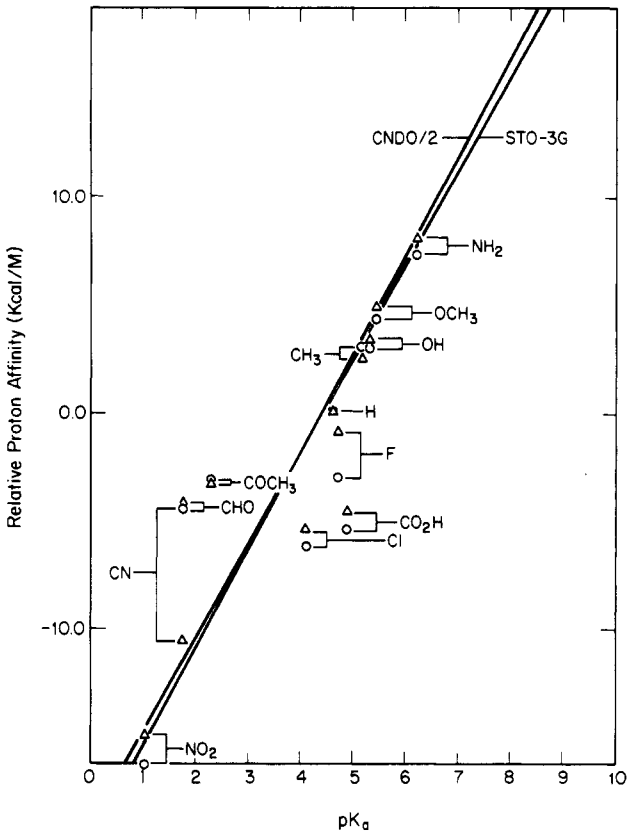
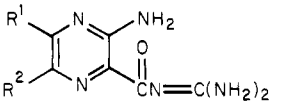


Figure 4. Plot of calculated proton affinity [(○) CNDO/2, (●) STO-3G] vs. pK_a for 12 para-substituted anilines. The values for the unsubstituted structures have been taken as zero and superimposed. Regression equations: CNDO/2, pK_a(calcd) = (0.22 ± 0.052) × PA_{calcd} + (0.82 ± 1.3), R^2 = 0.62, S = 1.07; STO-3G, pK_a(calcd) = (0.23 ± 0.040) × PA_{calcd} + (0.98 ± 1.0), R^2 = 0.75, S = 0.87.

For amiloride and its derivatives, various substituents were placed at the 5- and/or 6-position of the pyrazine ring. The site of protonation, the guanidine nitrogen bearing the acyl group, and its immediate environment remained constant throughout the series. In these cases, the site of substitution was far removed from the protonation site and, therefore, it was expected that the various substituents would have comparable influences on the solvation shell surrounding the site of protonation. With these restrictions, semiempirical methods could reproduce adequately the trend among the pK_a values. The PAs for the amiloride series calculated by the CNDO/2 method and experimental pK_a values are given in Table I. A least-squares analysis of the data shows a correlation which is similar in quality to that found for both the pyridine and aniline series (Figure 2). Here again, the deviations of the values observed for the hydroxyl and sulfhydryl groups may be attributed to tautomerism, since the OCH_3 and SCH_3 derivatives, which cannot tautomerize, afford PAs which fall predictably on the line.

Since the ionization state of a molecule, particularly that of a drug, may have profound effects on its solubility, absorption, membrane penetration, and conformation, a rapid first approximation of its pK_a value can be a valuable aid in target compound selection. The pK_a values derived for the amiloride series fall within a limit of 0.4 pK_a units. In our view, 0.4 pK_a units is within an acceptable range for making judgments concerning the choice of key compounds to synthesize from potentially hundreds of candidates. The usefulness and practicality of this method are therefore demonstrated. It is our expectation that this method of analysis, with suitable precautions, will prove to be of general utility as a means for predicting pK_a values.

