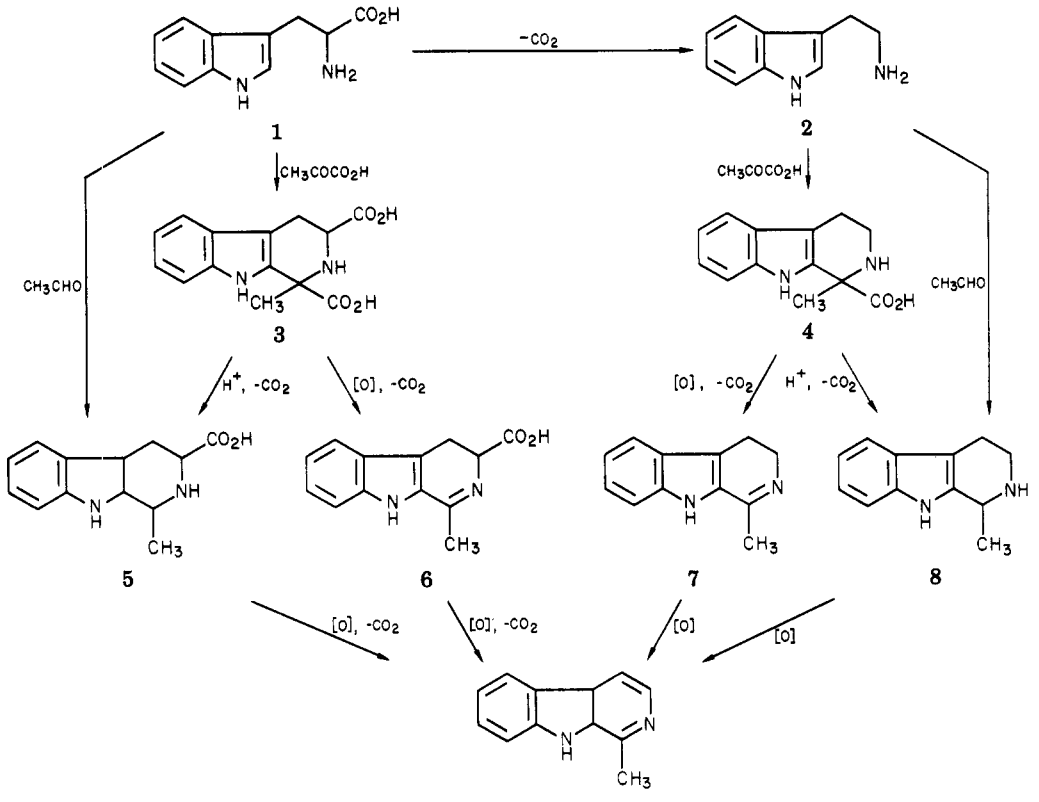
Scheme I



years ago by Jacobs and Craig[6] and Robinson.[7] If the 3-carboxyl group is retained through the ring-closure reaction, the crucial question becomes whether it can be easily removed or not. The second point of variation hinges upon whether acetaldehyde or pyruvic acid is the ring-closure reagent for the formation of the β-carboline ring. Both reagents react readily under "physiological conditions" to give the ring system, but it has long been assumed that acetaldehyde is actually the reagent (1 to 5 and 2 to 8). Recent studies in isoquinoline alkaloid biosynthesis[8] and our electrochemical work[1a] have opened the possibility that pyruvic acid is also a likely compound (for example, 1 → 3 → 6 → 9). The decarboxylation of tetrahydro-β-carboline-1-carboxylic acids without oxidation (3 → 5 and 4 → 8) is a well-known reaction in acid.[9] In summary, at least three of the possible routes from 1 to 9 go through various tetrahydro-β-carbolinecarboxylic acids.

We have prepared acids 3, 4, 5, and 6 as well as several reference compounds (Table I) and subjected them to electrochemical oxidation at a graphite felt anode. Indole and tetrahydrocarbazole have been investigated as specific reference compounds. The basic hypothesis was that the various carboxylic acids would be oxidatively decarboxylated through an initial oxidation of the indole ring. Chemical oxidations of similar systems do take place and, in fact, constitute one of the synthetic routes to β-carbolines.[10]

**Preparation of Starting Materials.** Compounds 3–5, 10, 11, 16 and 17 were prepared by reaction of a suitable carbonyl reagent with L-tryptophan or tryptamine in a version of the Pictet–Spengler synthesis of tetrahydroisoquinolines.[11a] Only 10 and 16 had not been previously prepared. Compound 6 was prepared by a Bischler–Napieralski reaction.[11b] Compounds 8, 12, and 13 were prepared by acid-catalyzed decarboxylation of 4, tetrahydro-β-carboline-1,3-dicarboxylic acid, and tetrahydro-β-carboline-1-carboxylic acid, respectively.[9] Compounds 14 and 15 were prepared by acetylation in methanol solution, an apparently new, high-yield method. Details and references are given in the Experimental Section.

Compounds 5 and 10 were separated into their diastereomers, but 3 and 11 were investigated as mixtures of isomers or as pure epimers of unknown stereochemistry. The stereochemistry of the isomers of 5 has been established by Yamada and Akimoto[12] and affirmed by Brossi and co-workers.[13] Both isomers, the 1*S*,3*S* and the 1*R*,3*S* compounds were investigated. The stereochemistry of the isomers of 10 is assigned on the basis of the relative spectra of the two isomers and by comparison of the data with the isomers of 5. Only one isomer, the 1*R*,3*S* compound, was completely purified, and it was the only one oxidized. The 1*S*,3*S* isomer was obtained in about 67% purity (by $^{13}C$ NMR). The stereochemistry of the major product is probably 1*R*,3*S* on the basis of the following arguments. Since the hydroxymethyl group can be equatorial in the 1*R*,3*S* isomer, it should be the less hindered isomer and the major product in a thermodynamically controlled process. The synthesis does seem to be so controlled since the less hindered isomer is the major product in the preparation of the known isomers of 5. The $^{13}C$ NMR spectra support the assignment. The methyl group ap-

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(7) R. Robinson, *J. Chem. Soc.*, 1079 (1936).
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(9) (a) Reference 4b, p 90; (b) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, p 239.
(10) Reference 4b, p 138.
(11) (a) W. M. Whaley and T. R. Govindachari, *Org. React.*, 6, 151 (1951); ref 9b, p 238; (b) W. M. Whaley and T. R. Govindachari, *Org. React.*, 6, 74 (1951).
(12) S. Yamada and H. Akimoto, *Tetrahedron Lett.*, 3105 (1969).
(13) A. Brossi, A. Focella, and S. Teitel, *J. Med. Chem.*, 16, 418 (1973).

