Structure *vs.* Reactivity in Quinoxalinecarboxylic Acids and Esters

WILSON F. GUM, JR.,[1] AND MADELEINE M. JOULLIÉ

John Harrison Laboratory of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received June 18, 1965

The electron densities at the various positions of quinoxaline have been calculated by Longuet-Higgins and Coulson,[2] Pullman,[3] and Basu and Bhattacharya.[4] The results of these calculations are shown in Table I.

TABLE I
ELECTRON DENSITIES IN THE QUINOXALINE RING

Atom	q_i[3]	q_i[2]	q_i[4]
1 and 4	1.346	1.383	1.322
2 and 3	0.866	0.836	0.894
9 and 10	0.917	...	...
6 and 7	0.933	0.946	0.925
5 and 8	0.938	0.990	0.956

Although these calculations gave a variety of results, the same general trend is apparent. From these data one would predict that the 2- and 3-positions are the most positive positions and hence the preferred sites for nucleophilic attack while the 5- and 8-positions are the most electron-dense positions, other than the nitrogen atoms, and hence preferred sites for electrophilic attack. Dewar and Maitlis[5] predicted that the 5-position of quinoxaline would be nitrated preferentially by calculating the π-electron energy difference between the parent aromatic compound and the transition state. They confirmed this prediction by showing that quinoxaline could be nitrated when treated for 24 hr. at 90° with a mixture of oleum and sulfuric and nitric acids, to give a 1.5% yield of 5-nitroquinoxaline as the only mononitro derivative.

In an attempt to establish a correlation between the electron densities in an unperturbed quinoxaline nucleus and the reactivities of some of its derivatives, the pK_A values of 2-, 2,3-, 5-, 6-, and 2,3-dimethyl-5-quinoxalinecarboxylic acids were measured, and the carbonyl frequencies of the corresponding methyl and ethyl esters were determined by infrared spectroscopy.

A. The Quinoxalinecarboxylic Acids.—The electron densities at the various positions of the quinoxaline ring should have an effect on the carboxylic acid group attached to them and this effect should be apparent on the acidity of this group. Table II lists the measured pK_A values of the quinoxalinecarboxylic acids and that of benzoic acid, all measured at 25°. Because of the insolubility of 2,3-dimethyl-5-quinoxalinecarboxylic acid in water, its pK_A and that of 5-quinoxalinecarboxylic acid were determined in 50% aqueous ethanol.

It can be seen from a comparison of Tables I and II that there was a correlation between the relative acid strengths of the isomeric carboxylic acids and the electron densities and the carbons attached to the carboxyl group. Compound I, in which the carboxyl group was attached to the position having the greatest positive charge, was found to be the strongest acid. The weakest acid, compound IV, had its carboxyl group attached to the position of greatest electron density. The introduction of another carboxyl group in the 3-position of compound I, compound II, produced a large increase in acidity as shown by the first ionization constant of this compound. The introduction of two methyl groups in the 2- and 3-positions decreased the electron-withdrawing effect of the nitrogen atoms and decreased the acidity of the 5-carboxylic acid group as shown by the pK_A values of compounds IV and V in aqueous ethanol.

TABLE II
pK_A OF QUINOXALINECARBOXYLIC ACIDS

Acid	pK_A Water	pK_A 50% aqueous ethanol
2-Quinoxalinecarboxylic (I)	2.875 ± 0.011[a]	...
2,3-Quinoxalinedicarboxylic (II)	1.62 ± 0.11 3.64 ± 0.02	...
6-Quinoxalinecarboxylic (III)	3.640 ± 0.009[a]	...
5-Quinoxalinecarboxylic (IV)	4.026 ± 0.018[a]	5.31 ± 0.02
2,3-Dimethyl-5-quinoxalinecarboxylic (V)	...	6.19 ± 0.02
Benzoic	4.20 ± 0.03[b]	5.68 ± 0.03[c]

[a] Expanded scale titrations, see Experimental Section. [b] D. H. McDaniel and H. C. Brown [*J. Org. Chem.*, **23**, 420 (1958)] report pK_A = 4.198 ± 0.012. [c] Lit.[9] pK_A = 5.74 ± 0.02.

It is apparent that the pK_A values of these acids are very sensitive to the electron densities in the quinoxaline nucleus. While a good correlation seems to exist between the observed pK_A values and the electron densities calculated by Longuet-Higgins and Coulson,[2] the values calculated by Basu and Bhattacharya,[4] and by Pullman[3] show only poor correlations. As a result, no firm conclusion can be reached concerning a relationship between q_i and the pK_A values of the quinoxaline carboxylic acids because there seems to be no good reason to choose one set of q_i values over another.