Table I. Pyrazinylguanidine Data



1

	R_1	R_2	concn, mM	pK_a	PA, kcal/mol
1	NH_2	H	1.66	9.30	16.91
2	NH_2	SC_6H_5	0.91	9.00	14.45
3	$N(CH_3)_2$	Cl	1.33	8.76	15.18
4	NH_2	F	1.60	9.00	16.39
5	NH_2	Cl	1.66	8.70	13.36
6	NH_2	SCF_3	1.33	8.22	11.13
7	CH_3O	Cl	1.33	8.25	8.89
8	SCH_3	Cl	1.33	8.05	10.12
9	H	Cl	1.33	7.10	9.30
10	OH	Cl	1.33	5.45	10.80
11	SH	Cl	1.33	4.00	6.84
12	Cl	Cl[a]	1.66	6.60	6.30

[a] All measurements were carried out at 24 °C, using water as solvent; entry 12 was determined in 30% aqueous ethanol.

Experimental Section

Calculations were performed by using the Merck molecular modeling system.[12] Standard bond lengths and angles were used to construct the pyrazine series. A single tautomer of the guanidine moiety was used as shown in Figure 1. The neutral guanidine geometry was as follows: C=N, 1.29 Å; C—N, 1.406 Å. A single value of 1.355 Å was used for the guanidinium geometry.

Acknowledgment. We thank Dr. P. Gund for helpful discussions and are especially grateful to Mr. Y. Lee for physical measurements in the pyrazine series and to Ms. J. de Solms for cataloguing and providing these data for us. We extend our appreciation to Drs. P. S. Anderson and R. L. Smith for their encouragement and support throughout the course of these studies.

Registry No. 1 (R^1 = NH_2; R^2 = H), 1134-13-0; 1 (R^1 = NH_2; R^2 = SC_6H_5), 70296-90-1; 1 (R^1 = $N(CH_3)_2$; R^2 = Cl), 1214-79-5; 1 (R^1 = NH_2; R^2 = F), 64078-02-0; 1 (R^1 = NH_2; R^2 = Cl), 2609-46-3; 1 (R^1 = NH_2; R^2 = SCF_3), 70296-89-8; 1 (R^1 = CH_3O; R^2 = Cl), 1863-23-6; 1 (R^1 = SCH_3; R^2 = Cl), 1140-85-8; 1 (R^1 = H; R^2 = Cl), 1203-87-8; 1 (R^1 = OH; R^2 = Cl), 76599-74-1; 1 (R^1 = SH; R^2 = Cl), 1136-97-6; 1 (R^1 = Cl; R^2 = Cl), 76599-75-2.

(12) Gund, P.; Andose, J. D.; Rhodes, J. B.; Smith, G. M. *Science* **1980**, *208*, 1425.

Oxidative Cleavage of 1,2-Diols with *N*-Iodosuccinimide

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As part of our continuing interest in the reactions of *N*-iodosuccinimide (NIS, **2**) with alcohols[1] we have found that 1,2-diols are easily cleaved with NIS. In organic synthesis the two major reagents presently used to cleave

(1) T. R. Beebe, M. Adkins, P. Kwok, and R. Roehm, *J. Org. Chem.*, **37**, 4220 (1972); T. R. Beebe, A. L. Lin, and R. D. Miller, *ibid.*, **39**, 722 (1974).

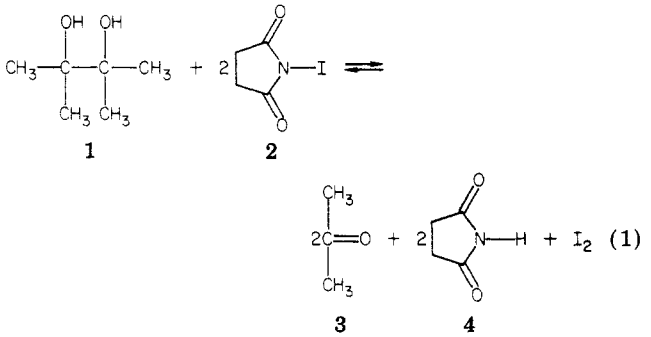
0022-3263/81/1946-1927$01.25/0

Table I

1,2-diols	carbonyl product	% yield	time	conditions
benzopinacol	benzophenone (2 mol)	90-98	15 min	dark
pinacol	acetone (2 mol)	90-97	1 h	dark
		90-95	30 min	irradiation
1,2-diphenyl-1,2-ethanediol	benzaldehyde (2 mol)	85-90	15 min	dark
2,3-butanediol	acetaldehyde (2 mol)	80-86	3 h	dark
1-phenyl-1,2-ethanediol	benzaldehyde (1 mol)	60-75	15 min	irradiation
		95-98	3 h	dark

1,2-diols are periodic acid, H_5IO_6, and lead tetraacetate, $Pb(C_2H_3O_2)_4$.[2] Periodic acid is primarily used for the degradation of water-soluble diols while lead tetraacetate is used mainly for water-insoluble diols. Our *N*-iodosuccinimide reagent successfully cleaved both water-soluble and water-insoluble 1,2-diols.

