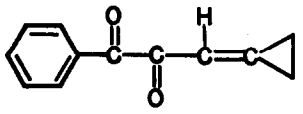
Tetrahedron Letters No.4, pp. 423-427, 1966. Pergamon Press Ltd.
Printed in Great Britain.

ACID CATALYZED REARRANGEMENT OF CERTAIN CYCLOPROPANE DERIVATIVES

Laszlo L. Darko and Joseph G. Cannon*
Laboratory of Medicinal Chemistry, College of Pharmacy,
University of Iowa, Iowa City, Iowa

(Received 26 November 1965)

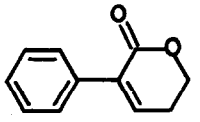
In the course of a study of the ozonolysis of phenylcyclopropylethynyl carbinol in attempts to form phenylcyclopropylglycolic acid, a compound was isolated which was neither the anticipated product nor the starting material (1). Structure I was



I

proposed for this anomalous product, based upon certain chemical reactions, nuclear magnetic resonance and infrared spectra, and elemental analytical data.

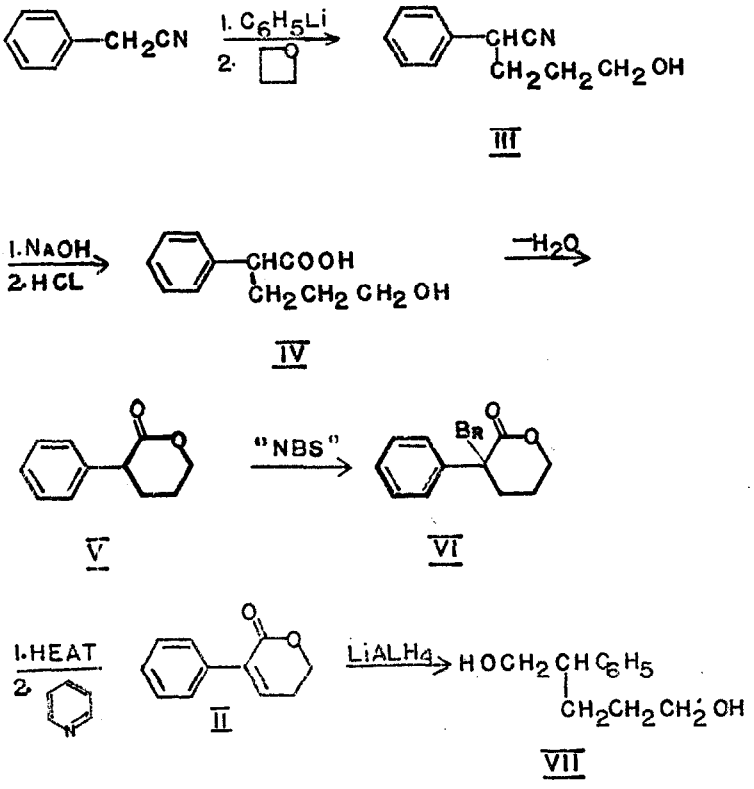
However, Roberts (2) on the basis of a reinterpretation of the nuclear magnetic resonance spectrum of the anomalous product, suggested the possibility that structure II might be the correct one.



II

* To whom correspondence should be addressed.

Scheme 1


CH2CN
1. C6H5Li
2.
CHCN
CH2CH2CH2OH
III
1.NaOH
2.HCL
CHCOOH
CH2CH2CH2OH
−H2O
IV
"NBS"
Br
V
VI
1.HEAT
2.
II
LiALH4
HOCH2CHC6H5
CH2CH2CH2OH
VII

That II, 3-phenyl-5,6-dihydro- α-pyrone, is indeed the anomalous product was proven unequivocally by the synthetic route shown in Scheme 1. 1-(3-hydroxypropyl)-phenylacetonitrile (III) was prepared from phenylacetonitrile by lithium exchange followed by a trimethylene oxide ring-opening reaction (3). Hydrolysis of III with either sodium hydroxide or hydrochloric acid gave the corresponding hydroxy acid (IV), and this product spontaneously cyclized to α-phenyl-δ-valerolactone. Introduction of a bromine atom alpha to the carbonyl with N-bromosuccinimide (VI) and subsequent elimination of hydrogen bromide yielded 3-phenyl-5,6-dihydro- α-pyrone (II). Reduction of (II) with excess lithium aluminium hydride yielded 2-phenyl-1,5-pentanediol, a known compound (4). The infrared spectrum of II was identical with that of the anomalous product of the ozonolysis of phenylcyclopropylethynyl carbinol (1).

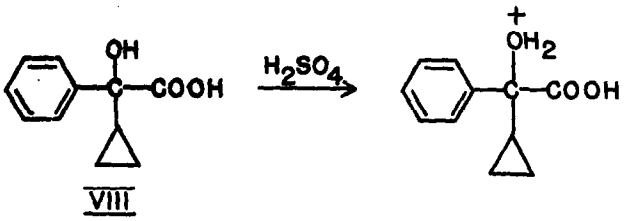
When phenylcyclopropylglycolic acid was refluxed with sulfuric acid, the reaction product obtained was 3-phenyl-5,6-dihydro- α-pyrone (II).

To explain the formation of II, deamination reactions were carried out on phenylcyclopropylglycine under various conditions. The results of these experiments were interpreted as indicating prime significance of carbonium ion formation in the rearrangement.

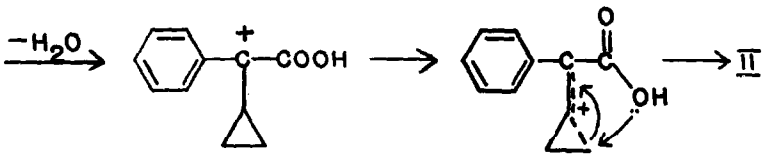
Deno and co-workers (5) showed that the cyclopropane ring strongly conjugates with an adjacent carbonium ion and stabilizes it. This effect manifests itself in the thermodynamic stability, nuclear magnetic resonance band positions [downfield shifts due to the deshielding effect of the carbonium ion (6)], and drastically

altered chemical reactivity of the cyclopropane ring. Based on these results of Deno and on our experimental data, a possible reaction sequence for the formation if II is shown in Scheme 2.

Scheme 2



VIII



IX X

Deno (5) found that in cyclopropane carbonium ions the sensitivity of the ring toward acids has been lost and has been replaced by a sensitivity to attack by bases. It seems reasonable that when the carbonium ion (IX) is formed by dehydration of the glycolic acid (VIII), the cyclopropane ring would stabilize it by conjugation (X) and thus X would become susceptible to nucleophilic attack by the electron rich hydroxyl group of the carboxyl function forming II.

REFERENCES

1. J. G. Cannon and L. L. Darko, J. Org. Chem., 29, 3419 (1964).

2. J. D. Roberts, Personal communication.

3. M. G. Reinecke and L. R. Kray, J. Org. Chem., 29, 1736 (1964).

4. K. Kawazu, T. Fujita and T. Mitsui, J. Amer. Chem. Soc., 81, 932 (1959).

5. N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, J. Amer. Chem. Soc., 87, 4533 (1965).

6. H. G. Richey, Jr., L. E. Rennich, A. S. Kushner, J. M. Richey and J. C. Philips, J. Amer. Chem. Soc., 87, 4017 (1965).