HETEROCYCLES, Vol. 4, No. 10, 1976

DECARBOXYLATION OF PHENOLIC TETRAHYDROISOQUINOLINE-1-CARBOXYLIC ACIDS IN AIR

James M. Bobbitt, Chidambar L. Kulkarni,
and Pichaet Wiriyachitra

Department of Chemistry, The University of Connecticut,
Storrs, Conn. 06268, U.S.A.

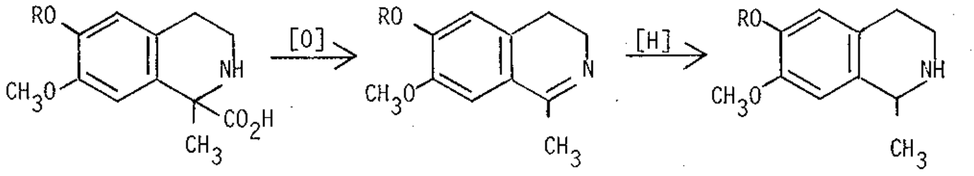
When stirred in air under basic conditions ($NaHCO_3$, triethylamine, or NaOMe), tetrahydroisoquinoline-1-carboxylic acids containing at least one free phenol group in the aromatic ring decarboxylate oxidatively to yield 3,4-dihydroisoquinolines.

Many years ago, Hahn[1] suggested that the isoquinoline ring in isoquinoline alkaloids was formed by a condensation between a suitably substituted β-phenylethylamine and derivatives of pyruvic acid, giving rise to 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids.[2] In recent years,[2,3] these carboxylic acids have been generally accepted as prime intermediate metabolites. One problem inherent in this hypothesis is the lack of a suitable mechanism to explain the loss of the carboxyl group to form the commonly observed 1,2,3,4-tetrahydroisoquinolines. We believe this reaction to be a unique oxidative decarboxylation triggered by the easily oxidizable phenol groups present in the aromatic ring (followed, of course, by a suitable reduction).

Recently, we have shown that such an oxidative decarboxylation takes place when phenolic tetrahydroisoquinoline-1-carboxylic acids are oxidized electrochemically.[4] Coutts, Hamblin and Tinley[5] have shown that a similar reaction takes place in dilute acid under the action of a crude laccase preparation from *Polystictus versicolor*. In this paper, we report that the oxidative decarboxylation takes place readily in air under slightly basic conditions. Thus, the possibility of an oxidative decarboxylation as a biogenetic reactions is enhanced, and the unexpected lability of phenolic tetrahydroisoquinoline-1-carboxylic acids to air is pointed out.

When compound 1 (240 mg) was stirred for 10 days in a mixture of water (10 ml), methanol (30 ml), and triethylamine (30 ml) in the presence of air, a tlc study showed that only 3 was present. Evaporation of the yellow solution under vacuum, acidification with conc. HCl (3 ml), and reevaporation yielded a residue which crystallized from MeOH-EtOEt (1:1) to give the hydrochloride of 3, mp 247-249° (lit. mp 250)[6] in 80% yield. When the reaction was carried out in 5% aqueous $NaHCO_3$, and the product was reduced with $NaBH_4$,[4] compound 4 was obtained in 40% yield. When the completely methylated compound 2 was treated similarly, neither oxidation nor decarboxylation occurred, and starting material was recovered.

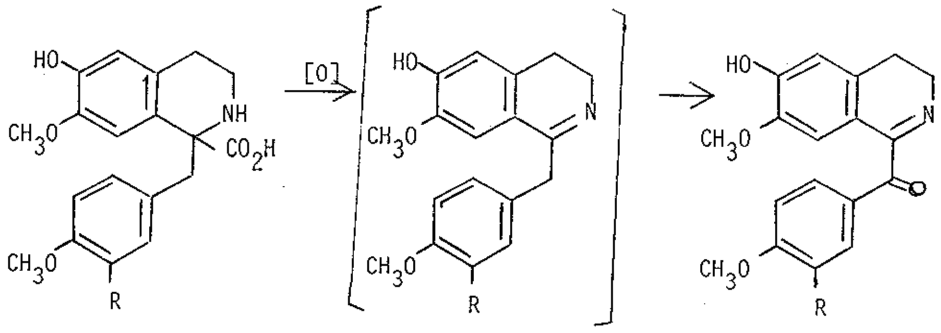
In the 1-benzyl series (5 and 6) the reaction is complicated by the facile air oxidation of the intermediate dihydroisoquinolines (7 and 8) to the keto derivatives (9 and 10).[7] The oxidation of 5 (170 mg) was carried out in 90 ml of 0.1 M NaOMe in MeOH for 15 days in the presence of air. During this time, a tlc study showed that the starting material was converted to an intermediate, 7 (recognized by a characteristic blue fluorescence under uv light[4]) and finally to the ketone, 9. When the reaction mixture was evaporated to dryness, acidified with conc. HCl, and neutralized with $NaHCO_3$, the product, 9, precipitated (65% of ketone, mp 184-186°, lit 186-188°[4]). A similar oxidation of 6 gave 10, mp 131-133° in 60% yield.[8] When 6 was oxidized in $NaHCO_3$ (0.1 M in $MeOH-H_2O$, 6:4) for 7 days, compound 10 was obtained in 49% yield. An attempted oxidation of 6 in the triethylamine system led to a complex reaction mixture.



1, R=H
2, R=CH_3

3, R=H

4, R=H



5, R=H
6, R=OH

7, R=H
8, R=OH

9, R=H
10, R=OH

As has been established for both the electrochemical and enzyme oxidations, the air oxidative decarboxylation takes place only when a free phenol group is present in the aromatic ring of the tetrahydroisoquinoline system. The implications of this work have been discussed in detail.[4]

This work has been partially supported by grant CA-10494 from the Cancer Institute of the National Institutes of Health.

REFERENCES

1 G. Hahn and F. Rumpf, Ber., 71, 2141 (1938).

2 The history of this hypothesis is well summarized in G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayez, Y. N. Vaishnav and H. M. Fales, J. Am. Chem. Soc., 92, 6943 (1970).

3 (a) I. J. McFarlane and M. Slaytor, Phytochemistry, 11, 235 (1972).
(b) M. L. Wilson and C. J. Coscia, J. Am. Chem. Soc., 97, 431 (1975).
(c) A. R. Battersby, R. C. F. Jones, and R. Kazlauskaš, Tetrahedron Lett., 1873 (1975).
(d) S. Tewari, D. S. Bhakuni and R. S. Kapil, Chem. Commun., 554 (1975).

4 J. M. Bobbitt and T. Y. Cheng, J. Org. Chem., 41, 443 (1976).

5 I. G. C. Coutts, M. Hamblin and E. J. Tinley, Trent Polytechnic, Nottingnam, England, private communication. This work was also presented by J. M. Bobbitt, T. Y. Cheng, and I. G. C. Coutts at the 6th Natural Products Symposium, University of West Indies, Mona, Jamaica, Jan. 1976.

6 J. F. Colaruotolo, Ph.D. thesis, University of Connecticut, 1975.

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

8 *Compound* 10 *is a new* material and gave good C, H, N analyses.

Received, 7th August, 1976