# Electrochemistry of Natural Products. VI. Oxidative Decarboxylation of Some Tetrahydroisoquinoline-1-carboxylic Acids[1]

J. M. Bobbitt* and Theresa Y. Cheng

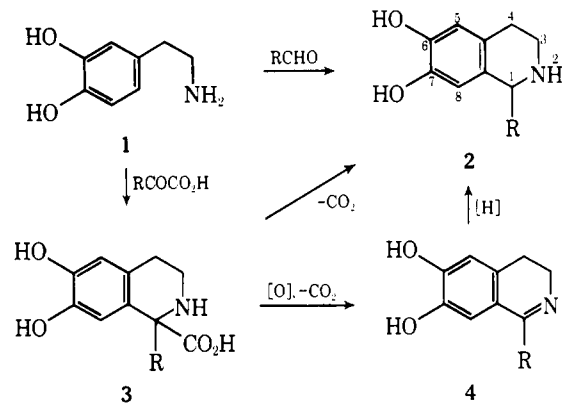
*Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06268*

*Received July 29, 1975*

A series of oxygenated 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids has been electrochemically oxidatively decarboxylated to yield 3,4-dihydroisoquinolines. The 3,4-dihydro derivatives were reduced chemically to tetrahydro derivatives for isolation. Overall yields were 50–90% in simple cases. The ease of decarboxylation was correlated with the electron density of the aromatic ring, and the decarboxylation is thought to be triggered by removal of electrons through the ring, making it an example of the pseudo-Kolbe reaction. The effect of various functional groups was studied, and a concerted two-electron mechanism is proposed. The reaction tends to support Hahn's theory of the biosynthesis of isoquinoline alkaloids by providing a laboratory analogy for the crucial decarboxylation step. The possible impact of this observation on classical ideas of oxidative phenol coupling reactions is discussed.

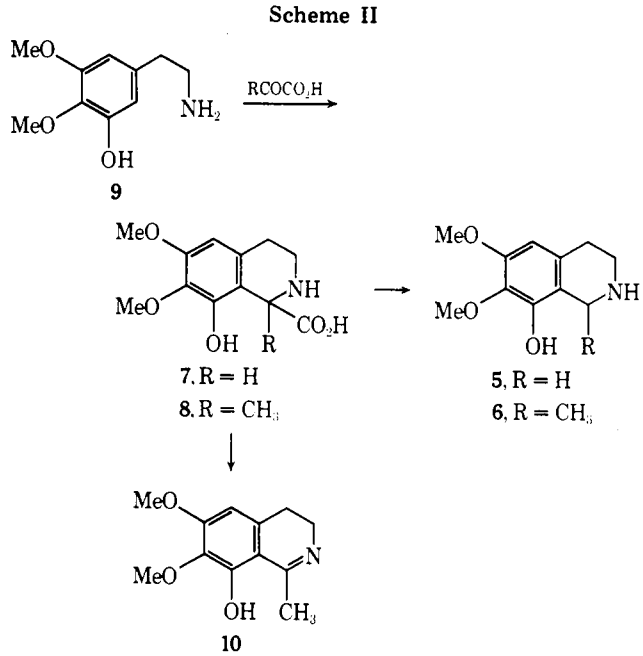
The nitrogen atom, carbons 3 and 4, and the aromatic ring of the isoquinoline portion of the isoquinoline alkaloids are derived biosynthetically from tyrosine, probably by way of 3,4-dihydroxyphenylalanine (Dopa) and β-(3,4-dihydroxyphenyl)ethylamine (dopamine, 1).[2] The source of carbon 1, the various groups attached to it, and the mode of ring closure have not been clearly established. Two major theories have emerged as shown in Scheme I.[3] According to one theory, carbon 1 is an aldehyde carbon; the ring closure is a classical Pictet–Spengler reaction; and the tetrahydroisoquinoline is formed directly (1 → 2). According to the second theory, generally attributed to Hahn,[4a] and recently considered by others,[4b,c] carbon 1 is derived from the ketone carbonyl of an α-keto acid (1 → 3) and a decarboxylation is needed to yield the final product (3 → 2). Both ring closures have been shown to take place readily under "physiological conditions" when a free phenol group is ortho or para to the point of closure. Since α-keto acids are more stable metabolites than aldehydes and are readily available by transamination reactions from amino acids, the Hahn route is the more plausible of the two possibilities. The problem with the Hahn theory is that no methods have been found for decarboxylating the tetrahydroisoquinoline-1-carboxylic acids (3) under any conditions that could be termed "physiological". In this paper, we would like to describe a decarboxylation reaction which may well suit this purpose.

Scheme I




Kapadia, Leete, Fales, and their co-workers[3] have recently shown that the cactus alkaloids, anhalamine (5) and anhalonidine (6), are definitely synthesized in the plant by the Hahn route (Scheme II). The intermediate carboxylic acids, 7 and 8, were isolated from the cactus and shown by radioactive tagging experiments to be intermediates. The interesting point to us was that when acid 8 was incubated with fresh cactus slices, the product of the decarboxylation reaction was not the alkaloid 6, but the 3,4-dihydroisoquinoline 10. Thus, it appeared that the crucial decarboxylation may be an *oxidative decarboxylation* (3 → 4) and that a reduction step (4 → 2) may be necessary to yield the alkaloid. Since the logical site for any oxidation of the carboxylic acids would be the phenol groups present in the aromatic ring, or even the ring itself, it appeared that our experience in the electrochemical oxidation of phenols[1b] might be applicable. Thus, a series of substituted isoquinoline derivatives, 11–20 (Table I), was prepared for study.

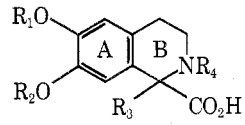
Scheme II




**Preparation of Starting Materials.** Compounds 11, 12, and 13 were prepared from the appropriate phenylethylamines and pyruvic acids by a classical Pictet–Spengler synthesis[5] (1 → 3) and suitably modified by methylation[6] and/or acetylation[7] to give 15, 17, and 18. Compounds 14 and 16 were prepared through a Bischler–Napieralski reaction[8] to yield 3,4-dihydroisoquinolines which were substituted at the 1 position by the Reissert sequence worked out by Shamma and Jones.[9] Compounds 19[10] and 20[4a] are known and were prepared by a Pictet–Spengler synthesis.