Table II. Half-Wave Potentials of Some 1,2,3,4-Tetrahydro-β-carboline Derivatives and Reference Compounds on a Platinum Anode

| | half-wave potentials,[a] V | | | |
|---|---|---|---|---|
| | 0.1 M $NaHCO_3$, $CH_3CN$-$H_2O$ (3:2) | | 0.1 M $LiClO_4$, $CH_3CN$-$H_2O$ (9:1) | |
| compd | 1st wave | 2nd wave | 1st wave | 2nd wave |
| 3 | 0.75 | 0.95 | | |
| 4 | 0.83 | | | |
| 8 | | | 0.73 | |
| 10 (1R, 3S) | 0.75 | 0.95 | | |
| 13 | | | 0.70 | |
| 14 | | | 0.94 | |
| 15 | | | 0.95 | |
| indole | 0.94 | | | |
| tetrahydrocarbazole | 0.66 | | 0.72 | 0.86 |

[a] Measured against a standard calomel electrode.

pears at 23.42 ppm in the 1R,3S isomer, slightly upfield from the 1S,3S isomer in which the peak is at 24.59 ppm. The hydroxymethyl group in the 1S,3S isomer is of slightly higher field (55.56 vs. 55.22 ppm) than in the 1R,3S isomer. The higher field values fit the fact that the appropriate groups are in the pseudoaxial or more hindered positions, as predicted.[14]

**Voltammetry.** Cyclic voltammograms were obtained by using a platinum-wire electrode, and the results are given in Table II. Indole and tetrahydrocarbazole were investigated as models for the indole moiety. All of the reactions were irreversible under the neutral or basic conditions used. In all cases, the first waves were in the region of 0.66–0.94 V vs. SCE (standard calomel electrode), indicating that the initial oxidation probably involved the indole portion of the various molecules.

Decomposition potentials[15] were measured under preparative oxidation conditions by using large graphite felt anodes, and the results are given in Table III. There are three main points in the data of Tables II and III.

The ease of oxidation increases as the pH becomes more basic. This was observed for tetrahydrocarbazole by cyclic voltammetry and by study of its decomposition potentials. It was also observed in the decomposition potentials for 1-methyltetrahydro-β-carboline (**8**) and 1-methyltetrahydro-β-carboline-3-carboxylic acid (**5**) (specifically in the series of phosphate buffers with pH's from 6.0 to 8.0). This data along with similar values in NaOMe for tetrahydrocarbazole (**4**) and **5** (0.11, 0.13, and 0.13 V) are a strong indication that, *in all cases*, the oxidation is similar and is taking place on the indole moiety. Furthermore, it would appear that the indole N is probably the point of oxidation since the hydrogen attached to it is somewhat acidic, and an anion derived from this nitrogen would be more likely to be oxidized than the protonated nitrogen. Such a pH dependency was also noted in the phenolic isoquinolines that we have previously investigated.[16] Since similar data are obtained for tetrahydrocarbazole and the two acids **4** and **5**, it would also be logical to conclude that the carboxylate ion is not being oxidized at these potentials.

A further point of interest lies in the different decomposition potentials of the diastereomers of **5**. The 1S,3S isomer appears to be oxidized at appreciably lower potentials than the 1R,3S isomer. Since the 1S,3S isomer would have both substituents in equatorial positions, it would be logical to assume that it can approach the anode more closely and would be more easily oxidized.

Table III. Decomposition Potentials under Various Conditions

| compd | conditions[b] | $E_D$,[a] V |
|---|---|---|
| indole | B | 0.64 |
| | C | 0.45 |
| tetrahydrocarbazole | C | 0.25 |
| | D | 0.11 |
| | B | 0.55 |
| 3 | A | 0.69 |
| 4 | A | 0.42 |
| | D | 0.13 |
| | C | 0.15 |
| 5 (1S,3S) | A | 0.50 |
| | D | 0.13 |
| | C | 0.55 |
| | E | 0.77 |
| | F | 0.47 |
| | G | 0.45 |
| | H | 0.40 |
| | I | 0.36 |
| | J | 0.35 |
| 5 (1R,3R) | A | 0.66 |
| | D | 0.13 |
| 6 | A | 0.58 |
| 8 | B | 0.26 |
| | D | 0.17 |
| 10 (1R,3S) | C | 0.25 |
| | A | 0.47 |
| 11 | A | 0.47 |
| 12 | A | 0.54 |
| 15 | B | 0.69 |
| 16 | D | 0.12 |
| | A | 0.58 |
| 17 | A | 0.87 |

[a] All potentials are positive and are measured against a standard calomel electrode by using a graphite felt anode[43] and a platinum cathode divided by a Nafion membrane.[44] [b] The solvent systems are as follows: A is an aqueous methanol system buffered to pH 7 and is described in the Experimental Section in the Oxidative Decarboxylations, General Procedure Section; B is 0.1 M $LiClO_4$ in $CH_3CN$-$H_2O$ (9:1); C is 0.1 M $NaHCO_3$ in $CH_3CN$-$H_2O$ (9:1); D is 0.1 M NaOMe in MeOH; E is 0.1 N $H_2SO_4$; F–J are aqueous phosphate buffers at pH's 6, 6.5, 7.0, 7.5, and 8.0, respectively.

