4-one (8).—To 100 mg (0.437 mmol) of **7** and in 10 ml of absolute methanol was added 17 mg (0.437 mmol) of sodium borohydride and 1.0 mg of sodium hydroxide and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between 50 ml of ethyl acetate and 100 ml of water. The water layer was extracted with additional ethyl acetate (three 25-ml portions). The combined ethyl acetate fractions were washed with water and saturated brine solution and dried ($MgSO_4$). Removal of the solvent afforded 45 mg (22.3% of theory) of a colorless oil: λ_{max}^{neat} 2.94, 3.38, 3.44, 6.05, 6.80, 7.00, 7.23, 7.70, 7.87, 8.05, 8.47, 9.10, 9.35, 9.50, 9.80, 10.02, 13.30, 14.10, 14.60, 15.30, and 15.80 μ; $\delta_{TMS}^{CDCl_3}$ 1.43 (s, CH_3), 2.43 (m, C-5 CH_2), 2.67 (s, $CH_2C(=O)N$), 2.95 (s, NCH_3), 3.50 (q, CHN, J = 4 and 10 Hz), 4.62 (q, CHO, J = 4 and 10 Hz), and 7.25 (m, 4 aromatic protons).

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-1,4-dione (5).—Bromination of ketone amide **1** was more efficiently performed using a mixture of benzene and tetrahydrofuran as cosolvents. To a solution of 1.55 g (5.0 mmol) of **1** in 100 ml of benzene and 25 ml of tetrahydrofuran was added over 30 min a solution of 850 mg (5.3 mmol) of bromine in 10 ml of tetrahydrofuran. After the addition was complete and the bromine color disappeared, the solution was diluted with ethyl acetate, washed with 5% aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$), and evaporated affording crude α-bromo ketone **3**, 1.05 g (67% of theory), identical spectrally with the product obtained from the acetic acid method.

To a solution of sodium methoxide in methanol prepared by adding 0.92 g (0.004 g-atom) of sodium to 25 ml of absolute methanol was added 0.825 g (2.3 mmol) of crude α-bromo ketone **3** in 10 ml of methanol. The mixture was refluxed for 2 hr during which time sodium bromide precipitated. The mixture was partitioned between water and ethyl acetate and extracted with several portions of ethyl acetate. The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), and evaporated affording a brown oil which was chromatographed on 40 g of silica gel eluted with chloroform. The benzazocinedione (**5**) was obtained in fractions 5–8 (100-ml fractions). A total of 350 mg (67% of theory), mp 163–164° (benzene–petroleum ether), was collected: λ_{max}^{KBr} 3.38, 3.42, 3.48, 5.92, 6.05, 6.25, 6.85, 7.18, 7.41, 7.56, 7.71, 7.83, 8.07, 8.59, 9.03, 9.48, 10.05, 10.30, 12.23, 12.78, 13.03, 13.74, and 14.08; $\delta_{TMS}^{CDCl_3}$ 1.52 (s, CCH_3), 2.39 (m, $W_h \simeq 6$ Hz, CH_2CH), 2.55 (s, broadened, $CH_2C(=O)N$), 2.95 (s, NCH_3), 3.97 (q, distorted, J = 4 and 3 Hz, CHN), 7.45 (m, 3 aromatic protons), 8.02 (d, distorted, 1 aromatic proton).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.61; H, 6.64; N, 6.38.

Deuterium exchange was performed in a manner similar to that described for exchange on **7**. Only the signal at δ 2.55 disappeared.

Registry No.—**1,** 27093-03-4; **1** *N*-hydroxysuccinimide ester, 27093-04-5; **3,** 27093-05-6; **5,** 27093-06-7; **7,** 27141-07-7; **8,** 27093-07-8; 4-methyl-1-tetralone-4-acetic acid, 27093-08-9.

Acknowledgment.—This investigation was supported by Grant GM-13,782 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and by the State of Washington Initiative 171 Funds for Research in Biology and Medicine.