The NMR spectra of compounds 12–18 are summarized in Table II as far as they were interpretable. In addition to the peaks noted, the compounds showed entirely predict-

Table I
Tetrahydroisoquinoline-1-carboxylic Acids



| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 11 | H | H | $C_6H_5CH_2$ | H |
| 12 | H | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | H |
| 13 | H | $CH_3$ | $p$-$HOC_6H_4CH_2$ | H |
| 14 | $CH_3$ | H | $C_6H_5CH_2$ | H |
| 15 | H | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | $CH_3CO$ |
| 16 | $CH_3$ | $CH_3$ | $p$-$HOC_6H_4CH_2$ | H |
| 17 | $CH_3$ | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | H |
| 18 | $CH_3$ | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | $CH_3CO$ |
| 19 | H | H | $CH_3$ | H |
| 20 | H | $CH_3$ | $CH_3$ | H |

A. Those containing two phenol groups (11 and 19) are oxidized at potentials 0.2–0.3 V lower than those containing one phenol group (20, 12–15), and those containing no phenol groups (17 and 18) are relatively difficult to oxidize. Second, it makes little difference whether the free phenol group is meta (14 and $m$-hydroxyphenylacetic acid) or para (12 and $p$-hydroxyphenylacetic acid) to the phenylacetic acid part of the molecule. This is of interest because a para phenol group is necessary to promote a facile isoquinoline ring closure (1 → 3). It is interesting, however, that a phenol group in ring A is not necessary for decarboxylation since 17 and 18 are decarboxylated, albeit with complicating secondary reactions.

As will be shown subsequently, the initial products of the preparative oxidations of compounds 11–15 and 17 at potentials similar to the values of the lowest half-wave potential are, indeed, the predicted 3,4-dihydroisoquinolines

Table II
NMR Spectral Data on Starting Materials and Products

| Compd | Solvent[a] | NMR Shift, $\delta$[b] $C_5$ H | $C_8$ H | 6-$OCH_3$ | 7-$OCH_3$ | $C_\alpha$ H | Other |
|---|---|---|---|---|---|---|---|
| 12 | $CD_3CN$–NaOD | 6.28 | 7.16 | | 3.80 | 3.25 AB, ics = 8 Hz $J_{AB}$ = 13 Hz | |
| 13 | $CD_3CN$–NaOD | 6.34 | 7.23 | | 3.81 | 3.14 AB, ics = 19 Hz $J_{AB}$ = 13 Hz | |
| 14 | $Me_2SO$–NaOD | 6.49 | 7.13 | 3.66 | | 3.12 AB, ics = 12 Hz $J_{AB}$ = 13 Hz | |
| 15 | Acetone-$d_6$ | 6.38 | 7.00 | | 3.75 | | 2.02, $CH_3CO$ |
| 16 | $Me_2SO$–NaOD | 6.48 | 7.24 | 3.74 | 3.67 | | |
| 17 | $CF_3CO_2H$ | 6.99 | 7.59 | 4.1 | 4.03 | | 3.99, $OCH_3$ |
| 18 | Acetone-$d_6$ | 6.51 | 7.11 | 3.82 | 3.76 | | 3.63, $OCH_3$ 3.0, $CH_3CO$ |
| 22 | $Me_2SO$–$CCl_4$–$CF_3CO_2H$ | 6.86 | 7.56 | | 3.86 | 4.47 | |
| 25 | $CDCl_3$ | 6.66 | 6.66 | | 3.83 | 4.15 | 3.83 4-$OCH_3$ |
| 26 | $CDCl_3$–NaOD | 6.81 | 6.57 | 3.83 | | 4.15 | 7.32, benzyl |
| 27 | $CDCl_3$–$Me_2SO$ | 6.81 | 6.81 | | 3.70 | | 3.80, 4-$OCH_3$ 7.53, AB, ics = 50 Hz, $J_{AB}$ = 8 Hz |
| 28 | $CDCl_3$ | 6.49 | 6.49 | 3.77 | 3.70 | | 7.16, benzyl |
| 29 | $Me_2SO$–HCl | 6.67 | 6.25 | | 3.57 | | 3.33 $C_\alpha$ $OCH_3$ |
| 30 | $Me_2SO$–HCl | 6.63 | 6.24 | | 3.56 | | 3.3, 3.2 two $C_\alpha$ $OCH_3$ |
| 32 | $CDCl_3$ | 6.80 | 7.00 | 3.80 | 3.88 | | 7.53, AB, ics = 58 |
| 33 | $CCl_4$–$CDCl_3$–NaOD | 6.52 | 6.40 | 3.75 | 3.67 | 4.15 | Hz, $J_{AB}$ = 9 Hz |
| 34 | $CDCl_3$ | 6.74 | 6.74, 7.30 | | 3.75, 3.80 | 4.92, 5.05 | 1.80 $COCH_3$ 4.1, 4-$OCH_3$ |
| 35 | $CDCl_3$ | 7.29 | 6.92 | | 3.90 | 4.17 | 1.9 $COCH_3$ |

[a] $Me_2SO$ is dimethyl sulfoxide; NaOD and DCl imply that the solvent was just basified or acidified with NaOD–$D_2O$ or DCl–$D_2O$, respectively. [b] The term ics refers to the distance between the inner peaks of a pattern.

able aromatic peaks for the protons on the benzyl ring and poorly resolved multiplets in the region of $\delta$ 2.5–3.5 corresponding to four protons on carbons 3 and 4. The most interesting feature is the presence of the $C_8$ H at exceptionally low fields (over $\delta$ 7), probably due to the conformation of the molecule dictated by the carboxyl group at $C_1$.

**Voltammetry.** Compounds 11–20, $m$- and $p$-hydroxyphenylacetic acids, and the reaction products 22 and 27 were studied by cyclic voltammetry in two solvent systems, 0.1 $M$ $NaHCO_3$ in MeOH–$H_2O$, 6:4, and 0.1 $M$ NaOMe in MeOH. The cyclic voltammograms (Figure 1 for 12 is representative) seem to indicate an irreversible EC process.[11] The half-peak potentials are given in Table III.

Several conclusions may be drawn from the data in Table III. First, the ease of oxidation can be directly correlated with the number of free phenol groups present in ring shown in Schemes I (4) and II (10). Since such a decarboxylation requires the loss of two electrons and a coulometric experiment on 12 indicated a two-electron reaction, it is reasonable to believe that the lowest half-wave potential is that of a two-electron oxidation. The second half-wave potential at about +0.3–0.4 V observed for most of the compounds and the products, 22 and 27 (Scheme II), is apparently associated with the 3,4-dihydroisoquinoline moiety in some as yet unknown way. It is of interest to note that the half-wave potential of the decarboxylated product (of 12, for example) is about 0.2 V higher than that of the starting carboxylic acid. Thus, the oxidation has a convenient "stopping place" which will be referred to in the Discussion.