For example, when 2,3-dimethyl-2,3-dihydroxybutane (1) in tetrahydrofuran was treated with NIS high yields of acetone (3) could be obtained at ambient temperatures by allowing the reaction to proceed for 30 min with irradiation, or for 4 h in the dark. Iodine and succinimide (4) were found in sufficient yields to support the reaction stoichiometry given in eq 1.

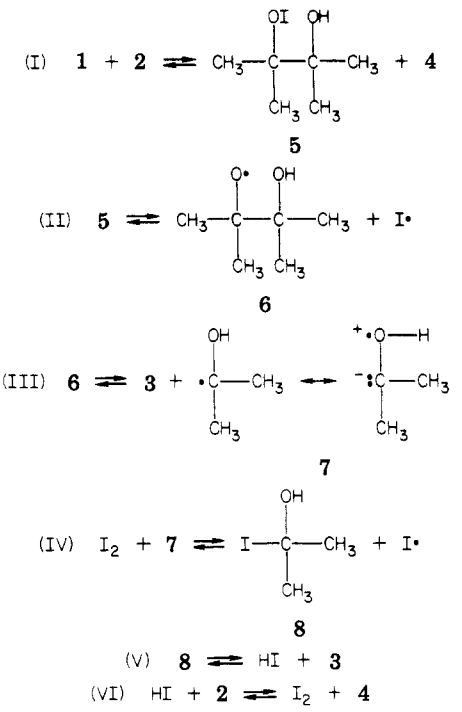


1 2 3 4 (1)

A postulated pathway for the formation of acetone (3) from pinacol 1 is given below by Scheme I. There is much evidence[1,3] for the formation of alkyl hypoiodites from the reaction of alcohols and *N*-iodosuccinimide and the subsequent decomposition of the alkyl hypoiodites to produce alkoxy radicals. Carbon–carbon bond cleavage of the pinacol occurs after the formation of the alkoxy radical 6. The alkoxy radical 6 was previously proposed as an intermediate in the peroxy disulfate oxidation of pinacol in the presence of silver ions.[4] The authors showed the decomposition of the radical 6 as presented in step III. The production of the stable acetone carbonyl system and the resonance-stabilized radical 7 permits the easy cleavage of the carbon–carbon bond. A second molecule of acetone is formed when the iodohydrin 8 eliminates hydrogen iodide. We do not know if the hydrogen iodide loss is ionic or radical in nature. The hydrogen iodide produced in step V rapidly reacts with *N*-iodosuccinimide to give iodine and succinimide. The last step is similar to the well-known reaction of *N*-bromosuccinimide with hydrogen bromide where bromine and succinimide are produced.

Vicinal diols previously have been cleaved[5] successfully by the use of HgO and I_2. Goosen and Lane suggest that

Scheme I



hypoiodites were formed and the fission reaction occurred by a heterolytic and/or a homolytic process. The presence of the mercuric oxide suggests the possibility of an ionic process for the formation of the carbonyl products.

We selected a series of five structurally different 1,2-diols to be oxidized by *N*-iodosuccinimide. We found that when either phenyl groups (benzopinacol, 1,2-diphenyl-1,2-ethanediol, 1-phenyl-1,2-ethanediol) or methyl groups (pinacol, 2,3-butanediol) were attached to the carbon atoms holding the 1,2-diols, excellent yields of products were obtained. Irradiation of the reactions increased the rate at which the diol cleavage occurred.

Table I outlines the oxidative cleavage of five different 1,2-diols with NIS. All reactions were performed in tetrahydrofuran at ambient temperature. Succinimide and iodine were recovered in good yields in all reactions.

