

Photochemical Preparation and Rearrangement of Some Symmetrical Methoxypyridyl Phenyl Glycols (Pinacols)

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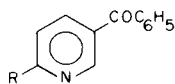
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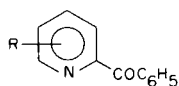
Solutions of 6-methoxy-3-pyridyl phenyl ketone and 3-, 4-, 5- and 6-methoxy-2-pyridyl phenyl ketones in isopropyl alcohol were subjected to ultraviolet radiation. All the ketones except 3-methoxy-2-pyridyl phenyl ketone were observed to undergo bimolecular reduction to give the corresponding pinacols in 30-100 percent yields. In cold concentrated sulfuric acid the pinacols were found to rearrange with the exclusive migration of the phenyl group. The pinacols bearing the 3-pyridyl groups rearranged at a much faster rate than the 2-pyridyl isomers.

The bimolecular reduction of phenyl 2- and 3-pyridyl ketones to the corresponding pinacols and the rearrangement of the pinacols in acidic medium have been reported (1,2). The pinacols were found to rearrange with the exclusive migration of the phenyl group. A reasonable explanation of this behavior was based on the electron-withdrawing nature of the pyridine nitrogen, which becomes even more so on protonation in the acidic medium. In order to determine the effect the strongly electron-releasing methoxyl group had on the migratory aptitude of the pyridine nucleus, a few symmetrical pinacols bearing methoxypyridyl nuclei were prepared and allowed to rearrange in a suitable acidic medium.

Solutions of ketones (structures I and II) in isopropyl alcohol were deaerated and irradiated by means of ultraviolet radiation. The resulting pinacols being insoluble in isopropyl alcohol were separated and subjected to rearrangement in cold concentrated sulfuric acid. The identification of the resulting pinacolones was based on the fragments found in their mass spectra.



Ia, R = H
Ib, R = OCH₃



IIa, R = H
IIb, R = 3-OCH₃
IIc, R = 4-OCH₃
IId, R = 5-OCH₃
IIe, R = 6-OCH₃

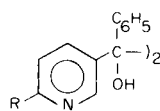
Results.

The results of the photochemical reduction of the ketones are summarized in Table I. The methoxyl group in the *para* position increased the yield of the pinacol

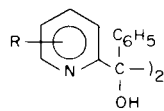
ketone Ib giving the pinacol, as the sole product. In the only case studied (ketone IIb), the methoxyl group in the *ortho* position reduced the yield of the pinacol to zero, the carbinol being the only product. This ketone also required much larger irradiation time. Ketone IIe yielded the pinacol as the major product and required the longest irradiation time of all the ketones studied. The behavior of ketones IIa and IIc was distinct, in that red solutions were obtained shortly on irradiation. On exposure to air a color change to green was observed almost immediately. A few hours of exposure resulted in the formation of a finely divided black solid. The yields of the pinacols, IIa and IIc, reported in Table I are the highest observed, since yields were found difficult to reproduce in these two cases. Longer irradiation periods resulted in smaller yields. Traces of impurities or oxygen could have been responsible for the difficulties in obtaining reproducible yields.

Cold concentrated sulfuric acid was found to be the best medium for the rearrangement of the pinacols giving the corresponding pinacolones in almost quantitative yields (above 90%). The solutions of the pinacols in concentrated sulfuric acid were allowed to stand at 5° until analysis (by tlc or nmr) showed no trace of the pinacols. The pinacolones were identified mainly by their mass spectra (Table IV). The results of the rearrangement may be summarized as follows:

1. The rearrangement of phenyl 3-pyridyl and 6-methoxy-3-pyridyl pinacols (structures IIIa and IIIb) was essentially complete within 45 minutes, while phenyl 2-pyridyl and methoxy-2-pyridyl pinacols (structures IVa, IVb, and IVd) required prolonged standing (over 24 hours) for completion of their rearrangement.