It appears from the data that the oxidative decarboxylation depends upon the relative electron density in the aro-

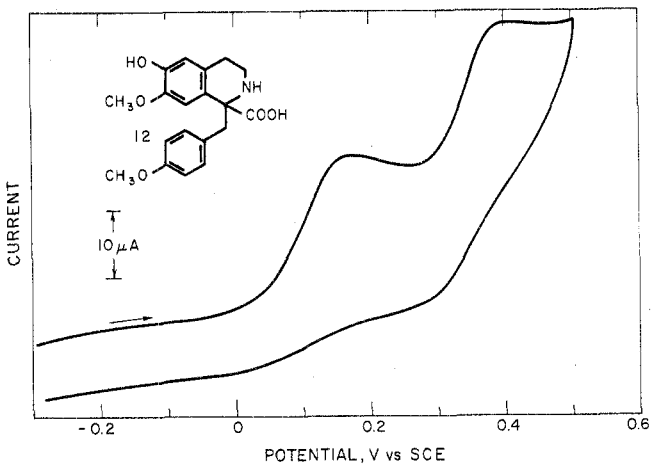



**Figure 1.** Cyclic voltammogram of compound 12.

matic ring and, further, that the electrons are probably withdrawn through the aromatic ring. Two recent papers in electrochemistry clearly point to the same conclusion. Coleman, Utley, and Weedon[12] studied the decarboxylation of a series of substituted phenylacetic acids (some are in Table III), and concluded that electron-rich ring systems tended to promote a two-electron, oxidative reaction leading to carbonium ion formation at the carbon containing the original carboxyl group.[13] Furthermore, the oxidations of some anthracene-10-acetic acids and their salts have supported this conclusion.[14] Eberson has called this type of reaction a "pseudo-Kolbe reaction".

**Preparative Oxidations and Products.** Preparative oxidations of compounds 11–18 were carried out in two solvent systems, 0.1 *M* NaOMe in MeOH and 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$ (2:1). The anode was graphite felt; the cathode was platinum; the potential was controlled by a potentiostat against a standard calomel electrode; and the reactions were carried out under nitrogen in a two-compartment cell.[15] The two solvent systems each had advantages and disadvantages. Oxidations in the NaOMe system took place at lower potentials and showed less electrode coating than those in the $NaHCO_3$ system. Frequently, however, overoxidation to 1-benzoyl-3,4-dihydroisoquinolines (such as **27, 31** and **32**) or to α-methoxy derivatives (such as **29** and **30**) was unavoidable in the NaOMe system. The $NaHCO_3$ system allowed cleaner reactions for some of the substrates, but frequently led to serious electrode coating. Furthermore, some of the substrates were not very soluble in the $NaHCO_3$ system.

The products of the various reactions are shown in Scheme III, and their NMR spectra are summarized in Table II. Under optimized conditions for each substrate, compounds **11, 12,** and **14** were decarboxylated to the dihydroisoquinolines **21, 22,** and **23,** and reduced in the electrolytic cell with $NaBH_4$ to give the tetrahydroisoquinolines **24, 25,** and **26.** Compounds **11** and **14** were decarboxylated in the NaOMe system whereas **12** was oxidized in the $NaHCO_3$ system. The diphenol **24** was methylated to the known compound **28**[16] in an overall yield of 66%. Compound **25** was obtained in a yield of 88%. It gave the correct analysis and had the NMR pattern expected. Compound **26** is known[17] and was obtained in 52% yield.

In the oxidations of **11, 12,** and **14,** the immediate products of electrooxidation, **21, 22,** and **23,** were observed by TLC to be the sole or major products. The TLC spots on silica gel GF254 had a characteristic blue fluorescence when viewed at 254 and at 360 nm. In the oxidation of **12,** the intermediate dihydro compound, **22,** was isolated and partially characterized. This oxidation, carried out in the

Table III
Half-Wave Potentials of Some Tetrahydroisoquinoline-1-carboxylic Acids and Reference Compounds

| Compd | Hydroxyl groups in ring A | Half-wave potentials: 0.1 *M* $NaOCH_3$ in MeOH, 1st wave | 0.1 *M* $NaOCH_3$ in MeOH, 2nd wave | 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$ (2:1), 1st wave | 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$ (2:1), 2nd wave |
|---|---|---|---|---|---|
| **Isoquinoline Acids** | | | | | |
| **11** | 2 | −0.17 | 0.32 | 0.00 | |
| **19** | 2 | −0.17 | 0.31 | 0.03 | |
| **20** | 1 | 0.08 | 0.30 | 0.18 | 0.38 |
| **12** | 1 | 0.08 | 0.30 | 0.13 | 0.36 |
| **13** | 1 | 0.05 | 0.30 | 0.13 | 0.36 |
| **14** | 1 | 0.10 | 0.27 | 0.22 | |
| **15** | 1 | 0.14 | 0.30 | 0.21 | 0.35 |
| **16** | 0 | 0.28 | 0.40 | 0.37 | |
| **17** | 0 | >0.60 | | >0.80 | |
| **18** | 0 | >0.60 | | >0.80 | |
| **Reference Compounds** | | | | | |
| *p*-Hydroxyphenylacetic acid | | 0.29 | | 0.38 | |
| *m*-Hydroxyphenylacetic acid | | 0.34 | | 0.43 | |
| *p*-Methoxyphenylacetic acid | | 1.39[a] | | | |
| Phenylacetic acid | | 2.5[a] | | | |
| **Representative Products** | | | | | |
| **22** | | 0.30 | | 0.34 | |
| **27** | | 0.36 | | 0.36 | |

