THE JOURNAL OF Organic Chemistry®

VOLUME 34, NUMBER 10

OCTOBER 1969

Quantitative Studies in Stereochemistry. Electrochemistry. III. The Ratio of Diastereomeric Pinacols Produced in the Electrolytic Bimolecular Reduction of 2-Acetylpyridine. Formation of Methyl-2-pyridylcarbinol as a Function of pH

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Received October 10, 1968

The electropinacolization of 2-acetylpyridine produced predominantly the *meso*-pinacol in acidic media and the preference for the *meso* diastereomer increased as the media were made alkaline. These results are the inverse of those observed previously for acetophenone. It is proposed that the hydroxylic proton of the intermediate ketyl radical may intraspecies hydrogen bridge with the ring nitrogen, minimizing the interspecies bridging that is held responsible for the production of the *dl* form. Methyl-2-pyridylcarbinol is the almost exclusive product in strongly acidic media. A protonated ketyl radical is invoked as responsible for its formation.

Previous papers from this laboratory have reported on the stereochemistry observed in the electrochemical bimolecular reduction of acetophenone,[1] propiophenone,[2] and benzaldehyde.[2] All three compounds produced a slight predominance of the *dl*-glycol (pinacol) over the *meso* form in acidic media. The ratio of *dl*- to *meso*-pinacol rose sharply to 3:1 in alkaline media for the two alkyl aryl ketones, while that for benzaldehyde showed but little change. A mechanism was proposed involving *inter*species hydrogen bonding between dimerizing radicals in acid solution, and between radicals combining with radical anions in alkaline media. An effective test of this mechanism would be provided by an examination of an appropriate ketone which permitted *intra*species hydrogen bonding of the intermediate ketyl. This would minimize the interspecies bonding leading to *dl*-pinacol formation and predict predominant formation of the *meso* form from simple steric considerations. 2-Acetylpyridine was chosen as an appropriate analog that met the above requirements. Use of this model compound made necessary the establishment of the stereochemical identities of the two derived diastereomeric pinacols as well as polarographic determination of suitable controlled potentials for the reduction at various pHs.

meso- and *dl*-pinacol identities have been assigned on the basis of melting point[3] and infrared[4] and nmr spectra.[5] Each of these three possibilities presented difficulties when applied to the 2-acetylpyridine pinacols. While the two diastereomers have been previously prepared and melting points of 136–137° and 140–141° reported,[6] analogous preparation in the present study, followed by careful purification, gave identical melting points, 142°, for *both* forms, precluding an assignment on this basis. The infrared spectra of both forms showed no free OH stretch and very broad bonded OH absorption. Using the position and intensity of these two absorption bands was therefore also precluded.[4] The position of the C–O stretch did, however, correlate with certain empirical observations[4] as well as the nmr assignments described below. The crystalline forms of the pinacols also showed the expected empirical correlation with past observations on the part of the authors.[7]

Nmr spectra of both pinacols showed the hydroxylic protons to be buried in the aromatic area, and prohibited assignment on the basis of a greater preference on the part of the *dl* form for intramolecular hydrogen bonding with a corresponding downfield shift for this proton in this diastereomer.[5] Construction of Fieser-type models of the two diastereomers did, however, indicate that the most favorable conformation of the *meso*-pinacol (all corresponding groups *trans*, the pyri-

(1) J. H. Socker and R. M. Jenevein, *J. Org. Chem.*, **33**, 294 (1968).

(2) J. H. Stocker and R. M. Jenevein, *ibid.*, **33**, 2145 (1968).

(3) The diastereomer showing the higher melting point is customarily designated the *meso* form. There appear to be only two established exceptions to this rule, the acetophenone pinacols [*cf.* Cram and Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959)] and the 4,4-dimethylhydrobenzoins [*cf.* Grimshaw and Ramsey, *J. Chem. Soc., C*, 653 (1966)].

(4) W. A. Mosher and N. D. Heindel, *J. Org. Chem.*, **28**, 2154 (1963).

(5) J. H. Stocker, *J. Amer. Chem. Soc.*, **88**, 2878 (1966).

(6) W. L. Bencze and M. J. Allen, *ibid.*, **81**, 4015 (1959). These authors report the higher melting compound to have been isolated from photochemical studies, while the lower melting compound was derived from the addition of methylmagnesium iodide to α-pyridil.