Finally, the nonindolic nitrogen appears to play some small role in the reaction since its acetylation tends to shift the potential to slightly higher values (Table II, **13** to **14** and **8** to **15**).

**Preparative Oxidations and Products.** Preparative reactions were carried out in phosphate buffered MeOH–$H_2O$ solutions in which phosphate served as electrolyte. Although some electrode coating occurred in all of the reactions with an accompanying loss of yield, this solvent system, of the many investigated, seemed to give the best results. The anode was graphite felt,[16] the cathode was either a platinum or a graphite rod, and the potentials were controlled against a standard calomel electrode. The reactions were carried out in a divided cell, and the course of reaction was monitored by TLC.

In general, all of the 1- and 3-carboxylic acids decarboxylated smoothly at a potential similar to the decomposition potentials observed for indole and tetrahydrocarbazole. The oxidation of the dicarboxylic acid **3** gave a mixture of **6** and **9** which could be completely converted to **9** on extended reaction. Oxidation of isolated **6** gave only **9**, indicating a stepwise conversion of **3** to **6** to **9**. The oxidation of the 1-carboxylic acid **4** gave **7** in 45% yield

(14) F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden, New York, 1976, p 29.
(15) C. W. Davies, "Electrochemistry", George Newnes Ltd., London, 1967, Chapter 15.
(16) J. M. Bobbitt, H. Yagi, S. Shibuya, and J. T. Stock, *J. Org. Chem.*, 36, 3006 (1971).

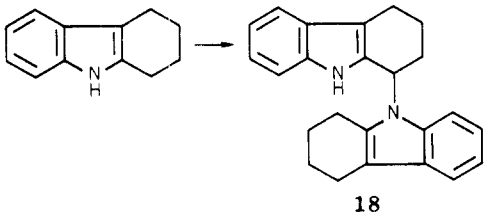
with a small amount of **9** (about 3–10%). Oxidation of the unsubstituted 3-carboxylic acid **12** gave β-carboline in 35% yield.

The oxidation of **5** gave only **9** in a yield of 60%. No intermediate products were observed by TLC, and none could be isolated. Two intermediates are possible, **6** (dehydrogenation followed by decarboxylation) or 1-methyl-1,2-dihyro-β-carboline (decarboxylation followed by dehydrogenation). Since we had **6** available and since it appeared to be sufficiently stable to be isolated from the oxidation of **3**, it would seem that **6** should have been observed if it had been an intermediate. Thus, we believe that the 1,2-dihydro derivative is an intermediate. An intermediate 1,2-dihydro-β-carboline has been postulated as being formed by the decarboxylation of a tetrahydro-β-carboline-3-carboxylic acid and has, in fact, been used in a synthetic sequence by van Tamelen and his co-workers[17a,b] and by Leete.[17c] However, no simple 1,2-dihydro-β-carboline has been isolated as such.

The two hydroxymethyl compounds **10** and **11** gave interesting results. Compound **10** was prepared to block aromatization and see whether a 1,2-dihydro-β-carboline with two substituents at carbon 1 could be isolated. Instead, the oxidation of **10** gave the β-carboline **9** in 52% yield. This reaction presumably takes place through an oxidative deformylation, with the $CH_2OH$ being lost as HCHO. The HCHO was not, however, isolated. Compound **11** was prepared with the hope that water would be lost from a possible 1,2-dihydro intermediate to yield the β-carboline **9**. Instead, the oxidation of **11** gave only 1-(hydroxymethyl)-β-carboline, a known natural product,[46] by the usual oxidative decarboxylation and dehydrogenation. Thus, we could not demonstrate a clear oxidative decarboxylation from **5** to any 1,2-dihydro derivatives. In further attempts to block the aromatization, compounds **16** and **17** were prepared. In neither case was any product isolated.

The oxidation of **15** gave **9** in 11% yield, but the reaction was accompanied by extensive electrode coating. The oxidations of indole and compounds **8**, **13**, **14**, and **15** were also hindered by coating and yielded no isolable products.

The oxidation of tetrahydrocarbazole gave an essentially quantitative yield of the dimer **18**,[18] a previously reported compound.[19] This interesting dimerization is being studied further.



**18**

## Discussion

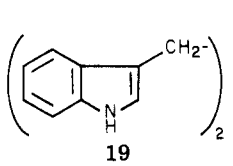
There have been few examples of the electrochemical oxidation of indole and its derivatives, and, as yet, no overall mechanistic interpretation has been presented.

In 1958, Allen and Powell[20] studied the voltammetry of some of the more complex indole alkaloids. They concluded that the loss of one electron *from the indole* was the rate-controlling step under acidic conditions, but no products were isolated. Under neutral conditions, a two-electron oxidation was observed. This was thought to be an *N*-oxide formation on a nonindolic nitrogen. If this interpretation is correct, one would expect to see an appreciable difference between the half-wave potentials in acid and in a neutral solution. Such a difference is not apparent from their data. The mechanisms proposed involved the simultaneous one-electron oxidation of the substrate and hydroxyl ions to yield radicals which then combined to form the product. Indole itself was found to have a half-wave potential of 0.796 (vs. SCE) in acidic medium.

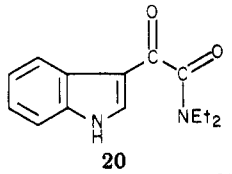
The electrochemistry of carbazole has been studied intensively by Nelson and his group[21] and by Lamm and his co-workers[22] and has been summarized by Nelson.[23] The products are invariably symmetrical bicarbazyls coupled through the nitrogen in basic solution or through carbon 3 when the nitrogen was substituted or when the reaction was carried out in acid. When carbon 3 was substituted, dimerization occurred through carbon 6. When carbons 3 and 6 and the nitrogen were all substituted, fairly stable cation radicals were formed. It was suggested that, in all cases, an initially formed cation radical dimerized and that the subsequently formed dication lost two protons to form product.