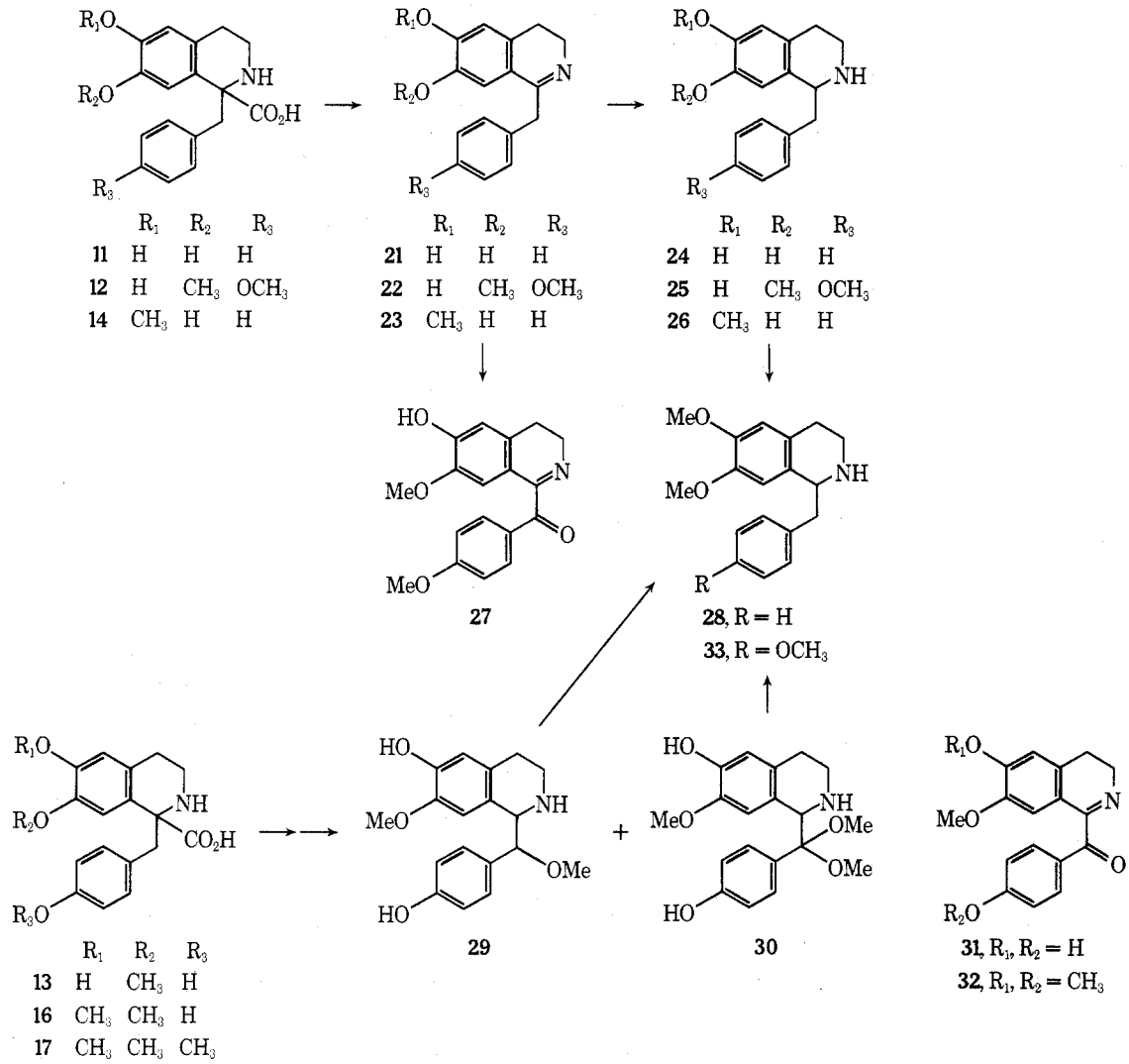
[a] These values were taken from ref 12 and may not be directly comparable with others.

NaOMe system, yielded a separable mixture of **22** and the product of the overoxidation, the 1-benzoyl derivative, **27.** Compound **22** had a typical C=N ir absorption at 1600 $cm^{-1}$ and an NMR peak attributable to the $C_\alpha H$ which varied from δ 4.05 in phosphate pH 7.5 buffer to 4.5 in $CF_3CO_2H$–$CDCl_3$ to 4.7 in DCl–$CDCl_3$. This striking behavior is presumably due to the difference in degree of nitrogen protonation in the various media. On recrystallization, **22** was partially converted to **27** by air oxidation.[18] The ketone **27** was characterized by its NMR spectrum, which showed an unusually large spacing between the two halves of the AB pattern due to the aromatic protons of the benzyl ring (50 Hz). This is due to the strongly electron-withdrawing effect of the keto group. Compound **27** was methylated to give the known compound **32.**[18] The overoxidation to the 1-benzoyl derivatives was not noticed when no oxygen was present in the benzyl group.

When free phenol groups were present in the para position[19] of the benzyl group and in the isoquinoline ring, oxidation at the α carbon of the benzyl group is unavoidable. Thus, **13** on oxidation in the NaOMe system followed by $NaBH_4$ reduction led to the methoxylated products, **29** and **30.** Compounds **29** and **30** had clear methoxyl peaks in their NMR spectra which were neither aromatic methoxy groups nor MeOH/ These peaks disappeared when **29** and **30** were hydrogenolyzed over Pd on carbon to give the known compound **33.**[20] The methoxylation reactions are charateristic anodic substitution reactions.[21,22]

When a free phenol was present in the benzyl ring and none was present in the isoquinoline ring (as in **16**), exten-

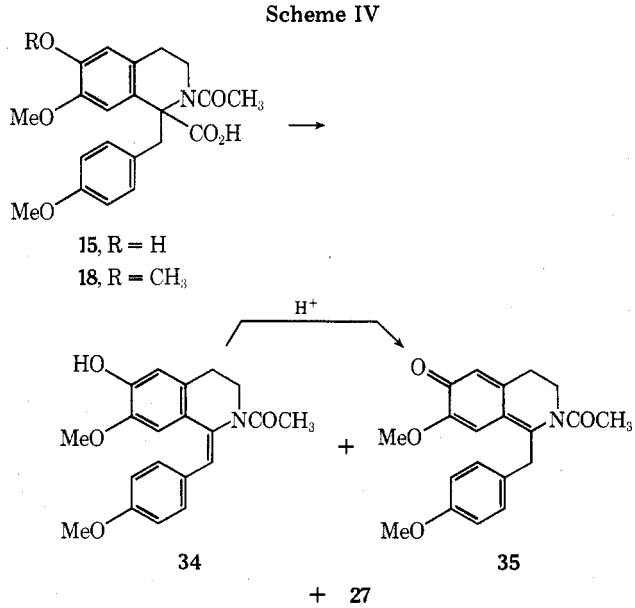
Scheme III




sive fragmentation resulted and no products were isolated. Such fragmentations have been previously noted.[23,24] When no phenol groups are present, as in **17**, decarboxylation did take place at a high potential in the NaOMe system to give 29% of the known 1-benzoyl derivative **32**[18] and 5% of the compound methyl anisate.[25] Compound **32**, like **27**, showed a large spacing (58 Hz) between the halves of the AB pattern in its NMR spectrum, due to the ketone.

The role, if any, of the isoquinoline nitrogen in the decarboxylation is not clear, although it certainly furnishes an electron pair for the formation of the 3,4-dihydroisoquinolines. It is known that N-acylated alanines can be decarboxylated electrochemically in MeOH to give methyl ethers,[26] and quinuclidene-2-carboxylic acid has been decarboxylated to yield 2-methoxyquinuclidine.[27] In our experiments, acetylation of the nitrogen has little effect on the ease of oxidation in one case (compare **12** and **15** in Table III), but seemed to block the reaction entirely in another case (compound **17** vs. **18**). The major product from the preparative oxidation of **15** in the $NaHCO_3$ system was the ketone **27** (Scheme IV) in 26% yield. Compound **27** is the product of decarboxylation, a remarkably easy deacetylation, and overoxidation at the $\alpha$ carbon. The more interesting products, however, are **34** and **35**, which were obtained in yields of 9 and 15%, respectively. When treated with acid, **34** is rearranged to **35**. Compound **34** showed essentially a double NMR spectrum, probably due to a cis–trans mixture around the double bond. Compound **35** was completely

Scheme IV




+ **27**

characterized by its NMR spectrum, especially the large shifts for $C_5H$ and $C_8H$ and the $C_\alpha H$ at $\delta$ 4.17 (Table II). Both **34** and **35** had carbonyl absorptions at 1650–1660 $cm^{-1}$ in their ir spectra. The isolation of **34** and **35** show how the decarboxylation reaction can lead to quinone methides and unsaturated compounds which may be of in-

terest in the "oxidative coupling" of phenolic isoquinolines (see Discussion).