IIIa, R = H
 b, R = OCH₃



IVa, R = H
 b, R = 4-OCH₃
 c, R = 5-OCH₃
 d, R = 6-OCH₃

2. Phenyl 2-pyridyl and 5-methoxy-2-pyridyl pinacols (structures IVa and IVc) rearranged completely within 48 hours while 4-methoxy-2-pyridyl and 5-methoxy-2-pyridyl pinacols (structures IVb and IVd) required over 120 hours.

3. In all cases, migration of the phenyl group alone was observed.

Discussion.

A. Photoreduction of Ketones.

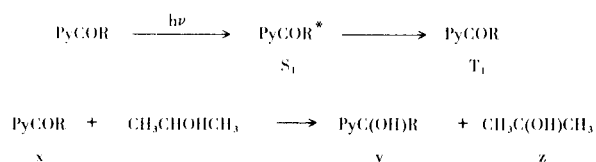
The formation of the triplet state is known to be the pre-necessity for photoreductions of ketones in solution (3). The ketone molecules in this metastable state are highly reactive towards hydrogen donors such as isopropyl alcohol molecules. The one electron reduction of the ketonic biradical x by the hydrogen donor results in the formation of two radicals y and z . Combination of two y radicals results in the formation of the pinacol (one

TABLE I

Photoreduction of Ketones R-CO-C₆H₅ in Isopropyl Alcohol (a)

Code	R-	Irradiation Time Hours	% Yield Diol	% Yield Carbinol
IIa		48	35	-(c)
Ia		20	70	15
Ib		20	100	0
IIb		48	0	20 (b)
IIc		48	30	-(c)
IIId		30	90	7
IIe		96	86	6

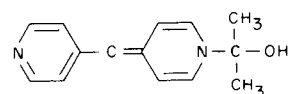
(a) Three g. of ketone in 40-45 ml. of isopropyl alcohol. (b) Reaction incomplete, unreacted ketone. (c) Not known.



electron process). On the other hand, if the radical y abstracts another hydrogen atom from the hydrogen donor, the final result is the formation of the carbinol (two electron process). The nature of the group Py is expected to affect the behavior of the radical y . For example, phenyl 4-pyridyl ketone is known to give only the carbinol as the photoreduction product in 2-propanol (1,2). A methoxyl group due to its strong electron-releasing resonance effect or its electron-withdrawing inductive effect is also expected to affect the nature of the pyridyl group and hence that of the radical y .

Formation of colored solution on irradiation of another pyridyl ketone has been reported (4). A dark red solution was obtained on irradiation of a solution of 4-pyridyl ketone in isopropyl alcohol. A color change to green was

also observed on exposure to air. The authors have proposed the following structure for the red intermediate:



Similar intermediates may be proposed for the 2-pyridyl ketones (IIa and IIc) which also give red solutions on irradiation.

The only ketone studied that did not furnish the pinacol on photoreduction was 3-methoxy-2-pyridyl ketone (IIb). Though no precise quantum yield studies were carried out, the conversion to the photoreduction product, the carbinol required much longer irradiation time as compared to phenyl 2-pyridyl ketone (Table I). Results of our limited experiments do not furnish an explanation of this finding. Additional steric hindrance caused by the *ortho* methoxyl may have prevented two y radicals from combining with each other. Similar reasoning cannot be applied to explain the relatively low quantum yield obtained in the case of 6-methoxy-2-pyridyl phenyl

TABLE II

R	M.p., °C	ir (a) O-H	Elemental Analysis Calcd. for C ₂₆ H ₂₄ N ₂ O ₄ C, 72.88; H, 5.64; N, 6.54
	172	3600 cm ⁻¹	C, 72.58; H, 5.74; N, 6.67
	142-143	3200 cm ⁻¹	C, 72.52; H, 5.31; N, 6.71
	144-145	3200 cm ⁻¹	C, 72.86; H, 5.49; N, 6.63
	147-150	3250 cm ⁻¹	C, 72.77; H, 5.65; N, 6.55

(a) In chloroform, 2-6% solution.