Yoshida[24] has shown that various substituted pyrroles and indoles can be oxidized in the presence of cyanide ion to yield a series of products containing a nitrile group on the aromatic ring. In a few cases where pyrrole contained methyl groups on carbons 2 and 5, some reaction occurred on the methyl group to yield cyanomethyl derivatives. Reactions were found to occur best when the nitrogen was substituted with a methyl or a phenyl group. A mechanism was suggested in which the initially formed cation radical reacted with cyanide to yield a radical which was further oxidized to a cation which could lose a proton to form product.

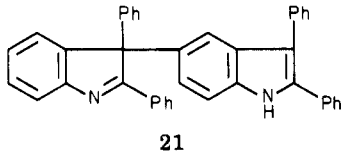
In addition to these more complete pieces of work, a series of single reactions has been observed. Indole-3-acetic acid was observed to decarboxylate and dimerize to form a dimer (**19**).[25] Indole was oxidized in acetonitrile with



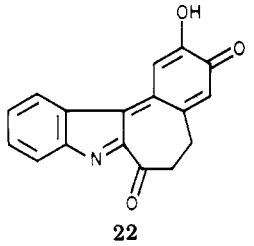
**19**



**20**



**21**



**22**

a tetramethylammonium perchlorate electrolyte to yield an anomalous product (**20**) in 11% yield which must be derived from the breakdown of solvent and electrolyte.[26]

(17) (a) E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, **24**, 687 (1968); (b) E. E. van Tamelen and L. K. Oliver, *J. Am. Chem. Soc.*, **92**, 2136 (1970); (c) E. Leete, *J. Chem. Soc., Chem. Commun.*, 821 (1979).

(18) J. M. Bobbitt and J. P. Willis, *Heterocycles*, **6**, 899 (1977).

(19) M. Aiura and Y. Kanaoka, *Heterocycles*, **2**, 319 (1974).

(20) M. J. Allen and V. J. Powell, *J. Electrochem. Soc.*, **105**, 541 (1958).

(21) J. F. Ambrose, L. L. Carpenter, and R. F. Nelson, *J. Electrochem. Soc.*, **122**, 876 (1975), and references cited therein.

(22) W. Lamm, F. Pragst, and W. Jugelt, *J. Prakt. Chem.*, **317**, 995 (1975).

(23) R. F. Nelson in "Technique of Electroorganic Synthesis, Part II", N. L. Weinberg, Ed., Wiley-Interscience, New York, 1975, p 269.

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2,3-Diphenylindole was oxidized to the dimer **21** in 90–95% yield, and a radical-coupling mechanism was proposed.[27] Sainsbury[28] oxidized 3-[3-(3,4-dimethoxyphenyl)-propanoyl]indole to **22** in an almost quantitative yield and suggested a mechanism involving oxidation of the dimethoxybenzene ring followed by ring closure. The voltammetry of several aminoindoles has been studied recently.[29]

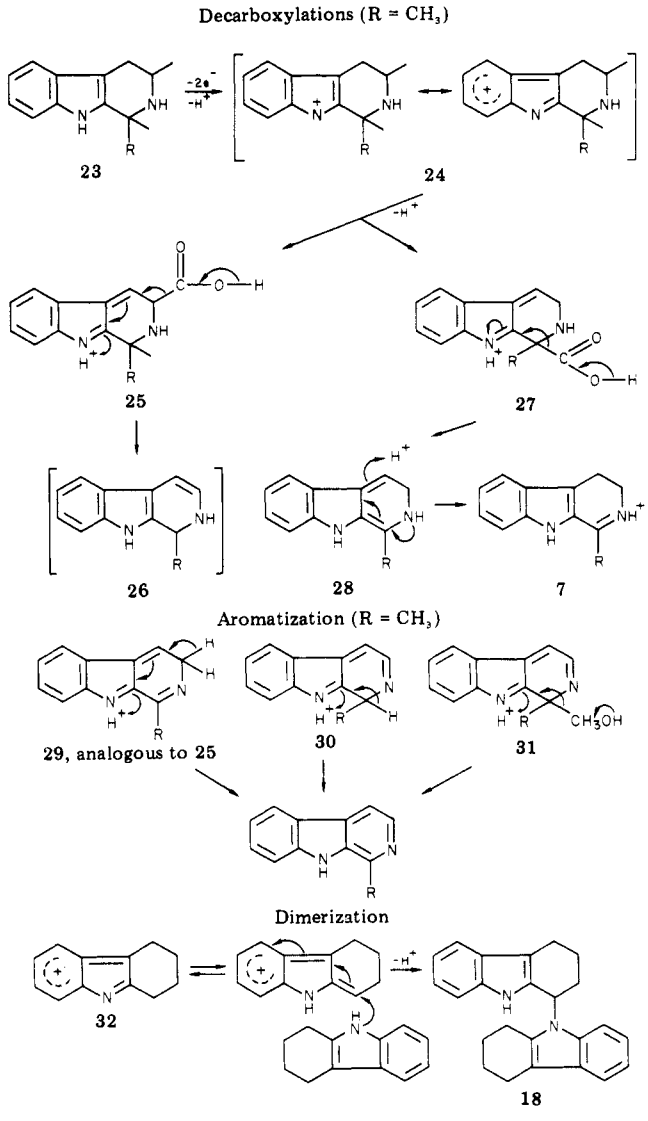
In our work, we have observed several different reactions which appear to take place as a consequence of an electrochemical oxidation of an indole nucleus. These are decarboxylation of a 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**4** to **7**) followed by loss of hydrogen at positions 3 and 4 to give **9**, decarboxylation of tetrahydro-β-carboline-3-carboxylic acid accompanied by loss of hydrogen at positions 1 and 2 (**5** to **9**), stepwise double decarboxylation of tetrahydro-β-carboline-1,3-dicarboxylic acid (**3** to **6** to **9**), decarboxylation of 1-(hydroxymethyl)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid accompanied by loss of a hydroxymethyl group (**10** to **9**), and, finally, a dimerization of tetrahydrocarbazole to yield **18**.