When the nitrogen was acylated and no phenol groups were present as in **18**, no decarboxylation took place up to about 1.0 V and starting material was recovered.

All of the products mentioned gave calculated mass spectral molecular ions and fairly predictable fragmentation patterns.[1d]

## Discussion

It appears that the oxidative decarboxylation involves the removal of electrons through the aromatic ring and is of the "pseudo-Kolbe" type.[14] Since it makes little difference whether the free phenol is in the 6 or 7 position, any mechanism must be a fairly general carbonium type.[12-14] The reaction could take place by two paths. In the first path the electrons might be removed one at a time in a conventional ECE process similar to that proposed by Coleman and Eberson for the "pseudo-Kolbe" reaction.[14] The second path might then be a concerted reaction in which two electrons "flow" out through the aromatic ring at the same time that $CO_2$ is lost. It is impossible to state whether either or neither of the paths is valid. However, it does appear from the voltammetry that a single two-electron wave is present at which, on preparative reaction, the appropriate products are obtained. This is supported by a crude coulometric study on **12** which indicated that about two electrons per mole of **12** were transferred during the reaction. Since the decarboxylations do take place at the same potentials as phenol oxidations and phenol oxidations certainly take place in natural environments,[28,29] these decarboxylations would appear to be plausible model reactions supporting Hahn's hypothesis for insoquinoline alkaloid biosynthesis.

The most interesting redox systems in isoquinoline biosynthesis are, however, surely the phenol coupling reactions which lead from the simple 1-benzyltetrahydroisoquinolines to a large number of complex alkaloids.[30] Most, but not all, of these coupled products involve the loss of two electrons per isoquinoline residue. Thus, coupling tends to be intramolecular (two electrons per molecule) or to involve the formation of a double coupled intermolecular dimer (four electrons, two per isoquinoline). If Hahn's hypothesis is correct, and if the decarboxylation is oxidative as we suggest, the 3,4-dihydroisoquinoline products have the correct oxidation state for the majority of the coupled isoquinoline alkaloids. The various coupled products would then be formed by some type of quinone addition[31] and *without further oxidation*. This would then be an example of what Hamilton[29] has called a NOC or nonoxidative coupling. A few examples of reactions which may involve such quinone additions in the isoquinoline series have been observed by Hoshino, Toshioka, and Umezawa[32] and by Kupchan and Liepa.[33]

Such an hypothesis has considerable appeal in that the decarboxylation could serve as a driving force for the oxidation. Furthermore, the oxidation would be expected to stop after the loss of two electrons due to the relative deactivation of the aromatic ring by the 1,2 double bond (see Table III, **22** and **27** vs. others). Much of the difficulty encountered in laboratory oxidations of phenols has been caused by overoxidation. It is quite likely that coupling reactions could be triggered by pH changes or by quaternization of the nitrogen in the 3,4-dihydro compounds. Experiments to check this hypothesis are in course.

It remains to be seen whether electrochemical decarboxylations can be made to serve an even wider role in biomimetic alkaloid synthesis. Van Tamelen and his co-workers[34] have made a case for the involvement of some oxidative decarboxylations of amino acids in biosynthesis. Some of these intermediates were 3-carboxy-1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-β-carboline-4-carboxylic acids. The oxidant used to test the hypothesis was hypochlorite, and the results were inconclusive. In that case, the point of oxidation was the nitrogen rather than, as in our case, the aromatic ring. The ring was also separated from the carboxylic acid by one additional saturated carbon atom.

## Experimental Section[35]

**Preparation of 11, 12, and 13.** Phenylpyruvic acid (2.3 g, 13.9 mmol) was added to 2.4 g (13.1 mmol) of β-(3,4-dihydroxyphenyl)ethylamine hydrochloride in 40 ml of $H_2O$, and the pH was adjusted to 4.5–5.0 with $NH_4OH$. The product crystallized during 5 days and was collected by filtration, washed (cold $H_2O$, then EtOH, then acetone), and dried to give 3.3 g (87%) of **11**. Compound **11** was crystallized from concentrated HCl–MeOH (1:2) to give **11** hydrochloride, mp 243–246° dec (lit.[10] 240° dec).

In a similar manner, **12** was prepared in 88% yield from *p*-methoxyphenylpyruvic acid and β-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride. The hydrochloride of **12**, prepared from concentrated HCl–MeOH (1:1), melted at 258–261° dec, mass spectrum $M^+$ *m/e* 343, calcd 343 ($C_{19}H_{21}NO_5$).

Anal. Calcd for $C_{19}H_{21}NO_5$·HCl: C, 60.02; H, 5.84; N, 3.68. Found: C, 59.79; H, 6.11; N, 3.54.

In a similar manner, **13** was prepared in 68% yield from *p*-hydroxyphenylpyruvic acid and β-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride. Compound **13**, as the free base, was crystallized from MeOH, and melted at 270° dec.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.77; N, 4.25. Found: C, 65.23; H, 6.07; N, 4.14.

**Preparation of 14 and 16.** Benzoyl chloride (16 ml, 135 mmol) was added dropwise to a vigorously cooled (10°), stirred solution of 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[36] (13 g, 49 mmol) in a two-phase system of 100 ml of $CH_2Cl_2$ and 40 ml of $H_2O$ containing 14 g of KCN.[37] The mixture was stirred for an additional 2 hr at room temperature. The $CH_2Cl_2$ layer was separated, washed ($H_2O$, 10% HCl, 5% NaOH, and saturated NaCl, successively), dried ($Na_2SO_4$), and evaporated to a gum. Trituration of the gum with MeOH gave 7.5 g (39%) of crystalline *N*-benzoyl-7-benzyloxy-6-methoxy-1-cyano-1,2,3,4-tetrahydroisoquinoline, mp 178–180°.

Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.11; H, 5.73; N, 7.10.

Benzyl chloride (3.23 g, 25.6 mmol) was added to a cooled (0–10°) suspension of the above nitrile (6.8 g, 17.1 mmol) in 30 ml of dried (molecular sieve 3 A) dimethylformamide. Sodium hydride (850 mg, 17 mmol in a 48% oil dispersion) was added slowly.[9] The cooling bath was removed, and the mixture was stirred for 15 hr during which time the suspension became a clear, light yellow solution. The reaction mixture was poured over crushed ice to give a white gum. The gum was collected by filtration and triturated with warm MeOH to give crude *N*-benzoyl-7-benzyloxy-1-benzyl-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinoline.

