2H-Cyclopenta[*d*]pyridazines. Synthetic, Spectral, and Protonation Studies[1,2]

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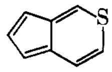
Contribution from the Department of Chemistry, University of Washington, Seattle, Washington 98105. *Received August 1, 1968*

Abstract: 2H-Cyclopenta[*d*]pyridazine (**4**) and the 2-methyl (**5**) and 2-phenyl (**6**) derivatives of this have been prepared by known methods or modifications of these, and **5** has been synthesized by two new routes: the methylation of **4** and the reaction of sodium cyclopentadienide with N-methyl-1,3,4-thiadiazolium iodide. The electronic absorption spectra of **4**, **5**, and **6** were found to be similar to those of azulene, cyclopenta[*c*]thiapyran (**1**), and 2-phenyl-2-pyrindine (**2**). Protonations of **4** and **5** have been shown to occur reversibly on the 5 and 7 positions despite the presence of a π-equivalent ring nitrogen. Compound **5** (pK_a = 1.95) was found to be more basic than azulene or **1** but appreciably less basic than **2**.

Previous studies in these laboratories[4] showed that several π-excessive heteroanalogs of azulene (**1**, **2**, and **3**) display ultraviolet and visible absorption spectra remarkably similar to those of the parent hydrocarbon and that protonation and, for **1** and **2**, electrophilic substitution occur at positions corresponding to the 1 and 3 positions of azulene. It was therefore of interest to investigate the properties of azulene heteroanalogs having two heteroatoms, one π excessive and one π equivalent.[5] With the exception of the azaindolizines,[6] which represent a special case because of the bridgehead nitrogen, little has been reported on the properties of such compounds, although 2H-cyclopenta[*d*]pyridazine (**4**)[7] and derivatives[8] and the 2H-cyclopenta[*c*]pyridazine (**7**)[9] and cyclopenta[*d*]-1,2-oxazine (**8**)[8] systems have been prepared.



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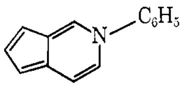

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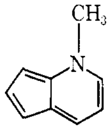

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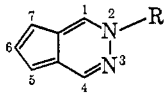
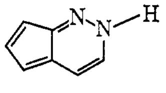


4, R = H
5, R = CH_3
6, R = C_6H_5



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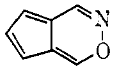

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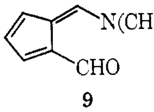
Synthesis. The best route found to **5** and **6** was taken from the approach of Linn and Sharkey[8] in their synthesis of 1,4-diphenyl-2H-cyclopenta[*d*]pyridazine and, later, of Hafner[7] for the synthesis of **4** and **6**. Thus the reaction of methylhydrazine or phenylhydrazine with dimethylamino-2-formylfulvene (**9**)[7] gave **5** (85%) or **6** (74%), respectively (eq 1). Compound **5** was also prepared from **9** by consecutive treatment with hydrazine, alkali, and methyl iodide. Treatment of 6-dimethylamino-2-dimethylimoniumformylfulvene fluoroborate with hydrazine hydrate gave **4** in good (66%) yield.



$$+ \ RNHNH_2 \longrightarrow 5 \text{ or } 6 \qquad (1)$$

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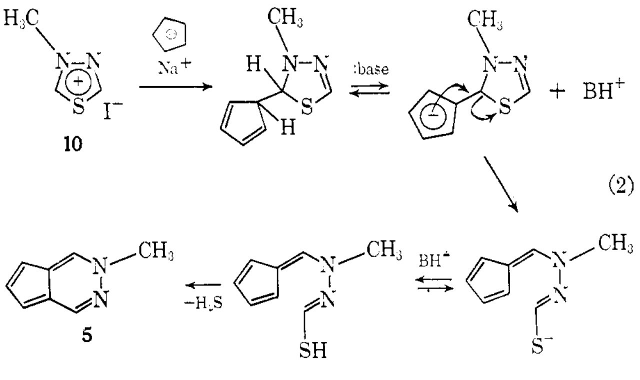
A second route investigated was patterned after the synthesis of azulene from pyridinium[10] and pyrylium[11] salts, and of **1** from an N-methylthiazolium salt.[12] It was reasoned that the N-methyl-1,3,4-thiadiazolium iodide (**10**) would react with the cyclopentadienide ion as shown (eq 2), and a yield of *ca.* 9% of **5** was obtained.