(7) For eight different diastereomeric pairs of pinacols, or hydrobenzoins, that have come under the authors' purvieu, the *dl* form has consisted in all cases of fine, silky needles, while the *meso* form was composed of either fat needles or chunky crystals.

TABLE I
ELECTROCHEMICAL REDUCTION OF 2-ACETYLPYRIDINE

Item	Electrode	Time, hr	Potential,[a] −V	Initial current, mA	Media[b,c]	Pinacol,[d] %	Ratio, *dl/meso*	Carbinol,[d] %
1	Hg	96	0.51	37	A-1	...	...	90
2	Hg	6.5	0.73	450	A-2	2.8[e]	0.77	51[e]
3	Hg	11	0.63	330	A-1	7.0[f]	0.78	68[f]
4	Hg	4	0.78	500	A-1	11.0	0.73	82
5	Hg	1	0.83	3600	A-1	0.9	0.7	94
6	Hg	6	0.99	480	Buffer-1	6.8	0.55	80
7	Hg	1.5	0.99	3000	Buffer-2	15.7	0.34	83
8	Hg	4	0.96	470	Buffer-2	67	0.28	29
9	Hg	0.33	1.22	5000	B-1	44	0.50	54
10	Hg	1.5	1.22	3800	B-1	68	0.46	32
11	Hg	1	1.20	1500	B-1	68	0.43	27
12	Cu	6	1.6	380	B-1	55	0.53	40
13	Cu	3.5	1.5	230	B-2	72	0.38	28
14	Cu	4.3	1.6	240	B-2	65[g]	0.38	22[g]
15	Hg	4	1.20	300	B-2	98	0.28	0
16	Hg	12	1.20	600	B-2	96	0.28	0
17	Hg	7.3	1.17	500	B-1	96	0.22	0
18	Hg	6	...	300	B-2	98% recovered *dl*[h]		0

[a] Measured against Ag/AgCl reference electrode. See ref 14. [b] All runs in 80% EtOH. [c] Media coded as follows: A-1, 1 *M* LiCl and 1.5 *M* AcOH; A-2, 1 *M* LiCl and 1 *M* CF_3COOH; Buffer-1, pH 6.5, 2.5 *M* AcOH and 2 *M* KOAc; Buffer-2, pH 8.5, 1 *M* NH_4OH and 2 *M* NH_4OAc; B-1, 1 *M* KOH; B-2, 2 *M* KOAc. [d] Based on starting ketone. [e] 42% ketone recovered. [f] 25% ketone recovered. [g] 8% ketone recovered. [h] Stability study at constant current, 500 mg of pure *dl*-pinacol starting material.

dine rings coplanar, and O–H–N bridging to produce two six-membered "rings") would lead to methyl groups that were strongly shielded by virtue of their position relative to the ring currents and should, accordingly, resonate at a higher field strength than those in the *dl* form. Similar conclusions would be drawn from an alternate, less satisfactory conformation involving two five-membered rings. There is no conformation for the *dl* form, involving either five- or six-membered rings, that does not involve less shielded methyl groups as well as nonbonded interactions.[8] On this basis, with the previously mentioned corroborative data, the pinacol from the organometallic route[6] was assigned *dl* and the other *meso*.

Polarographic examination indicated an $E_{1/2}$ of −0.66 V at pH 4[9] and an $E_{1/2}$ of −1.33 V at pH 14. Appropriate interpolations were used for the various media employed. Ethanol (80%) was selected as solvent to conform to earlier studies. All runs were conducted under conditions of controlled potential.

The data are tabulated in Table I.

Results and Discussion

The data in Table I permit several important conclusions.

(1) As predicted by the proposed mechanism, and in contrast to the corresponding *dl/meso* ratios observed for acetophenone, the *meso*-pinacol predominates in all cases.

(2) The carbinol (monomolecular reduction) is an important product and the almost exclusive product in strongly acidic media. This may be compared to a complete absence of carbinol from the ketones previously examined.[10]

(3) The use of appreciably larger currents (with slightly more negative potentials) increases the amount of carbinol produced at the expense of pinacol.