B. The Methyl and Ethyl Quinoxalinecarboxylates.—Infrared carbonyl frequencies are dependent on the immediate environment of the carbonyl group, and carbonyl stretching frequencies are very sensitive to the effects of substituents on electron densities near the carbonyl group.[6] It has been shown that correlations exist between the pK_A values of substituted benzoic acids and the carbonyl frequencies of aryl methyl ketones,[7,8] aryl aldehydes,[8] methyl and ethyl esters of arylcarboxylic acid,[8] and arylcarboxylic acid monomers and dimers.[8] Shifts in the carbonyl frequencies of substituted methyl 1-naphthoates have been shown to correlate with the σ constants of the substituents.[9]

(1) Abstracted in part from the forthcoming thesis of Wilson F. Gum, Jr.
(2) H. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.*, 971 (1949).
(3) A. Pullman, *Rev. Sci.*, **86**, 219 (1948).
(4) S. Basu and R. Bhattacharya, *Proc. Natl. Inst. Sci. India*, **A23**, 1 (1957).
(5) M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).
(6) (a) E. J. Hartwell, R. E. Richards, and H. W. Thompson, *ibid.*, 1436 (1948); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, Chapter 23.
(7) R. N. Jones, W. F. Forbes, and W. A. Mueller, *Can. J. Chem.*, **35**, 504 (1957).
(8) C. J. W. Brooks, G. Eglinton, and J. F. Morman, *J. Chem. Soc.*, 106 (1961).
(9) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3546 (1962).

TABLE III

CARBONYL FREQUENCIES (CM.$^{-1}$) OF QUINOXALINE ESTERS

Ester	Solvent: Carbon tetrachloride $\nu_{C=O}$	Carbon tetrachloride r^a	Acetonitrile $\nu_{C=O}$	Acetonitrile r	Chloroform $\nu_{C=O}$	Chloroform r
Ethyl pyrazinecarboxylate (VI)	1755 1726	1.78	1743 1724	1.08	1737 (sh) 1724	1.04
Methyl pyrazinecarboxylate (VII)	1760 1733	1.45	1750 1730	1.03	1742 (sh) 1732	1.09
Ethyl 2-quinoxalinecarboxylate (VIII)	1753 1724	2.15	1745 1723	1.22	1738 (sh) 1720	1.10
Diethyl 2,3-quinoxalinedicarboxylate (IX)	1786 (sh) 1751 1730	5.40 1.26	1745 1727	0.94	1735	...
Ethyl 5-quinoxalinecarboxylate (X)	1741 1724	1.06	...	...	1722	...
Methyl 5-quinoxalinecarboxylate (XI)	1743 1729	1.04	1735	...	1726	...
Ethyl 6-quinoxalinecarboxylate (XII)	1727	...	1723	...	1720	...

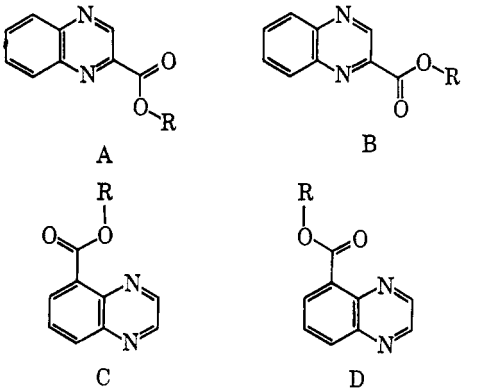
[a] r = $\%T$ (lower frequency band)/$\%T$ (higher frequency band).

Since the hydrolysis rates of ethyl azuloates were only slightly sensitive to the electron densities in the azulene ring[10] and since poor correlations had been obtained between the hydrolysis rates of esters of quinolinecarboxylic acids and the relative electron densities in the quinoline ring,[11] it was thought that a better correlation might exist between the electron densities of the three nonequivalent positions of the quinoxaline nucleus and the carbonyl frequencies of the ester groups attached to these positions. To accomplish this we measured the carbonyl frequencies of various esters of quinoxalinecarboxylic acids. The results of this infrared study are shown in Table III.