The above crude benzylisoquinoline nitrile (1.5 g, 3.06 mmol) was hydrolyzed by heating it to 100° in 10 ml of 85% $H_3PO_4$ for 15 min. The mixture was cooled, diluted with 10 ml of ice water, and filtered. The filtrate was carefully neutralized with $NH_4OH$. After standing overnight at 0–5°, the product precipitated to give, after collection by filtration, 0.9 g (66%) of **14**. Crystallization from concentrated HCl–MeOH (1:1) yielded the hydrochloride of **14**, mp 245–248° dec.

Anal. Calcd for $C_{18}H_{19}NO_4$·HCl: C, 61.80; H, 5.76; N, 4.00. Found: C, 61.88; H, 5.49; N, 3.82.

In a similar sequence, the known compound, *N*-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline,[9] was converted in 61% yield to *N*-benzoyl-1-(*p*-benzyloxybenzyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, mp 152–153° from MeOH.

Anal. Calcd for $C_{33}H_{30}N_2O_4$: C, 76.42; H, 5.83; N, 5.40. Found: C, 76.61; H, 6.00; N, 5.53.

Again, in a similar manner, the benzyloxybenzyl isoquinoline nitrile was hydrolyzed to give, in 66% yield, **16**. Recrystallization from concentrated HCl–MeOH (1:1) gave white microcrystals, mp 244–247° dec.

Anal. Calcd for $C_{19}H_{21}NO_5$·HCl: C, 60.08; H, 5.84; N, 3.69. Found: C, 60.45; H, 6.11; N, 3.42.

**Preparation of the *N*-Acetyl Derivatives, 15 and 18.**[7] Acetyl

chloride (1.1 g, 14 mmol) was added dropwise to a stirred mixture of 1 g (3 mmol) of **12** and 1.65 g of $K_2CO_3$ in 75 ml of acetone. The mixture was heated to reflux for 20 hr. The inorganic salts were removed by filtration, and the filtrate was evaporated to near dryness, taken up in $CHCl_3$, washed (10% HCl, $H_2O$, and saturated NaCl, successively), dried ($Na_2SO_4$), and evaporated to give 0.42 g (26%) of crystalline **15**. Recrystallization from $CCl_4$ yielded pure **15** as white needles, mp 143–145°.

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.64. Found: C, 65.28; H, 6.07; N, 3.57.

In a similar manner, acetylation of **17** yielded **18** in 24% yield. Compound **18** melted at 124–126° and had an NMR spectrum similar to that of **15** except that three $OCH_3$ peaks were present.

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.43; H, 5.95; N, 3.89.

**Preparation of 17.** A large excess of $CH_2N_2$ (from 7.5 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide)[6] in 200 ml of ether was added to 3.0 g of **12** in 50 ml of MeOH. After being stirred overnight at about 10°, the solvents were evaporated and the $CH_2N_2$ treatment was repeated. Evaporation of the solvents and partition of the residue between $CHCl_3$ and phosphate buffer (pH 7.5) afforded a $CHCl_3$ extract which, after evaporation, gave 3.2 g of the methyl ester of **17** as a light yellow oil. The oil was dissolved in $CHCl_3$–hexane (1:1) and purified by passing it over a short column of silica gel GF (2 × 1 in.). Evaporation of the solvents gave pure ester. This ester (3 g) was saponified by heating it to reflux with 1 g of KOH in 10% aqueous EtOH for 2 hr. Upon cooling the mixture in ice, the potassium salt of **17** precipitated and was collected by filtration. The salt was dissolved in 100 ml of alcoholic NaOH [10% in EtOH–$H_2O$ (1:1)] and acidified with HCl. The hydrochloride of **17** precipitated (2.8 g, 90%) and was recrystallized from concentrated HCl–MeOH (1:1) to give white needles, mp 278–281°.

Anal. Calcd for $C_{20}H_{23}NO_5 \cdot HCl \cdot H_2O$: C, 58.32; H, 6.36; N, 3.40. Found: C, 58.49; H, 6.33; N, 3.72.

**Oxidative Decarboxylations. General Procedure.** The oxidations were conducted on a graphite felt anode (6.2 × 16 cm) separated from a Pt cathode by a medium porosity glass frit.[15] The reactions were carried out under nitrogen at 15–25°. A standard calomel electrode was connected by a salt bridge to a point as close as possible to the anode, and the potential was electronically controlled. In general, about 1.5 mmol of substrate was added to a stirred, preequilibrated, preelectrolyzed, deoxygenated cell containing about 250 ml of electrolyte. The anode potential was adjusted so that 20–50 mA of current passed and the reaction was continued until the current dropped back to the residual of 5 mA or so or until TLC showed that no starting material remained. The reaction mixture, along with the anode, were blended in a Waring blender, and the suspension was filtered. The particles of anode were washed several times with MeOH, and the combined filtrate and washings were evaporated to a residue and processed for specific compounds.

**Oxidation of 11.** Compound **11** (500 mg) was oxidized at −0.28 V in 250 ml of 0.1 *N* NaOMe in MeOH. The initial current of 43 mA fell to a residual in 3 hr; the oxidation was stopped; and the reaction mixture was processed as described above. The residue so obtained was extracted twice with MeOH, and the MeOH extracts were treated with $CH_2N_2$ (from 7.5 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide). After about 15 hr, the solvents were evaporated, and the methylated compound was dissolved in 15 ml of MeOH, cooled in ice, and stirred while 0.5 g of $NaBH_4$ was added. The pH was maintained between 6 and 7 by periodic additions of 6 *N* HCl. After 2.5 hr, the MeOH was evaporated, and the residue was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The layers were separated; the aqueous portion was washed once more ($CHCl_3$); and the combined $CHCl_3$ extracts were washed (twice with saturated NaCl), dried ($Na_2SO_4$), and evaporated to yield 524 mg of crude product. Purification by preparative TLC yielded 310 mg (66%) of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**28**), the NMR spectrum of which checked exactly with the literature.[16]

**Oxidation of 12.** Compound **12** (515 mg) was oxidized at +0.01 V in 250 ml of 0.1 *N* NaOMe in MeOH. The initial current was 48 mA, and the reaction was continued until starting material was gone (TLC, $CH_3CN$–$H_2O$, 85:15), in about 3.7 hr. The mixture was processed as described above, and the residue was partitioned between $CHCl_3$ and aqueous, pH 7.5, phosphate buffer. The $CHCl_3$ layer was washed (saturated NaCl), dried ($Na_2SO_4$), and evaporated to give 485 mg of products (**22** and **27**) which was separated on a short column of silica gel G using $CHCl_3$ as an eluent. Compound **22** (130 mg, 29%) showed the expected C=N peak in its ir spectrum and has a predictable NMR and mass spectrum. Since it decomposed on attempted crystallization to give **27**, it was characterized by $NaBH_4$ reduction to give **25** as characterized below. Compound **27** (235 mg, 50%) melted at 186–188°: mass spectrum, $M^+$ *m/e* 311, calcd 311; ir ($CHCl_3$) 1645 $cm^{-1}$ (C=O). Compound **27** was methylated as described above to yield **32**, mp 103–106° (lit.[16] 105°).