The mechanistic pathways leading to these various products are, thus far, a matter of conjecture. The overall reactions involve the loss of two electrons, two protons, and, for the decarboxylations, carbon dioxide. Since the reactions take place at lower potentials in base, it is quite likely that the loss of the acidic hydrogen on the indole nitrogen plays a role in the reaction. While the exact sequence of events cannot be known without an exhaustive electrochemical study, it is possible to explain our results in a logical fashion (Scheme II).

The loss of two electrons and a proton from the general indole structure **23** can give a cation **24** which can lose a proton to give an unsaturated system which is formulated as **25** or **27** with the 1- and 3-acid groups in place. Compound **25** can decarboxylate by a conventional mechanism to give **26**, and **27** can decarboxylate to **28** and tautomerize to **7**. The removal of hydrogen, either at the 1,2 or the 3,4 positions, was normally observed to take place in order to complete the aromatization of the C ring (**26** or **7** to **9**). If **26** or **7** were oxidized as postulated (**23** to **25**), compound **29** would result from **7**, and, with suitable tautomerism, **30** would result from **26**. Further tautomerism of **29** and **30** give the observed **9**. Compound **31** represents an intermediate derived from **10** by oxidations similar to those of **23** through **26**. Deformylation of **31** also leads to **9**.

The observed dimerization of tetrahydrocarbazole can result from the nucleophilic addition of an unoxidized molecule to **32**, an intermediate derived from tetrahydrocarbazole in the same manner as **24** is derived from **23**. Compound **18** was postulated to arise via an ionic dimerization by Aiura and Kanaoka,[19] and a similar reaction has recently been suggested[48] in the biosynthesis of *Vinca* alkaloids. Free-radical reactions are, of course, possible.

**Scheme II**




## Experimental Section[30]

**Preparation of 3.** Pyruvic acid (1.32 g, 15 mmol) was added to 3.0 g of L-tryptophan (14.7 mmol) in 50 mL of 0.1 N $H_2SO_4$ which had been deaerated ($N_2$). The solution was stirred under $N_2$ for 12 h, and the product was collected by filtration, washed ($H_2O$), and air-dried to give 2.5 g of **3**: 62%; mp 216–220 °C dec (lit.[31] mp 212–214 °C).

**Preparation of 4.** Pyruvic acid (5.05 g, 57.3 mmol) was added to 9.0 g (45.8 mmol) of tryptamine hydrochloride dissolved in 135 mL of 1:1 MeOH–$H_2O$, which had been deaerated ($N_2$). The mixture was stirred under $N_2$ for 12 h, and the precipitated product was collected by filtration, washed ($H_2O$), and dried (110 °C) to give 8.6 g (82%) of **4**, mp 216–218 °C (lit.[32] mp 217–219 °C).

**Preparation of 5.** Acetaldehyde (2 mL, 36 mmol) was added to 6.0 g (29.4 mmol) of L-tryptophan dissolved in 40 mL of 0.1 N $H_2SO_4$, and the mixture was stirred under $N_2$ for 6–12 h. The precipitated product was collected by filtration, washed (small amounts of $H_2O$), and dried (110 °C) to yield 3.1 g of **5**. When the washings only (not the filtrate) were combined and basified to pH 6.5 (solid NaOH), an additional 2.5 g of **5** precipitated to give a combined yield of 83% of the 1*S*,3*S* isomer of **5**: mp 276–280 °C dec; $[\alpha]^{25}_D$ −105.6° (*c* 1.0, 1 N HCl–MeOH, 1:1) [lit.[13] mp 293 °C; $[\alpha]^{25}_D$ −106.6° (*c* 1.0, 1 N HCl–MeOH, 1:1)].

The filtrate from the initial filtration was concentrated to 10–15 mL and cooled to 6 °C for 12 h. The white crystals were collected

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(27) G. T. Cheek and R. F. Nelson, *J. Org. Chem.*, **43**, 1230 (1978).
(28) M. Sainsbury, *Heterocycles*, **9**, 1349 (1978).
(29) R. Andruzzi and A. Trazza, *J. Electroanal. Chem.*, **86**, 201 (1978).
(30) Melting points were measured on a Kofler micro hot stage and are corrected. NMR spectra were recorded on a Varian A-60 instrument for H or a Bruker WH-90 instrument, and mass spectra were obtained on an AEI MS-9 instrument with a direct inlet at 70 eV. TLC was carried out on 0.25-mm silica gel GF-254 layers (qualitative) or 1-mm layers (preparative). Cyclic voltammetry was carried out on a PAR Model 170 instrument. All evaporations were carried out under vacuum.
(31) R. Tschesche, H. Jenssen, and P. N. Rangachari, *Chem. Ber.*, **91**, 1732 (1958). Although a rotation is reported for this compound, and it appears to be pure, the stereochemistry is unknown.
(32) I. D. Spenser, *Can. J. Chem.*, **37**, 1851 (1959).

by filtration, washed (small amounts of ice-cold water), and dried under vacuum over KOH at 110 °C. The yield of the 1*R*,3*S* isomer of **5** was 0.6 g (9%): mp 225–228 °C dec; $[\alpha]^{25}_D$ −33° (*c* 0.5, 0.1 N NaOH) [lit.[13,33] mp 242–244 °C; $[\alpha]^{25}_D$ −69° (*c* 1, 1 N HCl–MeOH, 1:1)].