As can be seen from Table III, only ethyl 6-quinoxalinecarboxylate (XII) exhibited a single sharp carbonyl absorption peak in all media. All other esters showed a split carbonyl which was less apparent in chloroform because of the usual absorption band-broadening effects exhibited by this solvent. To determine the influence of the heterocyclic ring we prepared methyl 2-pyrazinecarboxylate and determined its infrared spectrum. This ester also showed a split carbonyl. The same behavior had already been observed for ethyl 2-pyrazinecarboxylate.[12] A number of aromatic esters have been shown to exhibit split carbonyl bands which were attributed to conformational equilibria rather than Fermi resonance.[8] The doublet nature of the carbonyl frequency of cyclopentanone has been ascribed to Fermi resonance.[13] Double carbonyl bands in other compounds have also been attributed to the existence of conformational equilibria.[14-16] Jones and his colleagues have shown that solvent- and temperature-dependent modifications of carbonyl frequencies, though often attributed to conformational equilibria, can be produced by Fermi resonance and other vibrational interactions.[17]

To investigate the possible cause of the doublet nature of the carbonyl group of the esters prepared, some solvent and concentration studies were carried out. These studies showed that the relative intensities of the double bands are essentially independent of concentration. Therefore one can eliminate intermolecular effects such as dipole–dipole association as a cause of the split nature of these bands. This leaves two possible explanations for the occurrence of a double carbonyl band in the compounds under consideration, namely, conformational equilibria and Fermi resonance.

The possible conformations for ester groups in the 2- and 5-positions are shown in structures A–D.



The ester groups are depicted in their normally preferred conformations. Coplanarity of the substituents and the nucleus is not implied in these representations although the dipole moment studies of 2-methoxy- and -ethoxyquinoxalines indicated that the –OR group preferred to be aligned in a plane with the R group pointed towards the π-electrons of the ring nitrogen.[18] It seems reasonable to assign the higher frequency bands to the more polar conformations (B and D) by analogy with the assignments made for other esters.[8]

From the data obtained, it would appear that the split carbonyl bands observed for the esters studied

(10) P. A. Leermakers and W. A. Bowman, *J. Org. Chem.*, **29**, 3708 (1964).
(11) R. C. Elderfield and M. Siegel, *J. Am. Chem. Soc.*, **73**, 5622 (1951).
(12) H. Shindo, *Chem. Pharm. Bull.* (Tokyo), **8**, 33 (1960).
(13) G. Allen, P. S. Ellington, and G. D. Meakins, *J. Chem. Soc.*, 1909 (1960).
(14) (a) L. J. Bellamy and R. L. Williams, *ibid.*, 4294 (1957); (b) *ibid.*, 3465 (1958).
(15) (a) M. L. Josien and M. R. Calas, *Compt. rend.*, **240**, 1641 (1955); (b) M. L. Josien and C. Castinel, *Bull. soc. chim. France*, 801 (1958).
(16) T. L. Brown, *J. Am. Chem. Soc.*, **80**, 3513 (1958).
(17) R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959).
(18) H. Otomasu, R. Y. Amaguchi, K. Ishigoaka, and H. Takahashi, *Yakugaku Zasshi*, **82**, 1434 (1962); *Chem. Abstr.*, **58**, 5159e (1963).

should be ascribed to conformational isomerism rather than Fermi resonance. The principal evidence in support of conformational equilibria is as follows.

(a) Removal of the aromatic ring from the quinoxaline structure or changing the alkyl group of the ester from ethyl to methyl did not alter the split carbonyl pattern.

(b) The carbonyl frequencies are lower in acetonitrile than carbon tetrachloride and the ratio of the lower frequency band to the higher frequency band (as measured by r) decreased in going from the less polar solvent carbon tetrachloride to the more polar solvent acetonitrile. This implies that the more polar solvent was able to favor the more polar conformation. A similar effect has been observed in other cases of conformational equilibria.[8,14b,16]

(c) The solvent shifts of the split carbonyl bands were not much different from the shifts shown by the single band exhibited by compound XII. In compounds whose split carbonyl bands have been attributed to Fermi resonance, solvent shifts have been reported to be irregular since neither of the observed bands represent the fundamental carbonyl frequency.[13,17]

(d) Where no interaction between the carbonyl group and the ring nitrogen atoms is possible as in compound XII, a single carbonyl peak is observed.

(e) The spectra of compounds VI and VIII, in carbon tetrachloride and in acetonitrile, show intensity changes which parallel those in the carbonyl region for at least two pair of bands in the 1400–900-cm.$^{-1}$ region (near 1045–1013 and 1300–1275 cm.$^{-1}$ for compound VI; near 1127–1100 and 1315–1280 cm.$^{-1}$ for compound VIII). This behavior is consistent with the existence of two rotational isomers[8] and is not observed for compound XII.