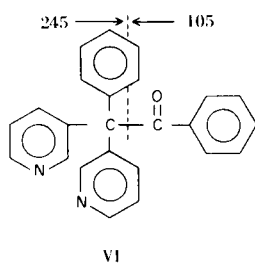
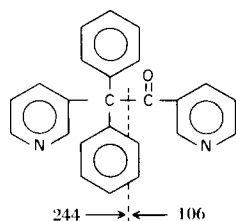
ketone (IIe) as the methoxyl group in the *meta* position is too distant to cause effective steric hindrance. The low quantum yields observed for many other aromatic ketones have been explained (4) on the basis of low efficiency of the singlet to triplet transition and by the lower energy requirement for $\pi \rightarrow \pi^*$ transition as compared to $n \rightarrow \pi^*$ transition.

B. Pinacol Rearrangement and Identification of Pinacolones.

Mass spectrometry was first employed by Brown and Frazer for the identification of the rearrangement products of phenyl 2-quinolyl and 8-quinolyl pinacols (5). On the basis of the fragments observed in the mass spectra of the products, it was decided that in the former case the pinacolone was formed by the migration of the phenyl group and in the latter, the quinolyl group. The fragments expected to arise from the other possible pinacolone were absent in each case.

a. Pinacolone from Phenyl 3-Pyridyl Pinacol (IIIa).

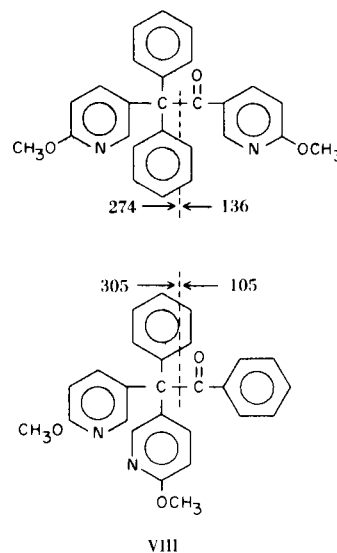
The sole rearrangement product of this pinacol has been previously identified (1) as possessing Structure V (formed by phenyl migration). The mass spectral data support



this conclusion. The base peak (100%) was at m/e 244. Peaks at m/e 165 and 166 must arise from the ion of phenyl and pyridyl groups by the ions with mass 244. Significant contribution was also made by ions with m/e 106. No peak was seen at m/e 105. The signal at m/e 245 (20.4%) was the isotopic abundance peak of mass 244 (calculated abundance for $p+1$ is 20.1%). Hence, pinacolone with Structure VI (expected by pyridyl migration) was not formed.

b. Pinacolone from 6-Methoxy-3-pyridyl Phenyl Pinacol (IIIb).

Mass spectral data support Structure VII for the pinacolone (formed by phenyl migration) and not Structure VIII. Major peaks were seen at m/e 274 and 136 but none at m/e 305 and 105.



c. Pinacolone from Phenyl 2-Pyridyl Pinacol (IVa).

The peaks at m/e 244 (100%) and 106 in the mass spectra of the pinacolone support structure similar to V (formed by phenyl migration).

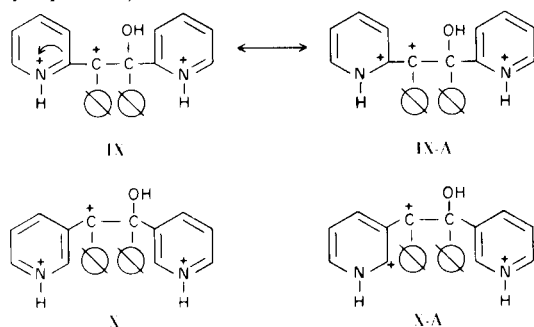
d. Pinacolones from 4-, 5- and 6-Methoxy-2-pyridyl Phenyl Pinacols (IVb, IVc, and IVd).