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[1] From the Ph.D. Thesis of David M. Forkey, University of Washington, 1967.

[2] Supported in part by Grant No. GP-5776 from the National Science Foundation. Reported in part at the 1967 Northwest Regional Meeting of the American Chemical Society, Richland, Wash.

[3] 3M Fellow, 1964–1965; National Science Foundation Summer Fellow, 1965.

[4] (a) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Am. Chem. Soc.*, **85**, 3448 (1963); (b) A. G. Anderson, Jr., and W. F. Harrison, *ibid.*, **86**, 708 (1964); (c) A. G. Anderson, Jr., and H. L. Ammon, *Tetrahedron*, **23**, 3601 (1967).

[5] A π-excessive heteroatom provides two electrons and a π-equivalent heteroatom provides one electron to the π structure.

[6] W. L. Mosby, "The Chemistry of Heterocyclic Compounds," Vol. XV, Parts I and II, A. Weissburger, Ed., Interscience Publishers, New York, N. Y., 1961; W. W. Pandler and H. G. Shin, *J. Org. Chem.*, **33**, 1638 (1968); W. W. Pandler and J. E. Kuder, *ibid.*, **32**, 2430 (1967), and references therein.

[7] K. Hafner, K. H. Vöpel, G. Ploss, and C. König, *Ann.*, **661**, 53 (1963).

[8] W. J. Linn and W. H. Sharkey, *J. Am. Chem. Soc.*, **79**, 4970 (1957).

[9] D. J. Cram and R. D. Partos, *ibid.*, **85**, 1273 (1963). Studies on this system are in progress.

[10] K. Hafner, *Angew. Chem.*, **67**, 301 (1955).

[11] K. Hafner, *ibid.*, **69**, 393 (1957); K. Hafner and H. Kaiser, *Ann.*, **618**, 140 (1958).

[12] R. Wagner and R. Mayer, *Z. Chem.*, **1**, 25 (1963).

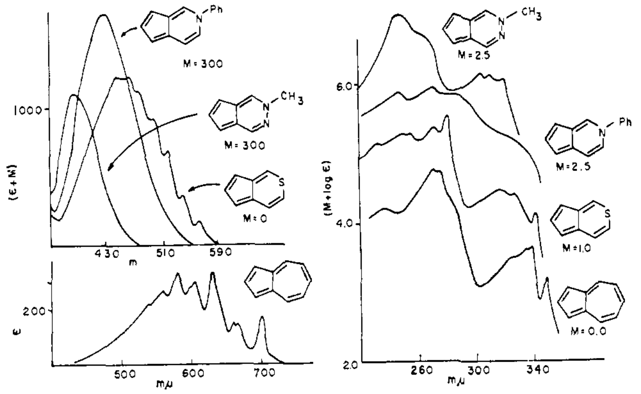


Figure 1. Ultraviolet and visible spectra of 2-methyl-2H-cyclopenta[*d*]pyridazine in anhydrous ether compared with those of azalene, cyclopenta[*c*]thiapyran, and 2-phenyl-2-pyridine in hexane.[4a]

Electronic Spectra. The electronic absorption spectra of **1** and **3** had been found[4] to be strikingly similar in band shapes, number of maxima, and intensities to those of azulene in the ultraviolet and visible regions, and the spectra of **2** were also very similar but displayed less fine structure. Thus the electronic transitions involved appeared to be closely related for all of these iso-π-electronic molecules, but the introduction of the relatively electronegative ring heteroatoms caused a noticeable hypsochromic shift in the longer wavelength band in the ultraviolet and in the visible. The spectra of **5** are shown in Figure 1 along with those of azulene, **1**, **2**, and **3**. The similarities are quite apparent and it is seen that the introduction of the second heteroatom has caused further hypsochromic shifts. The spectral curves obtained with **4** were essentially identical with those of **5** but displaced 4–6 mμ to shorter wavelengths. The spectra of the N-phenyl compound **6** were at still shorter wavelengths and showed little structure. They thus resembled those of the corresponding mononitrogen compound (**2**) but with a hypsochromic displacement of about 30 mμ.