**Preparation of 6.** Acetyl chloride (1.2 mL, 17 mmol) was added to 3.0 g (14.7 mmol) of L-tryptophan dissolved in 50 mL of anhydrous $CF_3CO_2H$. The reaction was stirred at room temperature for 0.5 h, and 1 mL of water was added. The solution was evaporated to dryness, and the last traces of acid were removed under vacuum. The residue was dissolved in 20 mL of $H_2O$, and the pH was adjusted to 4.5 with NaOAc. Cooling to 6 °C for 12 h caused the precipitation of 0.7 g (21%) of **6** as yellow needles. Recrystallization from dilute $NH_4OH$ raised the melting point to 189–190 °C (lit.[34] mp 186–188 °C).

**Preparation of 8.** Concentrated HCl was added, dropwise, to 2.0 g of **4** in 75 mL of hot $H_2O$ until dissolution occurred and until an additional 5 mL of acid was added. The solution was boiled for 15–30 min, cooled to room temperature, made strongly alkaline (solid NaOH), and extracted ($CHCl_3$). The extracts were washed ($H_2O$), dried ($Na_2SO_4$), and evaporated to yield an oil which crystallized from benzene to give 1.3 g (80%) of **8**, mp 182–182.5 °C (lit.[35] 180–181 °C).

**Preparation of 10.** Freshly distilled α-hydroxyacetone (14 mL, 204 mmol) was added to a solution of 6 g (29.4 mmol) of L-tryptophan dissolved in 40 mL of 1.0 N $H_2SO_4$. The mixture was stirred under $N_2$ for 24 h, and the pH was adjusted with cooling to 8 with solid NaOH. The mixture was evaporated to 25 mL, and the precipitated product was filtered, washed ($H_2O$), and dried (110 °C under vacuum) to yield 5.6 g (73%) of the 1*R*,3*S* isomer of **10**, mp 241–245 °C dec. Recrystallization from dilute $NH_4OH$ afforded the pure isomer as colorless prisms: mp 258–260 °C dec; $[\alpha]^{25}_D$ −150° (*c* 0.5, 0.1 N NaOH); $^1H$ NMR ($D_2O$, $Na_2CO_3$) δ 1.18 (s, 3 H, $CH_3$), 2.30–3.15 (AB, 2 H, $CH_2$), 3.51 (2 d, $J$ = 4 and 11 Hz, $CHCO_2H$), 3.51 and 3.82 (2 d, $J$ = 11.5 Hz, $CH_2OH$), 6.85–7.40 (m, 4 H, aromatic); $^{13}C$ NMR ($D_2O$, $Na_2CO_3$) 23.46 ($CH_3$), 27.11 (C-4), 55.56 ($CH_2OH$), 56.319 (C-1), 69.25 (C-3), 109.59 (C-4a), 112.64, 119.40, 120.50, 122.96, 127.488, 137.41, and 138.22 (aromatic), 182.30 ppm ($CO_2H$). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.41; H, 6.30; N, 10.94.

The filtrate from the initial product-isolation step was concentrated to 5–10 mL and cooled to 6 °C for 24 h. The crystals were collected by filtration, washed (iced $H_2O$), and dried under vacuum over KOH to yield 1.2 g (16%) of the two isomers of **10** (about 33% 1*S*,3*S* and 67% 1*R*,3*S* as white needles: mp 200–206 °C; $^1H$ NMR ($D_2O$, $Na_2CO_3$) δ 1.28 (s, 3 H, $CH_3$), 2.20–3.05 (AB, 2 H, $CH_2$), 3.41 (s, 2 H, $CH_2OH$), 3.38 and 3.55 (2 d, $J$ = 4 and 11 Hz, $CHCO_2H$), 6.75–7.40 (m, 4 H, aromatic); $^{13}C$ NMR ($D_2O$, $Na_2CO_3$; after subtraction of spectrum of the 1*R*,3*S* isomer) 24.59 ($CH_3$), 26.48 (C-4), 55.22 ($CH_2OH$), 56.03 (C-1), 67.28 (C-3), 108.75 (C-4a), 112.64, 119.40, 120.50, 122.96, 127.49, 137.41, and 138.22 (aromatic), 181.81 ppm ($CO_2H$). Anal. Calcd for $C_{14}H_{16}N_2O_3 \cdot H_2O$: C, 60.41; H, 6.51; N, 10.06. Found: C, 60.42; H, 6.50; N, 10.65. The material decomposed slowly with time.

**Preparation of 11.** Glycoaldehyde (2.0 g, 33 mmol) was added to a solution of L-tryptophan dissolved in 100 mL of 0.1 N $H_2SO_4$, and the solution was stirred under $N_2$ for 4–6 h. The precipitated product was collected by filtration, washed ($H_2O$), and dried to yield 5.0 g (69%) of **11**, mp 256–260 °C dec (lit.[32] mp 256–257 °C). The stereochemistry is unknown.

**Preparation of 12 and 13.** Glyoxylic acid monohydrate (3.0 g, 33 mmol) was added to 6.0 g (29.4 mmol) of L-tryptophan dissolved in 100 mL of 0.1 N $H_2SO_4$ and the mixture stirred for 12 h. The product was collected by filtration, washed ($H_2O$), and dried to yield 6.8 g (89%) of 1,2,3,4-tetrahydro-β-carboline-1,3-dicarboxylic acid, mp 269–271 °C dec (lit.[36] mp 270 °C).

Concentrated HCl was added dropwise to a suspension of 1 g of the dicarboxylic acid in 2 mL of hot water until the compound dissolved.[37] An additional 20 mL of acid was then added, and the solution was boiled down to about 10 mL. The mixture was cooled to 6 °C for 6 h whereupon **12** precipitated. The product was collected by filtration, washed ($H_2O$), and dried (110 °C) to yield 0.8 g (96%) of **12**, mp 295–299 °C dec. Recrystallization from dilute $NH_4OH$ gave cream-colored needles: mp 294–296 °C dec; $[\alpha]^{25}_D$ −135° (*c* 0.5, 0.1 N NaOH) (lit. mp 315[14] and 306 °C[36]).