The mass spectra of these pinacolones were similar. All had the base peak at m/e 274, no significant peak at m/e 305 being found. Major peaks were also found at m/e 136 (6-16%). These data support structures similar to VII (formed by phenyl migration). All the mass spectra showed a peak of rather appreciable intensity at m/e 105 (2-5%). This may seem to indicate the presence of some pinacolone with structures similar to VIII (formed by pyridyl migration), yet no fragments at m/e 305 were seen. Also, no metastables for the transition $410 \rightarrow 105$ were found. The fragment at m/e 105 may then be accounted for as being formed by rearrangement of molecular ions with structures similar to VII. Such rearrangements have been found in the mass spectrum of the pinacolone obtained from phenyl 8-quinolyl pinacol (5).

The results of the pinacol rearrangement may be explained on the basis of the accepted mechanism. Protonation of one of the hydroxyl groups takes place, after which the water molecule is lost, generating a positive charge on

the ethylene carbon. One of the groups on the neighboring carbon then migrates, being attracted by the positive charge. The rate of formation of the ions with the positive charge (an essential step in the process without which the migration cannot take place) would depend upon its stability.

In concentrated sulfuric acid, the pyridine nitrogen is certainly protonated. Structure IX (originating from 2-pyridyl pinacol) is seen to be destabilized relative to



Structure X (originating from 3-pyridyl pinacol) due to contributions by resonance structures such as IX-A showing two positive charges on adjacent carbon atoms. The rate of formation of the ions with structure IX is expected to be slower than that of X, hence 2-pyridyl pinacol rearranged at a slower rate than 3-pyridyl pinacol.

5-Methoxy-2-pyridyl phenyl pinacol (IVc) was found to rearrange within the same period as the unsubstituted pinacol. In other words, no appreciable stabilization of the positive charge (structure IX) by the resonance effect of the methoxyl group was observed. This may be due to protonation of the methoxyl oxygen under the reaction conditions (concentrated sulfuric acid). The electron releasing methoxyl group is converted to an electron-withdrawer due to the positive charge. The withdrawing effect is not felt by the rearrangement center (the ethylene carbons) being too far away (*para* position) for the inductive effect to operate effectively.

Such is not the case for the 4- and 6-methoxy isomers,

TABLE III

Properties of Pinacolones RCPH ₂ COR			
R	M.p., °C	ir (a) C=O	Elemental Analysis
	134	1675 cm ⁻¹	Calcd. for C ₂₄ H ₁₈ N ₂ O C, 82.26; H, 5.17; N, 8.12 Found: C, 81.92; H, 5.21; N, 8.12
	175	1665 cm ⁻¹	Found: C, 81.98; H, 5.02; N, 8.33
	132	1660 cm ⁻¹	Calcd. for C ₂₆ H ₂₂ N ₂ O ₃ C, 76.10; H, 5.40; N, 6.82 Found: C, 75.96; H, 5.56; N, 6.71
	152-154	1675 cm ⁻¹	Found: C, 76.17; H, 5.58; N, 6.85
	153-155	1680 cm ⁻¹	Found: C, 75.85; H, 5.61; N, 6.71
	148	1680 cm ⁻¹	Found: C, 75.96; H, 5.45; N, 6.76

(a) In chloroform, 2-6% solution. (b) Reported (2) m.p. 175-177°.

as the rate of the rearrangement was found to be slower than the unsubstituted pinacol. The methoxyl groups on protonation, being in the *meta* position, are in a better position to withdraw electrons inductively, making structures such as IX even less stable.


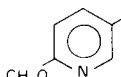

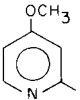
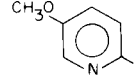
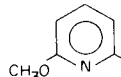
Phenyl 2-pyridyl and 3-pyridyl pinacols, in a refluxing mixture of acetic acid, acetyl chloride and benzene, have been reported to rearrange with the exclusive migration of phenyl groups (1). The same behavior was found in a sulfuric acid medium. The pyridine ring acquires a positive charge by accepting a proton from the acidic medium. This charge would then prevent the heterocyclic nucleus from approaching the similarly positively charged carbon atom toward which migration takes place in the pinacol rearrangement.