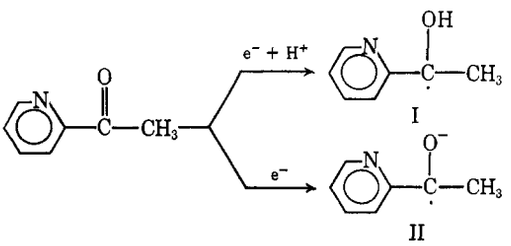
(4) The stereochemistry of the pinacol formation is related to the formation of carbinol; in general, the greater the yield of carbinol, the larger the *dl/meso* pinacol ratio.

(5) The pinacolization is pH dependent; the largest *dl/meso* ratios are observed in increasingly acidic media.

(6) The use of a copper electrode in a given medium (but at a more negative potential) gives rise to more carbinol and a larger *dl/meso* ratio than does a mercury pool electrode. This is in contrast to the absence of any changes in *dl/meso* ratios for the several electrodes investigated in the acetophenone studies.

The 2-acetylpyridine system is clearly a complex one, and, in contrast to acetophenone, may be considered a "sensitive" system. It is perhaps most effective to consider initially only those runs directly comparable to the earlier acetophenone studies, *i.e.*, use of a mercury pool electrode and relatively low initial currents (items 1–4, 6, 8, 15–17). These results show increasing amounts of *meso*-pinacol with increasing alkalinity, the ratios changing from 0.77 *dl/meso* in acid media to 0.22 *dl/meso* in strong base. The amounts of carbinol vary directly with the acidity, from approximately 90% in acidic media to 0% in strongly alkaline media. The following reasoning, modeled after that employed for the acetophenone system, may be invoked to explain these results.

Ketyl I would be formed from 2-acetylpyridine by the customary one-electron transfer in acidic media;



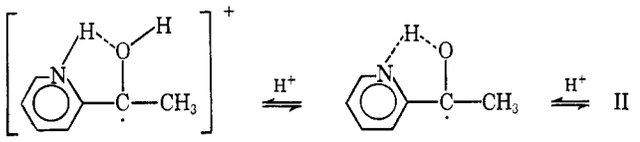
(8) An extensive nmr study of some twelve 2-pyridinealkanols, including diastereomeric pairs, will be submitted for publication shortly.

(9) É. Laveron [*Bull. Soc. Chim. Fr.*, **70**, 2326 (1961)] has reported values for pH range 2–7 in graphic form. An $E_{1/2}$ of −0.67 may be estimated from his data.

(10) Previous studies were limited to currents of less than 500 mA, and the statement carries this reservation.

the radical anion II would be anticipated in basic media.

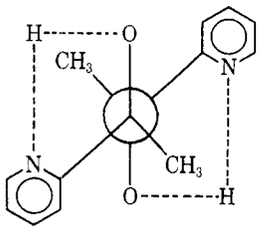
Ketyl I, either as such or in its *intra*molecularly bonded form III,[11] would be involved in a complex equilibrium, the amounts of each participating species reflecting the pH of the medium. Pinacol formation



IV III

could conceivably arise from six possible dimerizations or combinations. Ruling out the dimerization of II and of IV as involving combinations of like-charged species, and the combination of II and IV as unlikely on the grounds that they would not be expected to coexist, leads to the following more important possibilities: (A) III with IV (significant in acid media); (B) III with III (major route in both acid and base); (C) II with III (of possible significance only in strong base).

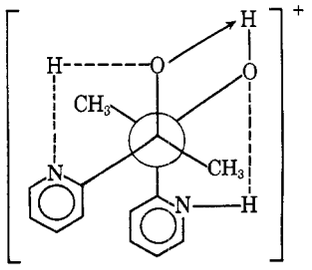
Route B, considered the major pathway, does not permit hydrogen bonding between species about to couple, and the stereochemistry would be dictated on simple steric grounds; *i.e.*, only formation of the *meso* form would permit all like groups to be in a *trans* arrangement V at the time of bond formation. The predominance of the *meso* form in all cases (Table I) is attributed to this pathway.



yields *meso*

V

Route A, the combination of radical cation and neutral radical, would permit interspecies hydrogen bonding. By analogy with the acetophenone system in which such interspecies hydrogen bonding appeared to be of major importance and to lead preferentially to the *dl* form, VI would be expected to make an important contribution.



yields *dl* (one of two forms, methyl groups *trans*)

VI

All analogous interspecies combinations leading to the *meso* form require two, rather than one, nonbonded interactions between like groups and would be less attractive. Therefore, the contribution of route A would be reflected in the form of an increased *dl/meso* ratio in acid media.[12]