In a similar manner and by the exact procedure of Ho and Walker,[37] **13** was prepared in 66% yield and had a melting point of 205–208 °C (lit.[37] mp 204–205 °C).

**Preparation of 14 and 15.**[39] To a stirred solution of 1.0 g (5.8 mmol) of **13** dissolved in 20 mL of anhydrous methanol was added 1.0 mL (10 mmol) of acetic anhydride. After a few minutes, the product precipitated. Water (5 mL) was added, and the mixture was warmed to 80 °C for 15 min and cooled. The product was collected by filtration, washed ($H_2O$), and dried (110 °C) to give 1.2 g (97%) of **14**, mp 237–239 °C (lit.[40] mp 237–238 °C).

In a similar manner, **15** was prepared in 97% yield from **8** and melted at 200–202 °C (lit.[40] mp 205–206 °C).

**Preparation of 16.** Acetone (15 mL, 327 mmol) was heated to reflux overnight with 5 g (24.5 mmol) of L-tryptophan in 40 mL of 1 M $H_2SO_4$. The mixture was neutralized with solid NaOH and cooled, and the acetone was evaporated. The product crystallized, was collected by filtration, and was dried to give 5.4 g (91%) of white needles: mp 227–228 °C dec; $[\alpha]^{25}_D$ −118° (*c* 0.5, 0.1 N NaOH); mass spectrum, *m/e* 244.1205 ($M^+$) (calcd for $C_{14}H_{15}N_2O_2$, *m/e* 244.1213); $^1H$ NMR ($D_2O$, $Na_2CO_3$) δ 1.20 (s, 6 H, $CH_3$'s), 3.35–3.68 (AX and BX of ABX, 1 H, $J$ = 16 Hz, $CHCO_2H$), 2.25–3.10 (AB of ABX, 2 H, $J$ = 16 Hz, $CH_2$), 6.75–7.35 (m, 4 H, aromatic). Satisfactory combustion analysis was not obtained.

**Preparation of 17.** 2-Oxoglutaric acid (2.4 g, 16.4 mmol) was added to a solution of 4.0 g (15.7 mmol) of L-tryptophan methyl ester hydrochloride in 50 mL of $H_2O$ and stirred under $N_2$ for 48 h. The solution was warmed to 80 °C for 0.5 h, cooled, and basified with solid NaOH to pH 12. The basic solution was heated to reflux for 6 h, cooled, and acidified to pH 5 with concentrated HCl. The product (**17**; 2.3 g, 52%) precipitated and was recrystallized from aqueous MeOH to give colorless platelets, mp 260–265 °C (lit.[41] mp 260–262 °C).[42]

**Oxidative Decarboxylations. General Procedure.** Oxidations were carried out in a 150-mL beaker loosely stoppered with a no. 12 neoprene stopper. Nitrogen was passed through the cell during the reactions. The anode was a piece of graphite felt[43] (3.5 × 15 cm) cut with a long piece on one side to extend out of the cell under the neoprene stopper. The anode fit around the inside of the beaker like a liner. The lead was connected to the felt with a common alligator clip. The cathode was a 1-$cm^2$ piece of Pt separated from the anode by a small sack of Nafion 425 membrane.[44] The standard calomel reference electrode was connected by a salt bridge to a point as near the center of the anode and as close to it as possible. The cathode and the salt bridge were placed in the cell through holes in the neoprene stopper, and the cell contents were stirred magnetically. The potentials were controlled by using a Wenking 61 TR potentiostat

(33) Although the physical constants of the isomers of **5** are not in complete agreement with the literature cited, the NMR spectra were quite clean, especially in the region from δ 3 to 4.5 where the compounds have quite different absorptions. The isomers also gave satisfactory elemental analyses.

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(37) This is the general procedure of B. T. Ho and K. E. Walker, *Org. Synth.*, **51**, 136 (1971).

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(39) We believe this to be a new and extremely facile method to prepare *N*-acetyl derivatives, at least of materials similar to these cyclic amines.

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(42) Compound **17** was also prepared in an overall yield of 40% by using a condensation method [J. Sandrin, D. Soerens, L. Hutchins, E. Richfield, F. Ungemach, and J. M. Cook, *Heterocycles*, **4**, 1101 (1976)] followed by saponification.

(43) WDF graphite felt was obtained from Union Carbide Corp., Carbon Products Division.

(44) This membrane was generously given to us by the E. I. du Pont de Nemours and Co., Inc., Plastics Dept.

(Brinkmann Instrument Co.) or a PAR 170 system (Princeton Applied Research).

In general, 100–500 mg of substrate was added to a stirred, preequilibrated, preelectrolyzed (+1.0 V), deoxygenated cell containing 120 mL of supporting electrolyte. (A solution of 9.56 g of $KH_2PO_4$ and 1.69 g of $K_2HPO_4$ dissolved in 500 mL of $H_2O$ and diluted with 500 mL of MeOH was used for all oxidations except that of 8. The electrolyte had a pH of 7.0 at 25 °C.) In some cases, warming was necessary to dissolve the substrate. The anode potential was increased until a current of 20–50 mA above the background was obtained, and the reactions were terminated when the current dropped back to near the background or when TLC showed the absence of starting material. The contents were then removed from the cell, and the felt anode was ground up in a Waring blender under MeOH. The blender contents were filtered, and the graphite fibers were washed with more MeOH. The combined cell contents and anode washings were evaporated to dryness, dissolved in 50 mL of $H_2O$, basified to a pH of 12 with 4 N NaOH, and extracted with ether. The ether extracts were washed ($H_2O$), dried ($Na_2SO_4$), and processed as described in each case.