In earlier studies on azulene and 1- and 1,3-disubstituted azulenes, **1** and **2**,[4a,b] it was found that an increase in solvent polarity resulted in a shift of the electronic absorption maxima to shorter wavelengths. For azulene and its derivatives this behavior was compatible with the prediction that the excitation involved a reversal of the dipole, and the properties of the heteroanalogs pointed to a similar photoinduced change in their electronic distribution. This property was observed for **5** (Table I) and again indicates a dipolar ground state with a significant decrease, or possibly reversal, of the dipole in the excited state.

Table I. Effect of Solvent Polarity on the Long-Wavelength Transition of 2-Methyl-2H-cyclopenta[*d*]pyridazine

	Heptane	Ether	Methanol	Water	Formamide
Dielectric constant[a]	1.9	4.3	32.6	78.5	109
λ_{max}, mμ	400	395	391	383	387

[a] N. A. Lange and G. M. Forker, "Handbook of Chemistry," Revised 10th ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1967, pp 1234–1237.

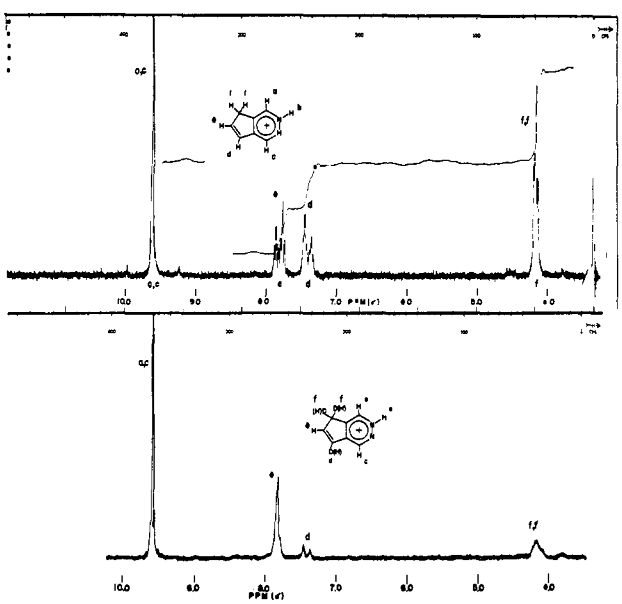
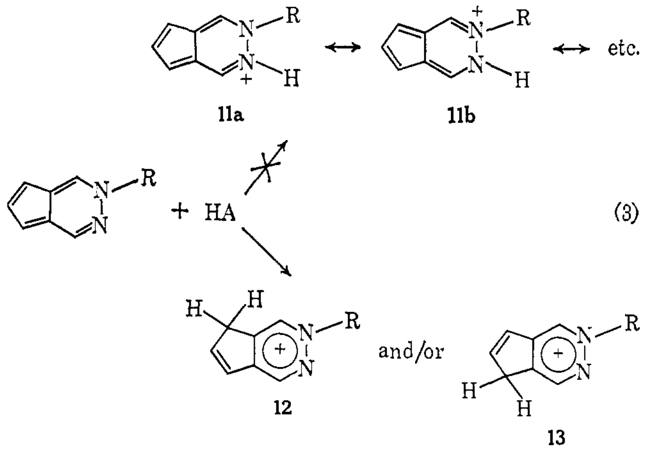


Figure 2. The nmr spectrum of 2H-cyclopenta[*d*]pyridazine in trifluoroacetic acid (upper) and in deuteriotrifluoroacetic acid (lower).