The ketone and aldehyde products produced by the cleavage were not oxidized further by the NIS reactant or the iodine product. We believe the NIS reagent can be used successfully in organic synthesis when cleavage of 1,2-diols is required.

Experimental Section

Analyses were performed on a Perkin–Elmer 810 VPC and a Varian Aerograph Model 700 VPC. Liquid chemicals used in reaction mixtures and standard VPC mixtures all had greater than 99.5% purity as determined on the gas chromatograph. The tetrahydrofuran solvent was spectroscopically pure and was used without further purification. VPC analyses of the tetrahydrofuran solutions were done on a 6 ft × 0.25 in. copper column of 7% SE-30 and 3% carbowax 20M. All oxidations were run at ambient temperatures. The *N*-iodosuccinimide was determined to have

(2) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Inc., Menlo Park, CA, pp 353 and 359.

(3) C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experienta*, 17, 475 (1961); K. Heusler, J. Kalvoda, C. Meystre, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 45, 2162 (1962); K. Heusler and J. Kalvoda, *Angew. Chem.*, 76, 518 (1964).

(4) G. D. Menghani and G. V. Bakore, *Bull. Chem. Soc. Jpn*, 41, 2574 (1968); E. S. Huyser and C. G. Love, *J. Org. Chem.*, 37, 649, 851 (1972).

(5) A. Goosen and H. A. H. Lane, *J. Chem. Soc. C*, 383 (1969); A. Goosen and H. A. H. Lane, *J. Chem. Soc. B*, 995 (1969).

98.0–99.5% active iodine and was used as purchased. Irradiation of reaction mixtures was effected with a G.E. Projector Spot 150-W, 130-V tungsten lamp.

Oxidation of 1,2-Diphenyl-1,2-ethanediol. A tetrahydrofuran solution (5 mL) containing 4.00 mmol of pinacol (1,2-dimethyl-1,2-ethanediol) was added to a 10-mL round-bottomed flask. To this solution was added 0.482 g (2.14 mmol) of *N*-iodosuccinimide. The mixture was stirred and samples of the solution were removed periodically. Aluminum foil covered the reaction flask except for the time samples were taken. Reaction times and percent yields were 15 min (22%), 30 min (32%), 1 h (47%), 2 h (62%), and 4 h (96%).

Iodine Determinations. To find the concentration of the iodine produced in the oxidation of 1,2-diols with NIS the completed reactions were added to 25 mL of 1:1 mixture of acetic acid and water. A few drops of concentrated hydrochloric acid was added and the iodine was titrated with a standardized solution of thiosulfate. The iodine was found in 85–90% yield, assuming that 1 mol of iodine is produced from 2 mol of *N*-iodosuccinimide during the reaction.

Succinimide Determination. Succinimide was recovered from the completed reactions by pouring the reactions into diethyl ether and extracting the ether solution with water. The combined water extracts were washed with fresh ether and the water solution was evaporated. Succinimide was recovered in yields of 85–96%.

Acknowledgment. We are grateful to the Research Corporation for financial support of this research.

Registry No. 1, 76-09-5; 2, 516-12-1; benzopinacol, 464-72-2; 1,2-diphenyl-1,2-ethanediol, 492-70-6; 2,3-butanediol, 513-85-9; 1-phenyl-1,2-ethanediol, 93-56-1.

Thermolysis of Dimethyl 3,3-(2,2′-Biphenylyl)-3*H*-pyrazole-4,5-dicarboxylate

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The photolysis of 3*H*-pyrazoles is a well-known preparative method for cyclopropenes.[1] Although some examples of thermal elimination of nitrogen affording cyclopropenes have been reported,[2] the Van Alphen–Hüttel rearrangement[3,4] is usually the predominant reaction pathway, giving 4*H*- and/or 1*H*-pyrazoles according to Scheme I.