**Oxidation of 3.** Compound 3 (100 mg) was oxidized for 19 h at +0.7 V with an initial current of 61 mA. Evaporation of the ether extract yielded 50 mg (75%) of **9**, mp 233–236 °C (lit.[45] mp 238 °C). The pH of the aqueous layer from the ether extraction was adjusted to 5 with concentrated HCl, and the solution was evaporated to dryness. The residue was dissolved in MeOH, filtered to remove salts, concentrated to about 1 mL, and separated by preparative TLC on four 1-mm layers to give 20 mg (23%) of **6** which was identical with the synthetic sample.

**Oxidation of 4.** Compound 4 (200 mg) was oxidized for 6 h at +0.8 V with an initial current of 32 mA. Evaporation of the ether extract gave 96 mg of crude product which was separated by preparative TLC (as described for **3**) to yield 67 mg (42%) of **7** and 22 mg (14%) of **9**.

**Oxidation of 5.** The 1*S*,3*S* isomer of **5** (200 mg) was oxidized for 5 h at +0.9 V with an initial current of 27 mA. Evaporation of the ether extract gave 95 mg (60%) of **9**. In a similar manner, oxidation of the 1*R*,3*S* isomer yielded 40 mg (25%) of **9**.

**Oxidation of 6.** Compound 6 (250 mg) was oxidized for 3 h at +0.9 V with an initial current of 26 mA. Evaporation of the ether layer yielded 100 mg (50%) of **9**.

**Oxidation of 8.** Compound 8 (300 mg) was oxidized for 5.5 h at +0.16 V in 120 mL of 0.1 M NaOMe in MeOH at an initial current of 22 mA. The solution was neutralized with concentrated HCl, evaporated to dryness, dissolved in 25 mL of MeOH, filtered to remove salts, evaporated to dryness, and separated by preparative TLC to give 37 mg of starting material and 30 mg (10%) of **9**. Overoxidation was apparent since much of the product remained at the base line of the chromatograms.

**Oxidation of 10.** The 1*R*,3*S* isomer of **10** (200 mg) was oxidized for 5 h at +0.7 V with an initial current of 22 mA. Evaporation of the ether extract yielded 73 mg (52%) of **9**.

**Oxidation of 11.** Compound 11 (250 mg) was oxidized for 5 h at +0.7 V with an initial current of 56 mA. Evaporation of the ether layer gave 151 mg (75%) of 1-(hydroxymethyl)-β-carboline, mp 228–229 °C, after recrystallation from acetone and sublimation (lit.[46] mp 228–230 °C).

**Oxidation of 12.** Compound 12 (200 mg) was oxidized for 5 h at +1.0 V with an initial current of 30 mA. Evaporation of the ether extract gave 53 mg (35%) of β-carboline as a light brown crystalline solid, mp 194–195 °C (lit.[47] mp 194–195 °C).

**Dimerization of Tetrahydrocarbazole to 18.** Recrystallized tetrahydrocarbazole (250 mg) was oxidized for 1.5 h at +0.7 V in 120 mL of 0.1 M $LiClO_4$ in $CH_3CN$–$H_2O$ (9:1) with an initial current of 44 mA. The reaction mixture was basified to pH 12 with 4 N NaOH and evaporated to near dryness. The residue was partitioned between $H_2O$ and $CHCl_3$. The $CHCl_3$ layer was washed ($H_2O$), dried ($Na_2SO_4$), and evaporated to yield 244 mg (98%) of a light brown oil which was homogeneous by TLC. The oil was treated with 2–3 mL of acetone and cooled to −10 °C whereupon 150 mg of **18** crystallized; mp 223–228 °C (lit.[19] mp 223–225 °C).

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**Registry No.** 1, 6912-86-3; **2**·HCl, 343-94-2; **3**, 18070-61-6; **4**, 6543-83-5; (1*S*,3*S*)-**5**, 40678-46-4; (1*R*,3*S*)-**5**, 42438-72-2; (*S*)-**6**, 39537-10-5; **7**, 525-41-7; **8**, 2506-10-7; **9**, 486-84-0; (1*R*,3*S*)-**10**, 73246-29-4; (1*S*,3*S*)-**10**, 73198-01-3; **11**, 73198-02-4; **12**, 6052-68-2; **13**, 16502-01-5; **14**, 58100-29-1; **15**, 6649-98-5; **16**, 73198-03-5; **17**, 73198-04-6; **18**, 52784-14-2; pyruvic acid, 127-17-3; acetaldehyde, 75-07-0; acetyl chloride, 75-36-5; α-hydroxyacetone, 116-09-6; glycolaldehyde, 141-46-8; glyoxylic acid, 298-12-4; 1,2,3,4-tetrahydro-β-carboline-1,3-dicarboxylic acid, 59132-30-8; acetone, 67-64-1; 2-oxoglutaric acid, 328-50-7; L-tryptophan methyl ester hydrochloride, 7524-52-9; 1-(hydroxymethyl)-β-carboline, 21236-66-8; tetrahydrocarbazole, 942-01-8; indole, 120-72-9; β-carboline, 244-63-3.

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# Use of Organoiron Complexes in β-Lactam Synthesis. Preparation of 2-Methylcarbopenam

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A short synthesis of a 2-methylcarbopenam (**9**), employing organoiron complexes as intermediates, is described. Allylacetone is transformed to the π-complex **1**, and this on treatment with ammonia is converted to the pyrroline complex **2**. Reduction with sodium borohydride affords a mixture of stereoisomeric pyrrolidine complexes, only one of which is transformed to a chelate complex (**8**). Oxidation of the chelate with silver oxide gives the carbopenam as a single stereoisomer (**9**).

As part of a program designed to examine a range of synthetic applications for complexes of the $CpFe(CO)_2$ radical (hereafter designated by the symbol Fp), we recently reported a new sequence for the synthesis of β-lactams based on the addition of a primary amine to Fp-(olefin) cations and subsequent oxidative lactamization of

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