It was expected that the methoxyl group would increase the electron density of the pyridine ring sufficiently to exhibit a migratory aptitude higher than that of the phenyl group. This was not found to be the case, as in both the 2- and 3-pyridyl series, the phenyl group migrated to the exclusion of the methoxypyridyl groups. Protonation of the methoxyl group is expected to take place in concentrated sulfuric acid (ethers are soluble in sulfuric acid) which would make the pyridine ring even more electron-poor, thus reducing its migratory aptitude.

EXPERIMENTAL

All melting points are uncorrected and were obtained using a Fisher-Johns melting block. Infrared spectra were recorded with

TABLE IV
Relative Abundances of Major Positive Ions in the
Mass Spectra of Pinacolones RCPH₂COR

m/e	R-					
						
105	---	---	2.3	4.2	2.1	1.5
106	3.8	---	2.2	1.2	1.3	1.1
108	---	3.1	6.2	10.2	7.1	2.1
136	---	12.2	---	6.1	9.2	15.7
137	---	2.2	---	1.2	2.8	3.9
165	12.3	4.9	8.1	3.2	3.1	19.6
166	15.1	1.6	10.2	2.1	6.2	22.0
167	6.2	2.6	3.1	1.2	12.9	2.1
243	5.9	1.2	8.2	---	---	---
244	100.0	1.2	100.0	---	---	---
245	20.4	---	20.2	---	---	---
258	---	3.1	---	4.1	1.2	3.1
259	---	5.3	---	6.2	5.9	20.2
260	---	1.2	---	3.1	1.2	2.1
273	---	---	---	5.2	6.1	10.2
274	---	100.0	---	100.0	100.0	100.0
275	---	24.8	---	23.9	25.1	24.9
350	4.6	---	20.3	---	---	---
351	1.4	---	7.1	---	---	---
410	---	1.36	---	10.2	32.1	35.3
411	---	0.37	---	2.9	9.3	10.9

a Beckman IR 8 Spectrometer. The mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6E spectrometer at the ionization potential of 70 eV. Thin layer chromatograms were obtained using silica gel Eastman chromatogram sheets No. 6060.

Phenyl 2- and 3-pyridyl ketones were prepared according to the procedures described by Kegelman and Brown (1). Methoxypyridyl phenyl ketones were prepared by oxidation of the corresponding carbinols as described earlier (6,7).

Preparation of the Pinacols.

The corresponding ketones (3.0 g.) were dissolved individually in 40-45 ml. of isopropyl alcohol contained in 50 ml. Pyrex volumetric flasks. The solutions were irradiated by placing the flasks very close (within 0.5 cm) to a Hanovia lamp (No. 679 A, Type L, 450 watt obtained from Englehard, Inc., N. J.). Prior to irradiation, the solutions were deoxygenated by passing dry nitrogen through the hot solutions for 10 minutes. The solutions were cooled in ice-salt baths and the pinacols were isolated by filtration.

Rearrangement of the Pinacols.

To 25 ml. of concentrated sulfuric acid in an Erlenmeyer flask cooled by an ice bath, 1 g. of the pinacol was added. The mixture was stirred magnetically until a clear solution was obtained. The solution was maintained at 0-5° for suitable period. In each case, a small aliquot, on dilution and neutralization of the acid, was analyzed for the unreacted diol by tlc. Pinacols IIIa and IIIb

were found to react within 45 minutes, while pinacols IVa and IVc remained partly unreacted after 24 hours, but reacted completely in 48 hours. Solutions of pinacols IVb and IVd were similarly analyzed after 24 hour intervals. No appreciable reaction was seen after 24 hours, but after 154 hours no trace of the pinacols was found. In all cases, 90-95% yields of the pinacolones were obtained.

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