Protonation. Azulene is weakly basic (pK_a = -1.7 in aqueous perchloric acid[13]) and the nmr spectra of its solutions in strong acids and acid-catalyzed hydrogen–deuterium exchange showed that reversible protonation occurs on the 1 position.[4b,14] Similarly, the heteroanalogs **1**, **2**, and **3** were found to protonate on the five-membered ring at positions adjacent to the ring juncture.[4] Compounds **4**, **5**, and **6**, however, possess a ring nitrogen having an unshared electron pair. Spectral data reported for other such ten π-electron systems, *e.g.*, 5-azaazulene,[15] imidazo[1,2-*a*]pyridine,[16] imidazo[1,5-*a*]pyridine,[16] and pyrazolo[1,5-*a*]pyridine,[16] indicate protonation on the π-equivalent nitrogen with the preservation of the aromatic π-electron structure in each case. Contributing to the stability of the N-protonated conjugate acid (**11**) of **4**, **5**, or **6** would be the resonance structure (**11b**) having the charge on the other nitrogen (eq 3).



11a **11b** **12** **13**

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(13) F. A. Long and J. Schulze, *J. Am. Chem. Soc.*, **86**, 327 (1964).

(14) S. S. Danyluk and W. G. Schneider, *Can. J. Chem.*, **40**, 177 (1962); S. S. Danyluk and W. G. Schneider, *J. Am. Chem. Soc.*, **82**, 998 (1960).

(15) K. Hafner and M. Kreuder, *Angew. Chem.*, **73**, 657 (1961).

(16) W. L. F. Armarego, *J. Chem. Soc.*, 4226 (1964).

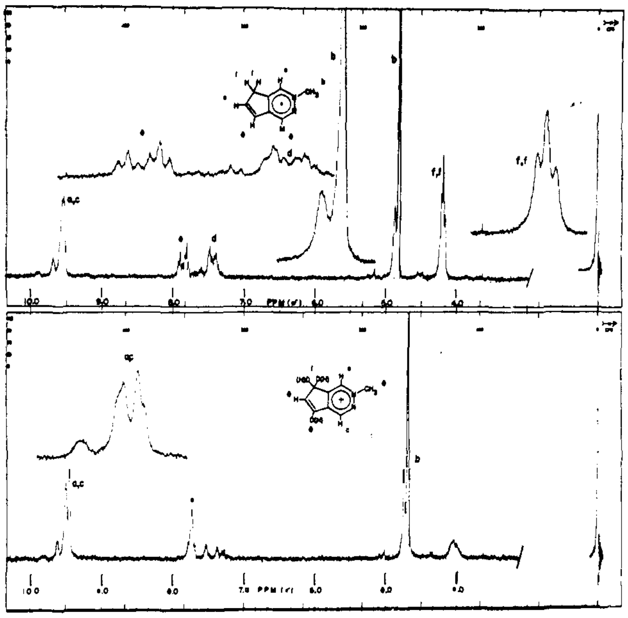
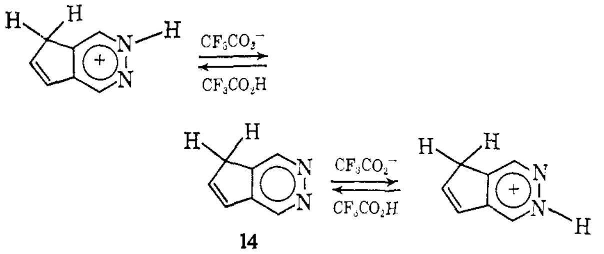


Figure 3. The nmr spectrum of 2-methyl-2H-cyclopenta[*d*]pyridazine in trifluoroacetic acid (upper) and in deuteriotrifluoroacetic acid (lower).