The contribution of route C, the combination of radical anion with neutral radical, is more difficult to predict. To the extent that II and III combine without interspecies hydrogen bonding, simple steric control should produce predominantly the *meso*-pinacol. To the extent that II is a strong enough base to compete for the *intra*molecularly bound hydrogen in III, it could bond with that hydrogen and subsequently produce less *meso* product than simple dimerization of III. It may be further argued that the intramolecular bonding in III is sufficiently strong that it is unlikely that II is present to any appreciable extent in protic media. The observed ratios suggest that, for whichever of the above reasons, it is not necessary to invoke species II for the results under consideration.

In summary, for these runs, the largest *dl/meso* ratios would be expected from media in which the concentration of IV was highest, *i.e.*, strongly acidic media. As the concentration of IV decreased with the increasing alkalinity of the media, the *dl/meso* ratios would correspondingly decrease.

If the further reasonable assumption is made that IV is an uniquely reducible species, it also becomes the precursor of the carbinol, and the almost exclusive production of carbinol in acidic media is thereby explained. To the extent that IV is "siphoned off" to yield carbinol, it is not available to produce preferentially the *dl*-pinacol. The observed *dl/meso* ratios would be even larger if no carbinol was produced in acidic media.[13] As the media are made more basic, less IV is present, and less carbinol, as well as lowered *dl/meso* ratios, are observed. Thus IV is acting in a double capacity.

The results from the "high current" runs (items 5, 7, 9–11) and those employing a copper electrode (items 12–14) suggest that the above rationale may be oversimplified. While the copper runs also show a decrease in carbinol and *dl/meso* ratios with increasing alkalinity, the ratios are still substantially higher than those found in the analogous studies with mercury pool electrodes in which no carbinol was observed. The "high current" runs, involving somewhat more negative constant potentials (for a given pH), produced in all cases more carbinol than the lower current, lower potential runs. As much as 54% carbinol was now observed in KOH where no carbinol had been observed previously. Once again, the *dl/meso* ratios rose with increasing carbinol production. It is difficult to see, however, how IV could be invoked in strongly alkaline media as the preferred carbinol precursor.

The fact that the stereochemistry *does* change in a consistant fashion with carbinol production must mean that an intermediate in pinacol formation is also a carbinol precursor; *i.e.*, carbinol production is a two-

(11) It may be argued that III, with its favorable five-membered ring, would be the predominant species present. Experimental data for such bonding in neutral ketyl radicals, however, is not available. Whether III actually arises from the ketyl as shown or is derived from the protonated nitrogen moiety receiving the electron is not critical to the discussion.

(12) It is urged that construction of Fieser–Dreiding models be used to verify these comments, strongly condensed to conserve journal space. Reference to the earlier material for acetophenone should also prove particularly helpful.

(13) In analogous photopinacolization studies where no carbinol is observed, the higher *dl/meso* ratios of 0.75–0.98 are observed for 2-acetylpyridine in acidic media (J. H. Stocker and D. H. Kern, unpublished results).

step process. It further indicates that more than one route is involved in pinacol formation.

If it is argued that the ketyl radical III is the intermediate reduced to carbinol at higher pH's, an active role must be assigned to anion II. Then the combination of II and III (route C), in the presence of decreased amounts of III due to its loss to form carbinol, could be increasingly important and account for the higher *dl/meso* ratios. Thus, the high current, the more negative potentials on the mercury electrodes, and the appreciably more negative potentials observed with the copper electrodes would all represent the same phenomena: an increasing ease of reduction of III to carbinol, a consequent decrease in dimerization of III, and an increase in the combination of II with III. The above presupposes that the solution equilibria involved must be slow enough to be effectively disturbed by the withdrawal of some constituent; there would otherwise be no change in the stereoselectivity observed.

It may be added that the controlled potential reduction of 2-acetylpyridine should be considered attractive for the synthesis of preparative scale amounts of the carbinol and the *meso*-pinacol, the former in strongly acidic media and the latter in alkaline media at moderate current levels.

Experimental Section

The routine chemicals employed were either reagent grade or the best research grade obtainable and were further purified by conventional techniques where necessary.