Compound **12** (515 mg) was also oxidized at 0.28 V in 250 ml of 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$, 6:4. The initial current of 34 mA dropped rapidly to about 12 mA, and the reaction was continued for 6.5 hr. The electrolyte solution, still in the cell, was made slightly acidic (pH about 6.5) with HCl and treated with 1 g of $NaBH_4$. The solution was kept acidic by periodic acid additions. The mixture was processed as described above, and the residue was acidified with HCl. Crystallization from MeOH gave 445 mg (88%) of **25** as its hydrochloride, mp 233–234°.

Anal. Calcd for $C_{18}H_{22}NO_3Cl$: C, 64.37; H, 6.55; N, 4.17. Found: C, 64.62; H, 6.61; N, 4.11.

**Oxidation of 14.** Compound **14** (300 mg) was oxidized in the methoxide system for 5.5 hr. The potential was slowly raised from 0.0 to +0.2 V to maintain a current of 37 mA during the reaction. The reaction mixture was acidified, reduced with $NaBH_4$, and processed as described above for **12**. The residue was dissolved in 5 ml of MeOH–HCl (1:1) and precipitated with 10 ml of acetone to yield 153 mg (52%) of the hydrochloride of **26**, mp 115–119°, which was identical with a known sample.[17]

**Oxidation of 13.** Compound **13** (500 mg) was oxidized in the methoxide system at −0.12 V for 4.5 hr. Preliminary attempts to isolate the two observed products, probably the 3,4-dihydroisoquinolines corresponding to **29** and **30**, were unsuccessful owing to their instability. The reaction mixture was then reduced with $NaBH_4$ as described for **12**. Compounds **29** and **30** were isolated by preparative TLC ($CHCl_3$–MeOH–$NH_4OH$, 100:25:0.1) in yields of 77 (16%) and 16 mg (3%), respectively. These compounds showed methoxyl groups in their NMR spectra at $\delta$ 3.33 for **29** and at $\delta$ 3.2 and 3.3 for **30** along with the presence of one and no protons on $C_\alpha$, respectively. The remainder of the spectra were as predicted. Further characterization was not possible, and both compounds were methylated with $CH_2N_2$ and hydrogenolyzed over Pd/C in EtOH to give **33**. Compound **33** was found to be identical with a sample prepared from **25** which had the properties recorded.[18]

**Oxidation of 15.** Compound **15** (423 mg) was oxidized in the bicarbonate system for 3.5 hr at +0.15 V. The contents of the cell were processed as described in the general procedure, and the residue was separated by preparative TLC ($CHCl_3$–EtOH, 9:1) to give 0.088 g (26%) of **27**, identified previously, and a pair of tautomers, **34** and **35**, in amounts of 35 (9%) and 55 mg (15%), respectively. Neither compound gave a satisfactory analysis owing to instability. Compound **34** melted at 224–226° as crystallized from MeOH and had the following spectral properties: NMR in Table II; mass spectrum $M^+$ *m/e* 339, calcd 339.

Compound **35** was not crystalline and had the following spectral properties: NMR in Table II; mass spectrum $M^+$ *m/e* 339.1468, calcd 339.1470.

Compound **34**, when allowed to stand overnight in $CHCl_3$–MeOH–HCl, 2:1:1, was converted to **35** (by TLC) with a small amount of decomposition. In an experiment 7.3 mg of **35** (46%) was obtained from 16 mg of **34**.

**Oxidation of 16 and 18.** Compound **16** was oxidized in the methoxide system at +0.2 V. Extensive decomposition resulted, and no products could be isolated. When **18** was oxidized in the methoxide system at +0.6–0.8 V, no current flowed, and starting material was recovered.

**Acknowledgment.** In addition to the financial assistance previously acknowledged, we would like to thank Dr. I. G. C. Coutts of Trent Polytechnic, Nottingham, England, for help in the Reissert synthesis.

**Registry No.**—**11**, 57256-22-1; **12**, 57256-23-2; **12** HCl, 57256-24-3; **13**, 57256-25-4; **14**, 57256-26-5; **14** HCl, 57256-27-6; **15**, 57256-28-7; **16**, 57256-29-8; **16** HCl, 57256-30-1; **17**, 57256-31-2; **17** HCl, 57256-32-3; **18**, 57256-33-4; **19**, 57256-34-5; **20**, 31758-50-6; **22**, 57256-35-6; **25**, 31804-74-7; **25** HCl, 31804-73-6; **26**, 57256-36-7; **26** HCl, 57256-37-8; **27**, 57256-38-9; **28**, 3423-37-8; **29**, 57256-39-0; **30**, 57256-40-3; **32**, 17052-80-1; **33**, 41498-37-7; **34**, 57256-41-4; **35**, 57256-42-5; phenylpyruvic acid, 156-06-9; β-(3,4-dihydroxyphenyl)ethylamine hydrochloride, 62-31-7; *p*-methoxyphenylpyruvic acid, 28030-16-2; β-(3-hydroxy-4-methoxyphenyl)ethylamine hy-

drochloride, 645-33-0; *p*-hydroxyphenylpyruvic acid, 156-39-8; benzoyl chloride, 98-88-4; 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 15357-92-3; *N*-benzoyl-7-benzyloxy-6-methoxy-1-cyano-1,2,3,4-tetrahydroisoquinoline, 57256-43-6; benzyl chloride, 100-44-7; *N*-benzoyl-7-benzyloxy-1-benzyl-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 57256-44-7; *N*-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 10174-83-1; *N*-benzoyl-1-(*p*-benzyloxylbenzyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 57256-45-8; acetyl chloride, 75-36-5; diazomethane, 334-88-3.

## References and Notes


(1) (a) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., August 1973. (b) Part V: J. M. Bobbitt, I. Noguchi, R. S. Ware, K. N. Chiong, and S. J. Huang, *J. Org. Chem.*, **40**, 2924 (1975). (c) This work was supported by a Research Fellowship given to T. Y. Cheng by Merck and Co., Inc., Rahway, N.J., and by Research Grant CA-10494 from the Cancer Institute of the National Institutes of Health. (d) Taken in part from the Ph.D. Dissertation of T. Y. Cheng, University of Connecticut, 1974. (e) Discussed briefly by J. M. Bobbitt, *Heterocycles*, **1**, 181 (1973).

(2) (a) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology", Academic Press, New York, N.Y., 1972, pp 32, 75, 505; (b) T. Kametani, "The Isoquinoline Alkaloids", Hirokawa Publishing Co., Tokyo, 1968, p 13.

(3) The historical background and pertinent references are given in the elegant paper of G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayez, Y. N. Vaishav, and H. M. Fales, *J. Am. Chem. Soc.*, **92**, 6943 (1970).