Conclusions.—It is apparent that the infrared frequencies of the carbonyl bands of the esters studied are very sensitive to the electronic environment in which they find themselves. However, because of the conformational equilibria exhibited by these compounds, no correlation with electron densities in the quinoxaline ring could be observed. However, relative pK_A values of the quinoxalinecarboxylic acids were found to be predictable from electron densities of the unsubstituted quinoxaline ring even though the carboxylate anions formed during the determination surely perturb the ring densities. This effect is apparently small in relation to the perturbed electron densities caused by the ring nitrogens in the unsubstituted quinoxaline nucleus.

Experimental Section[19]

Acid pK_A Values.—The relative strengths of the quinoxalinecarboxylic acids were determined by a potentiometric titration technique. The pK_A values were calculated from the titration curve by means of the Henderson–Hasselbach equation. This

$$pK_A = pH - \log \frac{[\text{neutralized acid}]}{[\text{residual acid}]}$$

equation relates the pH of a partially neutralized aqueous solution of a weak acid with the degree of neutralization. The pK_A values were calculated at 20, 30, 40, 50, 60, and 70% neutralization from the titration curves. Corrections for hydrogen ion concentration and solution volume change during the titration were applied. No activity corrections were applied since the concentrations were always between 0.01 and 0.001 M. The acids were dissolved in a known volume of ion-free water and titrated with standardized potassium hydroxide (0.0504 N) using a calibrated 5-ml. side-arm buret fitted with a soda lime drying tube. The potentiometric titration was performed in a constant-temperature cell at 25.0 ± 0.1° using a combination glass and saturated calomel electrode system. The cell was covered with a sheet of Parafilm and purged with purified nitrogen. Stirring was effected with a magnetic stirrer and the pH values were read as a function of the volume of standard potassium hydroxide from a Beckman Expandomatic pH meter calibrated in 0.1 pH units on the standard scale and in 0.01 pH units on the expanded scale. The meter was calibrated with aqueous buffers before and after the titration, and no correction for liquid junction potentials was made.

The titration of compound II yielded a curve with only one inflection point at the end point of the titration of 2 equiv. of hydrogen ion. This type of curve is usually obtained when the titration of the second hydrogen begins before the first is completely titrated. This results in overlapping pK_A values which can be separated by using equations developed by Noyes.[20]

For the determinations in 50% aqueous ethanol, samples of acids sufficient to give 0.01 to 0.003 M solutions were weighed into stoppered volumetric flasks and diluted with ethanol (25 ml.) and ion-free water (25 ml.). The solutions were partially neutralized with a known quantity of standard potassium hydroxide and an equal volume of ethanol was added. The resulting solutions were kept in a constant-temperature bath (25 ± 0.1°) for 2 hr. The pH of these solutions were measured as described above and the pK_A values were calculated from the Henderson–Hasselbach equation.

Infrared Measurements.—Infrared spectra were recorded linearly in reciprocal centimeters as per cent transmission with a Perkin-Elmer 521 double-beam grating recording infrared spectrophotometer. The wave number scale was calibrated against the atmosphere and indene. Measurements are accurate to ±1 cm.$^{-1}$. The carbonyl bands were scanned at 50 cm.$^{-1}$/min. in all solvents. The frequency values given are the mean of at least three determinations. Matched sodium chloride cells either of 0.092 or 0.211 mm. thickness were used. Spectral grade carbon tetrachloride, acetonitrile, and chloroform from Eastman Organic Chemicals were used without further purification.

Preparation of Compounds. 2-Quinoxalinecarboxylic Acid (I).—This compound was synthesized by the procedure described by Maurer and Boettger[21]: yield 61%, m.p. 211–212° dec. (lit.[21] m.p. 209–211°), $\nu_{C=O}^{KBr}$ 1737 and 1704 cm.$^{-1}$.

5-Quinoxalinecarboxylic Acid (IV).—3-Nitro-2-aminobenzoic acid[22] (5 g., 0.0274 mole) was dissolved in 10% aqueous potassium carbonate (100 ml.) and reduced in a Parr hydrogenator using 10% palladium on charcoal (0.5 g.) as the catalyst. The catalyst was removed by filtration and the solution containing the sodium salt of 2,3-diaminobenzoic acid was transferred to a 250-ml. three-necked flask fitted with a mechanical stirrer and thermometer. The solution was stirred and glyoxal bisulfite (10 g.) was added to it followed by the addition of 50 ml. of 10% aqueous potassium carbonate solution. Stirring was continued for 3 hr. at 60°. The reaction mixture was then cooled to 5° and acidified to pH 5 with 30% aqueous sulfuric acid. The yield of red crystalline solid was 85%, m.p. 168–170°, $\nu_{C=O}^{KBr}$ 1717 cm.$^{-1}$.