The nmr spectra of solutions of **4** (Figure 2) and **5** (Figure 3) in trifluoroacetic acid indicated protonation on a ring carbon. For **4** the highest field absorption was a triplet (2 H) which was assigned to the methylene hydrogens. As with azulene in this medium,[14] the coupling (J = 1.6 Hz) with the adjacent ring hydrogen was detectable. The vinylic hydrogen absorption occurred as doublets (J = 5.3 Hz) which were further split with the triplet for H-6 being clearly resolved. The remaining singlet (2 H) thus was attributable to super position of the signals for H-1 and H-4. Scanning the spectrum from 0 to 31.6 ppm with integration did not reveal absorption from the N–H, which was therefore not present as an independent peak. This could be the result of equilibration (eq 4) of the conjugate acid species with the tautomeric base (**14**) whereby the N–H hydrogen would appear as a part of the solvent peak. In partially deuterated trifluoroacetic acid exchange occurred at H-5 and H-7 and, consequently, the peak for H-6 became almost a singlet. This result confirmed the protonation assignments and also showed the reversibility of the process. The sharpness and simplicity of these spectra indicated the presence of only one protonated species in appreciable concentration. This could be explained with the argument presented earlier[4b] with the analogous studies of **1** and **2**, *i.e.*, that **12** (R = H) would be expected to be more stable than **13** (R = H). In addition, positions **5** and **7** can become exchanged through tautomeric equilibration of the N–H between the two ring nitrogens (*e.g.*, *via* **14** in acidic media as depicted in eq 4) and if this were sufficiently rapid only one protonated species would be detected.



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In the conjugate acid of compound **5** the N-methyl prevents any interchange of C-5 and C-7 through tautomeric equilibria and the spectrum in trifluoroacetic acid (Figure 3) gave indications of the presence of two species. The characteristics (area, shape, chemical shift, coupling constant) of the major peaks corresponded to those for the conjugate acid of **4** and were so assigned, with the addition of the N-methyl hydrogens at 4.8 ppm and the partial resolution of the signals for H-1 and H-4. Several lesser peaks were attributed to the presence of an isomeric ion: N-methyl at 4.88 ppm, vinylic absorption apparent between the major peaks in this region, and H-1 or H-4 at 9.68 ppm. On the basis that the total area of the signals at 9.68, 9.53, and 9.55 ppm represented two hydrogens and that the signal at 9.68 was caused by only one hydrogen, the ratio of the two species present was determined to be 2.7:1. The corresponding ratio of the N-methyl signals was 2:5 to 1 (with less certainty because of the overlap of the two peaks). Again, the argument given previously[4b] points to **12** (R = CH_3) as the major isomer.[17] The changes in the spectrum obtained in partially deuterated trifluoroacetic acid indicated exchange of both H-5 and H-7 with equilibration within a few minutes.

Qualitative experiments have shown[4b] that azulene and **1** are not appreciably protonated by glacial acetic acid and are thus appreciably weaker bases than acetate ion, whereas **2** is a stronger base than acetate ion. The basicity of the cyclopenta[*d*]pyridazine structure was thus of interest. The pK_a of **5** in aqueous hypochloric acid was determined by the method described by Albert and Serjeant.[18] The value obtained, 1.95 ± 0.03 at 25°, when compared to the basicity found for **2**, probably can be attributed to the inductive effect of the additional, π-equivalent nitrogen. Similar relative basicities are observed for pyridazine and pyridine in the benzenoid series.

Experimental Section

General. Melting points were taken on a Kofler hot stage and are uncorrected. Ultraviolet and visible spectra were recorded on a Cary Model 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model A-60 spectrometer in δ (parts per million) in reference to internal tetramethylsilane unless otherwise indicated. Reagent grade trifluoroacetic acid was used without additional purification. Deuteriotrifluoroacetic acid was prepared by the slow addition of an equivalent amount of fresh trifluoroacetic anhydride to 99.5% deuterium oxide.