Dimethyl 3,3-(2,2′-biphenylyl)-3*H*-pyrazole-4,5-dicarboxylate (1) was reported[4] to rearrange into 1*H*-pyrazole **2** in hot acetic acid and into 1*H*-pyrazole **3** in hot concentrated sulfuric acid (Scheme II). It was also reported[5] that 1 extrudes nitrogen in refluxing CH_2Cl_2, giving the corresponding cyclopropene **4** in 16% yield together with recovery of 1 in 65% yield. Recently, we reported[6] that the thermally labile 3*H*-pyrazoles **5**, the thieno analogues of 1, rearrange into the corresponding 3*H*-pyrazoles **6**

Scheme I

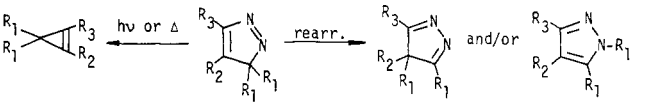
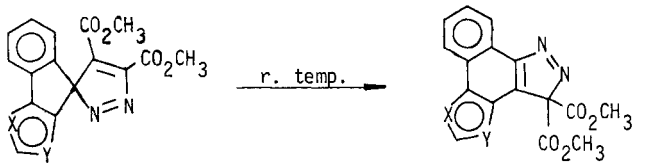


Table I. Pyrolysis of Dimethyl 3,3-(2,2′-Biphenylyl)-3*H*-pyrazole-4,5-dicarboxylate (1)

run	solvent	time, h	product yields, % 3	4	7	8	9
1	toluene	1		35	21	3	
2	benzene	1		70		7	1
3	acetonitrile	1	2	47		17	11
4	methanol	2	4	18		16	14
5	ethanol	1	3	35		16	15

which are formed via Van Alphen–Hüttel rearrangement followed by the migration of an ester group.



5 6

(X=S, Y=CH; X=CH, Y=S)

In this context, we investigated the pyrolysis of 1 in various solvents and the results are given in the present paper.

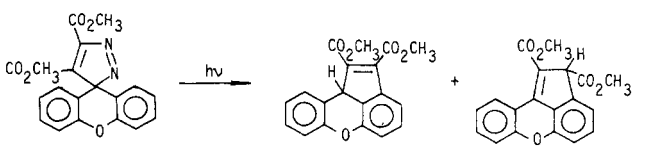
The pyrolysis of 1 was carried out at reflux in the solvent shown in Table I. The initial color of the reaction mixture faded away smoothly. Besides the expected cyclopropene **4**,[5] the compounds, **7–9** and **3**[4] were obtained in the yields summarized in Table I.

Although the structures of **7–9** are present, the cyclopropene formation is predominant in benzene, while the rearrangement into phenanthropyrazoles **3**, **8**, and **9** becomes a significant reaction pathway in polar solvents such as acetonitrile, methanol, and ethanol.

Compound **7** was obtained only in the pyrolysis in toluene. When **4a** was heated at reflux in toluene for 4 h, **7** was obtained in 48% yield. The structure of **7** was deduced as dimethyl 9b*H*-cyclopenteno[1,2,3-*l*,*m*]-fluorene-1,2-dicarboxylate (**7-1**) or its tautomer dimethyl

7-1 7-2

2*H*-cyclopenteno[1,2,3-*l*,*m*]fluorene-1,2-dicarboxylate (**7-2**) on the basis of analytical and spectral data as well as the chemical conversion mentioned above. It was reported[7] that photolysis of the cycloadduct of α-diazoxanthene with dimethyl acetylenedicarboxylate in ether yields **10** and **11**



10 11

(1) See the references cited in: Durr, H.; Gleiter, R. *Angew. Chem.* **1978**, *90*, 591.
(2) (a) Gale, D. M.; Middleton, W. J.; Krespan, C. G. *J. Am. Chem. Soc.* **1966**, *88*, 3617. (b) Komendantov, M. I.; Bekmukhametov, R. R. *Khim. Geterstsikl. Soedin.* **1975**, *79*; *Chem. Abstr.* **1975**, *82*, 111337.
(3) Baumes, R.; Elguero, J.; Jacquier, R.; Tarrago, G. *Tetrahedron Lett.* **1973**, 3781.
(4) Van Alphen, J. *Recl. Trav. Chim. Pays-Bas* **1943**, *62*, 491; *Chem. Abstr.* **1944**, *38*, 1743*q*.
(5) Reimlinger, H. *Chem. Ber.* **1967**, 3097.
(6) Mataka, S.; Takahashi, K.; Ohshima, T.; Tashiro, M. *Chem. Lett.* **1980**, 915.
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