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.08. Found: C, 61.99; H, 3.59; N, 16.21.

6-Quinoxalinecarboxylic Acid (III).—3,4-Diaminobenzoic acid sulfate (12.5 g., 0.050 mole) was dissolved in 200 ml. of 10% aqueous potassium carbonate in a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and thermometer. Glyoxal bisulfite (25 g., 0.088 mole) was added to this solution with stirring. Stirring was continued for 1 hr. at 50° after which the solution was cooled and acidified to pH 2 with 30% aqueous sulfuric acid. The yield of beige crystals was 24%, m.p. 240–

(19) All compounds were recrystallized from ethanol unless otherwise noted. All melting points were determined in a Thomas–Hoover capillary melting point apparatus. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and Dr. A. Bernhardt, Max Planck Institut, Mülheim (Ruhr), West Germany.

(20) H. T. S. Britton, "Hydrogen Ions," D. Van Nostrand Co., Inc., New York, N. Y., 1956, p. 217.

(21) K. Maurer and B. Boettger, *Ber.*, **B71**, 1383 (1938).

(22) E. Chapman and H. Stephen, *J. Chem. Soc.*, 1791 (1925).

243° dec. (lit.[23] m.p. 266° dec.), $\nu_{C=O}^{KBr}$ 1704 cm.$^{-1}$. Since our melting point did not agree with the literature value of this compound which had been prepared by a different method, analytical data were obtained.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 62.07; H, 3.47; N, 16.08. Found: C, 61.99; H, 3.50; N, 15.89.

2,3-Dimethyl-5-quinoxalinecarboxylic Acid (V).—3-Nitro-2-aminobenzoic acid (5.0 g., 0.0274 mole) was suspended in absolute ethanol (150 ml.) and reduced in a Parr hydrogenator using 10% palladium on charcoal (0.5 g.) as the catalyst. The catalyst was removed by filtration and the solution was treated immediately with 200 ml. of 10% aqueous potassium carbonate and diacetyl (6 ml., 0.070 mole). The resulting solution was stirred at room temperature with a magnetic stirrer for 15 min. and then poured into 400 ml. of ice–water. The yield of bronze-colored solid was 65%, m.p. 186–187°, $\nu_{C=O}^{KBr}$ 1698 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.23; H, 4.97; N, 14.02.

2,3-Quinoxalinedicarboxylic Acid (II).—This compound was prepared by the procedure described by Hinsberg and König[24]: yield 53%, m.p. 188–189° dec. (lit.[24] m.p. 190°), $\nu_{C=O}^{KBr}$ 1719 cm.$^{-1}$.

Ethyl 2-Quinoxalinecarboxylate (VIII).—This compound was prepared according to the method of Maurer and Boettger[21]: yield 86%, m.p. 83.5–85° (lit.[21] m.p. 85°).

Ethyl 6-Quinoxalinecarboxylate (XII).—This compound was prepared by the method of Birkofer and Widmann[23]: yield 72%, m.p. 70–71° (lit.[23] m.p. 66°).

Ethyl 5-Quinoxalinecarboxylate (X).—5-Quinoxalinecarboxylic acid (1.7 g., 0.01 mole) was dissolved in 75 ml. of anhydrous benzene in a 250-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, reflux condenser, and silica gel drying tube. Purified thionyl chloride (1.6 g., 0.013 mole) was added to the solution and the reaction mixture was stirred and heated for 12 hr. Absolute ethanol (25 ml.) was added to the solution and heating was continued for 12 hr. The solution was then evaporated to dryness and the residue was extracted with two 100-ml. portions of a 50% mixture of cyclohexane and anhydrous ether. The extracts were treated with anhydrous potassium carbonate and then with anhydrous magnesium sulfate. After the drying agents were removed, the filtrate was reduced to a volume of 20 ml. and 20 ml. of Skellysolve H[25] was added to it. A solid was formed which could not be identified but was definitely not the desired product.

The original residue was extracted again with two 150-ml. portions of anhydrous ether and the extracts were treated with potassium carbonate. The drying agent was removed and the filtrate was reduced in volume until a precipitate formed. This solid was recrystallized from cyclohexane to yield 1% of the desired product, m.p. 215–216°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.50; H, 4.85; N, 14.04.