2H-Cyclopenta[*d*]pyridazine (4). In the manner described by Hafner, *et al.*,[7] from 0.99 g (3.75 mmol) of 6-dimethylamino-2-dimethyliminiumformylfulvene fluoroborate, 0.19 ml (3.87 mmol) of hydrazine hydrate, and 30 ml of methanol was obtained 0.267 g (66%) of **4** as a yellow crystalline solid. The lack of a definitive melting point and the absorption spectra agreed with the proper-

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[17] The ratio of N-methyl to methylene areas showed that both species present were C-protonated, and that the minor species was not the N-protonated ion.

[18] A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases; A Laboratory Manual," Methuen & Co., Ltd., London, 1962, pp 69–92.

ties reported.[7] An nmr spectrum (DMSO) with sodium 3-(trimethylsilyl)propanesulfonate as an internal standard showed δ 6.84 (d, 2, J = 3.6 Hz), 7.35 (t, 1, J = 3.6 Hz), and 8.85 ppm (s, 2).

2-Methyl-2H-cyclopenta[*d*]pyridazine (5). Method A. A mixture of 1.29 g (8.66 mmol) of 2-formyl-6-dimethylaminofulvene (**9**),[7] 0.45 ml (14 mmol) of methylhydrazine, and 15 ml of absolute ethanol was swirled to effect solution and then allowed to stand at room temperature. A yellow precipitate formed (10 min) and after 8 hr the collected precipitate together with the residue from the filtrate (solvent removal under reduced pressure with a rotary evaporator) was sublimed twice at 45° (*ca.* 10^{-5} mm) giving 0.93 g (85%) of **5** as a yellow solid: mp 128.8–129.0°; uv max (anhydrous ether) 248 (29,400), 253 (28,900), 268 (15,400), 307 (sh, 12,200), 312 (3810), 317 (3610), 324 (3310), and 395 mμ (ϵ 821); nmr (CH_2Cl_2) δ 3.95 (s, 3), 6.78 (d, 2, J = 3.4 Hz), 7.38 (t, 1, J = 3.4 Hz), 8.28 (poorly resolved t, 1, J = 0.8 Hz), and 8.67 ppm (broad s, 1). The ir ($HCCl_3$) was recorded.

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.28; H, 6.42; N, 21.12.

Method B. To 150 ml of methanol (freshly distilled from magnesium methoxide) in a 500-ml, three-necked flask containing 0.415 g (7.69 mmol) of sodium methoxide under dry nitrogen was added 0.5 ml (6.05 mmol) of freshly cracked cyclopentadiene and, after 10 min, 0.949 g (4.16 mmol) of vacuum-dried N-methyl-1,3,4-thiadiazolium iodide (**10**). The color of the solution became golden. The mixture was refluxed for 1.5 hr and then steam distilled (Eastman condenser) for 1 hr. The yellow distillate was extracted with dichloromethane until the extracts were colorless. The residue left after removal of the solvent from the combined, dried ($MgSO_4$) extracts was extracted with boiling heptane. Evaporation of the heptane solution and sublimation (45° (*ca.* 10^{-5} mm)) gave 47.7 mg (8.7%) of **5**, mp 129–130°, identical (uv, ir) with the product from A.

Method C. A mixture of 1.8 g (11.9 mmol) of **9**,[7] 0.58 ml (11.7 mmol) of hydrazine hydrate, and 30 ml of absolute ethanol was refluxed under nitrogen for 2.25 hr, allowed to cool, and was then treated in order with 1.7 ml of 25% sodium hydroxide and 2 ml of methyl iodide. After 4 hr, the solvent was removed (rotary evaporator, aspirator) and the residue was extracted several times with ether under reflux (1 hr). The residue from the combined ether extracts was extracted with several 150-ml portions of *n*-hexane under reflux (1 hr). Sublimation (45° (*ca.* 10^{-5} mm)) of the residue from the *n*-hexane solutions gave 428 mg (27%) of **5** identical (melting point, uv, ir) with the product from A.