The general procedure has been reported in detail.[1,2,14] All runs involved 1 g of ketone in 60 ml of solution. Modifications in the general procedure are described in Table I. *dl/meso* ratios were determined by a comparison of peak heights of the methyl groups of the two diastereomers. Yields were based on a comparison, after normalization, of the integrated area of the methyl groups with the total aromatic area. Recovered ketone was evaluated similarly.

***meso*-2,3-Di(2-pyridyl)-2,3-butanediol.**—This material was isolated by simple crystallization from reaction mixtures corresponding to item 16 in Table I (2 *M* KOAc, 80% EtOH, −1.15 V, and initial current 600 mA). Two recrystallizations from hot heptane yielded chunky white crystals, mp 142–143°. Photochemical bimolecular reduction of 2-acetylpyridine was also employed.[6]

***dl*-2,3-Di(2-pyridyl)-2,3-butanediol.**—A modification of the procedure reported by Bencze and Allen[6] was employed. To an ether solution of methylmagnesium iodide (from 0.25 mol of Mg and 0.25 mol of CH_3I) was added 12.1 g (0.06 mol) of α-pyridil. Following an 18-hr reflux and conventional work-up, 7.9 g of *dl*-pinacol (55%), mp 139–140°, was isolated. Two recrystallizations from hexane yielded fine needle crystals, mp 142°.

Registry No.—2-Acetylpyridine, 1122-62-9; methyl-2-pyridylcarbinol, 18728-61-5; *meso*-2,3-di(2-pyridyl)-2,3-butanediol, 20445-38-9; *dl*-2,3-di(2-pyridyl)-2,3-butanediol, 20445-39-0.

Acknowledgment.—Financial support from the U. S. Atomic Energy Commission under Contract AT-(40-1)-2833 (ORO-2833-21) is gratefully acknowledged. The nmr instrument utilized, an A-60 (Varian Corp.), was awarded to Louisiana State University in New Orleans by the National Science Foundation under Grant GP-3674.

(14) A Ag/AgCl reference electrode was used in place of the previously employed standard calomel electrode. As used with saturated KCl, it is 0.04 V more negative than the latter.

Quantitative Studies in Stereochemistry. Photochemistry. VII. Electrochemistry. IV. The Photochemical and Electrochemical Bimolecular Reduction of Aldehydes and Unsymmetrical Ketones; a Common Stereochemistry[1]

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Received October 10, 1968

New and previously published data in the two title areas are tabulated and the stereochemical results from the two techniques are compared. In all cases, both photochemical and electrochemical pinacolizations gave essentially the same ratios of diastereomeric *dl*- to *meso*-pinacols in acid solution with corresponding changes of ratios in basic media. Mechanisms previously proposed for the photochemical and the electrochemical routes are shown to be mutually compatible. Several examples of contrasting behavior, *i.e.*, successful pinacolization by only one of the two techniques, are reported and discussed.

A number of papers from this laboratory have reported the *dl/meso* ratios of diastereomeric pinacols formed in the photochemical[2-7] and electrochemical[8-10] bimolecular reduction of benzaldehyde and unsymmetrical ketones. As the roughly parallel studies in the two areas progressed, it became increasingly apparent that the diastereomeric ratios observed could only be explained by the two techniques sharing a common mechanism at some terminal point. This present report brings together data from all previous papers, selected to facilitate comparisons, with additional unpublished

(1) Presented in part before the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **31**, 3755 (1966). (Acetophenone in neutral and acid media)

(3) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 291 (1968). (Acetophenone in basic media; benzaldehyde)

(4) J. H. Stocker, D. H. Kern, and R. M. Jenevein, *ibid.*, **33**, 412 (1968). (*p*-Substituted acetophenones)

(5) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 1270 (1968). (Acetophenone in amine media)

(6) J. H. Stocker and D. H. Kern, *ibid.*, **33**, 1271 (1968). (Deoxybenzoin)

(7) J. H. Stocker and D. H. Kern, submitted for publication in *J. Org. Chem.* (2-Acetylpyridine)

(8) J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, **33**, 294 (1968). (Acetophenone)

(9) J. H. Stocker and R. M. Jenevein, *ibid.*, **33**, 2145 (1968). (Benzaldehyde and propiophenone)

(10) J. H. Stocker and R. M. Jenevein, *ibid.*, **34**, 2807 (1969). (2-Acetylpyridine)