Methyl 5-Quinoxalinecarboxylate (XI).—5-Quinoxalinecarboxylic acid (1.0 g., 0.0057 mole) was suspended in 1,2-dimethoxyethane (100 ml.) in a 250-ml. erlenmeyer flask fitted with a magnetic stirrer. The solution was cooled in an ice–water bath and stirred magnetically while diazomethane (0.96 g. 0.023 mole) was added to it. The acid dissolved and the solution was allowed to stand overnight. Decolorizing carbon was added to the reaction mixture. The mixture was heated and the carbon was removed by filtration. The filtrate was concentrated to 20 ml. and treated with Skellysolve H[25] (50 ml.) and evaporation was continued until a solid formed. This product (63%) was recrystallized from cyclohexane, m.p. 73–74°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.88. Found: C, 63.96; H, 4.42; N, 14.80.

Diethyl 2,3-Quinoxalinedicarboxylate (IX).—This compound was prepared by the method of Chattaway and Humphrey[26]: yield 85%, m.p. 82–83.5° (lit.[26] m.p. 83°).

Ethyl 2-Pyrazinecarboxylate (VI).—This compound was prepared according to the procedure of Shindo[12]: yield 87%, m.p. 48.5–51° (lit.[21] m.p. 52–53°).

Methyl 2-Pyrazinecarboxylate (VII).—The method of Hall and Spoeri[27] was used: yield 72%, m.p. 58.5–61° (lit.[27] m.p. 62°).

Acknowledgment.—The authors wish to thank Dr. E. Rosenbaum of Drexel Institute of Technology for helpful discussions concerning the infrared data. This investigation was supported by a grant (AM07684-02) from the National Institutes of Health, U. S. Public Health Service.

(23) L. Birkofer and A. Widmann, *Ber.*, **86**, 1295 (1953).

(24) O. Hinsberg and F. König, *ibid.*, **27**, 2185 (1894).

(25) Skellysolve H is a petroleum fraction (b.p. 70–74°) obtained from Skelly Oil Co., Kansas City, Mo.

(26) F. D. Chattaway and W. G. Humphrey, *J. Chem. Soc.*, 645 (1929).

(27) S. A. Hall and P. E. Spoerri, *J. Am. Chem. Soc.*, **62**, 664 (1940).

Diimide Reductions Using Potassium Azodicarboxylate

J. WARREN HAMERSMA[1] AND EUGENE I. SNYDER

Department of Chemistry, University of Connecticut, Storrs, Connecticut

Received June 2, 1965

Use of reagents which generate diimide—at least formally—in the reduction of olefinic bonds is a relatively recent synthetic innovation which would appear to hold much promise in its scope.[2a] Except for a recent communication by van Tamelen,[2b] no limitations to this reaction have been described. To the best of our knowledge no extensive description of the experimental aspects of these reductions using potassium azodicarboxylate (PADA) has yet appeared. In this paper we describe the effects of several experimental variables on the course of the reduction and furnish adequate descriptions of the experimental methods employed. It will become apparent that this paper constitutes a phenomenological description of the behavior of one type of diimide reduction. Because we have not been able to formulate an integrated, self-consistent mechanistic description of this reaction we have chosen to limit our remarks on this latter aspect of the reaction. We also hope to indicate clearly that conclusions which might be drawn from yield data[2b] might need to be modified in light of our results.

Results

Although reductions were routinely performed in a nitrogen atmosphere, expt. 13–15 (Table I) indicate that air has no deleterious effects on the reaction. However, because the reaction is extraordinarily sensitive to the adverse effects of water (*vide infra*), suitable precautions for a dry atmosphere are indicated.

Solvents have an important influence on the reaction. Our work suggests solvents are less effective in the order pyridine > dioxane > dimethyl sulfoxide (DMSO) ~ methanol < ethanol ~ butanol (expt. 1–3, 5, and 13–20). As might be anticipated, the magnitude of the differences in solvent effects increases as the reactivity of the substrate decreases. Thus, azobenzene is reduced virtually quantitatively in the less effective solvents DMSO and methanol; the less

(1) NASA Predoctoral Fellow, 1963–1965.

(2) (a) See C. E. Miller, *J. Chem. Educ.*, **42**, 254 (1965), for a recent review; (b) E. E. van Tamelen, M. Davis, and M. F. Deem, *Chem. Commun.*, 71 (1965).