2-Phenyl-2H-cyclopenta[*d*]pyridazine (6). The crude product, prepared as described by Hafner, *et al.*,[7] was chromatographed on a short silica gel column with dichloromethane as the eluent. The material obtained was crystallized from absolute ethanol and then sublimed to give **6** as a yellow solid: mp 167–168° (lit.[7] mp 161–162°); uv max (anhydrous ether) 248 (22,400), 258 (sh, 19,800), 287 (28,400), 318 (sh, 7330), and 408 mμ (ϵ 2850); nmr (CH_2Cl_2) δ 6.83 (pair of doublets, J = 4 Hz, subsplit into triplets, J = 1 Hz, 1), 7.36–7.92 (m, 6), and 8.88 ppm (m, 2).

N-Methyl-1,3,4-thiadiazolium Iodide (10). The red solution formed when a mixture of 3.09 g (36 mmol) of 1,3,4-thiadiazole,[19] 2.5 ml of methyl iodide, and 30 ml of dry dimethylformamide was heated on a steam cone under reflux for 45 min was poured into a beaker and 400 ml of dry ether was added. After filtration, the collected precipitate was washed with ether and vacuum dried (removing an odoriferous impurity) giving 6.67 g (81.5%) of **10** as a light yellow solid, mp 230° dec (lit.[20] 241°), which was used without further purification.

pK_a of 2-Methyl-2H-cyclopenta[*d*]pyridazine (5). A 1.40×10^{-3} M stock solution of **5** was prepared by vigorous stirring of 18.5 mg of **5** in 100 ml of distilled water for 3 hr. Individual test solutions were prepared by diluting 10-ml aliquots to 25 ml (5.6×10^{-4} M in **5**) with hydrochloric acid of different concentrations such that different solutions having pHs of 1.50–2.72 were obtained as determined on a calibrated (pH 4.01 with phthalate buffer) Beckman Research pH meter at 24–25°. The method used for the pK_a determinations was that described by Albert and Serjeant.[18] Optical densities at 380 mμ were read at 25.0 ± 0.1° on a Beckman Model DU spectrophotometer fitted with a Gifford Absorbance Indicator Model 2000. Maximum slit widths were 0.14 mm. The value of d_m[18] was determined in aqueous sodium formate solution at pH 7.38 and d_i[18] was determined in *ca.* 7.2 N hydrochloric acid. The six pK_a values obtained ranged from 1.92 to 1.98 and the average was 1.95.

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[19] K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 1124 (1961).

[20] J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Ber.*, **89**, 1534 (1957)

Chromic Acid Oxidation of Isopropyl Alcohol. Preoxidation Equilibria[1a]

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*Contribution from the Department of Chemistry, Yale University,
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Abstract: The rate and equilibrium constants for the rapid reaction of chromium(VI) with isopropyl alcohol in 97% acetic acid to give the mono- and diesters have been determined by following the change in absorbance with time. The ionization constant of acetochromic acid and the monomer–dimer equilibrium constant for chromium(VI) also have been determined. The results are compared with those for the reaction of *t*-butyl alcohol.

The chromic acid oxidation of alcohols has been examined by many workers.[2] However, the details of the sequence of steps are still not well understood. As a result of the work of Westheimer and his coworkers,[3] it is known that a chromium(VI) ester is an intermediate in the reaction, that carbon–hydrogen bond cleavage is rate determining, and that chromium(IV) is the product of the first step of the reaction. The induced oxidation experiments of Watanabe and West-

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[1] (a) This investigation was supported by the National Science Foundation. (b) Organic Chemistry Institute, University of Göttingen.

[2] The subject has been reviewed by K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965, p 69 ff.

[3] F. Westheimer and A. Novick, *J. Chem. Phys.*, **11**, 506 (1943); F. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949); W. Watanabe and F. H. Westheimer, *J. Chem. Phys.*, **17**, 61 (1949); J. Roček, F. H. Westheimer, A. Eschenmoser, L. Moldoványi, and J. Schreiber, *Helv. Chim. Acta*, **45**, 2554 (1962).