(4) (a) G. Hahn and F. Rumpf, *Ber.*, **71**, 2141 (1938); (b) I. J. McFarlane and M. Slaytor, *Phytochemistry*, **11**, 235 (1972); (c) M. L. Wilson and C. J. Coscia, *J. Am. Chem. Soc.*, **97**, 431 (1975); (d) A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Lett.*, 1873 (1975); (e) S. Tewari, D. S. Bhakuni, and R. S. Kapil, *J. Chem. Soc., Chem. Commun.*, 554 (1975).

(5) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951).

(6) J. A. Moore and D. E. Reed, *Org. Synth.*, **41**, 16 (1961).

(7) W. Dilthey and H. Passing, *J. Prakt. Chem.*, **153**, 26 (1939); *Chem. Abstr.*, **33**, 6288 (1939).

(8) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).

(9) M. Shamma and C. D. Jones, *J. Org. Chem.*, **35**, 3119 (1970).

(10) G. Hahn and K. Stiehl, *Ber.*, **69**, 2627 (1936).

(11) A. J. Fry, "Synthetic Organic Electrochemistry", Harper and Row, New York, N.Y., 1972, Chapter 3.

(12) J. P. Coleman, J. H. P. Utley, and B. C. L. Weedon, *Chem. Commun.*, 438 (1971).

(13) A one-electron decarboxylation forming radical intermediates which dimerize is the traditional Kolbe reaction. The two-electron decarboxylation yielding carbonium ions is generally called the Hofer–Moest reaction. See L. Eberson in "Chemistry of the Carboxylic Acids and Esters", S. Patai, Ed., Wiley, New York, N.Y., 1969, Chapter 2, and ref 11, p 283.

(14) J. P. Coleman and L. Eberson, *Chem. Commun.*, 1300 (1971).

(15) J. M. Bobbitt, H. Yagi, S. Shibuya, and J. T. Stock, *J. Org. Chem.*, **36**, 3006 (1971).

(16) G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Am. Chem. Soc.*, **89**, 329 (1967).

(17) R. C. Hallcher, Ph.D. Dissertation, University of Connecticut, 1972, p 91.

(18) J. A. Weisbach, J. L. Kirkpatrick, E. Macko, and B. Douglas, *J. Med. Chem.*, **11**, 752 (1968).

(19) Recent work by C. L. Kulkarni in our laboratory has shown that a compound with a meta phenol in the benzyl ring, specifically 1-(3-hydroxy-4-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, can be cleanly decarboxylated to the 3,4-dihydroisoquinoline with little or no overoxidation.

(20) M. Tomita and F. Kusuda, *J. Pharm. Soc. Jpn.*, **72**, 793 (1952).

(21) Reference 11, p 295.

(22) A. Ronlán and V. D. Parker, *J. Chem. Soc. C*, 3214 (1971).

(23) J. M. Bobbitt and R. C. Hallcher, *Chem. Commun.*, 543 (1971).

(24) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974).

(25) L. G. Radcliffe and W. H. Brindley, *Perfum. Essent. Oil Rec.*, **13**, 414 (1922).

(26) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 2854 (1951).

(27) P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **32**, 480 (1967).

(28) B. R. Brown in "Oxidative Coupling of Phenols", W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N.Y., 1967, p 167.

(29) P. D. McDonald and G. A. Hamilton in "Oxidation in Organic Chemistry", W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973, p 97.

(30) A. R. Battersby in ref 28, p 119.

(31) H. Musso in ref 28, p 78.

(32) O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, 1533 (1971); 740 (1972).

(33) S. M. Kupchan and A. J. Liepa, *J. Am. Chem. Soc.*, **95**, 4062 (1973).

(34) E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, **24**, 687 (1968).

(35) Melting points were taken on a Kofler hot stage apparatus and are corrected. Elemental analyses were carried out by Baron Consulting Co., Orange, Conn. The NMR spectra were measured on a Varian A-60 instrument, and the mass spectra were recorded on a AEI MS-9 instrument using a direct inlet system at 70 eV. TLC was carried out on silica gel GF layers. Cyclic voltammetry was carried out on a P. A. R. Electrochemistry System (Model 170), and preparative electrolyses were carried at potentials controlled against a standard calomel electrode by a Wenking potentiostat (Model 61TR). All evaporations were carried on a rotary vacuum evaporator.

(36) This known compound [M. Tomita and H. Watanabe, *J. Pharm. Soc. Jpn.*, **58**, 783 (1938)] was prepared in 25% yield by the $POCl_3$ cyclization of the appropriate *N*-alkylformamide in $CHCl_3$ at room temperature in a similar manner to that used by M. P. Cava and K. T. Buck, *Tetrahedron*, **25**, 2795 (1969). The formamide was prepared from ethyl formate and β-(4-benzyloxy-3-methoxyphenyl)ethylamine by a procedure detailed in a footnote to I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, and F. Rosendahl, *Org. Synth.*, **41**, 13 (1961).

(37) F. D. Popp and W. Blount, *J. Org. Chem.* **27**, 297 (1962).


# The Polyphenolic Acids of *Lithospermum ruderale*. II. Carbon-13 Nuclear Magnetic Resonance of Lithospermic and Rosmarinic Acids


Charles J. Kelley, Richard C. Harruff, and Marvin Carmack*

*Contribution No. 2739 from the Department of Chemistry*
*Indiana University, Bloomington, Indiana 47401*


*Received May 7, 1975*


The $^{13}C$ NMR spectra of caffeic acid (**3a**) and 3-(3,4-dihydroxyphenyl)lactic acid (**4a**) and a series of their O-alkylated derivatives in neutral aqueous solutions are fully assigned. These chemical shifts are used to assign the carbons of rosmarinic (**2**) and chlorogenic (**5**) acids. The foregoing compounds serve as models to interpret the $^{13}C$ NMR spectrum of lithospermic acid (**1**), $C_{27}H_{22}O_{12}$. Also discussed are the $^{13}C$ NMR spectra of quinic acid (**6**) and two morphinane derivatives, oxymorphone (**10**), and oxycodone (**11**), containing aromatic rings structurally similar to **1**.


In recent work on the constituents of the roots of *Lithospermum ruderale* (Dougl. ex Lehm.), we postulated structure **1** for lithospermic acid, the principal polyphenolic acid in the plant.[1] Rosmarinic acid (**2**) was also identified as a minor plant constituent. Evidence for structure **1** and for the presence of **2** in *L. ruderale* rested largely on $^1H$ NMR and mass spectral data from derivatives of **1** and **2**. To obtain further confirmation for structure **1** and to develop an analytical method for the assay of fractionated aqueous extracts from the plant, we undertook a study of the $^{13}C$ NMR spectra of **1**, **2**, and a series of model compounds.

Compounds **1** and **2** are composed of phenylpropanoid subunits. For convenience in comparing chemical shift data, each subunit (the aromatic ring and the attached