Synthesis of 2-Acetyl-1,4,5,6-tetrahydropyridine, a Constituent of Bread Aroma

G. Büchi* and H. Wüest

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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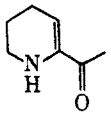
Of the aromas associated with man's food, that of baked bread is one of the most perishable. Efforts to stabilize the taste of fresh bread have met with little success mainly because the compounds responsible for this unique aroma remained unknown. Recent analysis of a methylene chloride extract of freshly baked bread led to the isolation of a compound with an overpowering odor of crackers.[1] This aroma principle was identical with a substance produced in low yield by heating proline with dihydroxyacetone[2] or glycerol,[1] and structural studies suggested the presence of 2-acetyl-1,4,5,6-tetrahydropyridine (**1**).[3] To confirm this and to further evaluate the organoleptic properties of this important compound, we have developed a rational synthesis.

Hydrogenation of 2-acetylpyridine (**3**) over a rhodium-on-alumina catalyst yielded 2-(1-hydroxyethyl)-piperidine (**4**) in 78% yield.[4] Oxidation of the alcohol **4** with Celite suspended silver carbonate[5] in benzene solution did not give the anticipated saturated ketone but the desired enamino ketone **1** directly. This one-step procedure should be useful for the preparation of other α-amino-α,β-unsaturated ketones from 1,2-amino alcohols. The nuclear magnetic resonance spectrum of synthetic material was identical with that of the natural bread aroma constituent,[3] but a series of resonances previously[3] attributed to decomposition products are in fact caused by the imino tautomer **2** (see Experimental Section). Oxidation of the amino alcohol **4** for a short period of time gave a mixture of tautomers with ultraviolet absorption (pentane) at 312 nm (ϵ 2020) judged by nmr analysis to contain approximately two-thirds of the imine **2** and one-third of the enamine **1**. Further heating in benzene produced a new mixture with ϵ 3360 containing approximately two-thirds of the enamine **1** and one-third of the imine **2**. Consequently imine **2** is the initial product of oxidation while the enamine **1** represents the more stable tautomer. Infrared spectra confirmed the identities of synthetic and natural material and are in full accord with the presence of tautomers. Mixtures rich in imine form show intense absorption at 1695 cm^{-1}, while the enamine tautomer gives rise to bands at 1670 and 1650 cm^{-1}. Synthetic 2-acetyl-1,4,5,6-tetrahydropyridine (**1**) has the organoleptic properties characteristic of the bread constituent. In agreement with earlier findings the substance is exceptionally sensitive to air, but we have stored the corresponding



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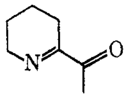

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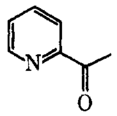

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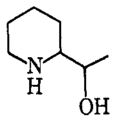

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hydrochloride with little change in a sealed ampoule for three months.

Experimental Section

Microanalyses were performed in the laboratory of Dr. F. Gautschi, Firmenich et Cie., Geneva. Boiling points are uncorrected. Vapor phase chromatography was performed on a F & M 720 instrument. The following spectrometers were used: nmr, Varian T-60 and HA-100; ir, Perkin-Elmer Models 237 and 247; uv, Cary Model 14; mass spectrum, Hitachi RMU6D.

Hydrogenation of 2-Acetylpyridine (3).—A solution of 8.4 g (69 mmol) of 2-acetylpyridine in 75 ml of absolute ethanol was hydrogenated in the presence of 1.5 g of 5% rhodium on alumina. Absorption was complete after uptake of 6490 cm^3 of H_2 [22° (760 mm), 3.9 equiv]. The mixture was filtered through Celite, evaporated, and distilled to give 6.94 g (78%) of alcohol **4**: bp 48° (0.1 mm) [lit.[6] bp 101–102° (23 mm)]; ir ($CHCl_3$) 2400–3650 cm^{-1}; nmr (CCl_4) δ 1.0 (3 H, d, J = 7 Hz), 0.8–3.2 (9 H, m), 3.3 (1 H, s, disappears on exchange with D_2O), 3.4 (1 H, s, disappears on exchange with D_2O), 3.4 (1 H, m).

Oxidation of Alcohol 4.—A stirred suspension of silver carbonate on Celite (prepared[5] from 50 g of Celite, 60 g of silver nitrate, and 37 g of sodium bicarbonate), 7.0 g (54 mmol) of alcohol **4**, and 400 ml of benzene was heated at reflux for 20 hr under nitrogen. Filtration, evaporation *in vacuo*, and distillation afforded 3.84 g (57%) of approximately a 2:1 mixture of ketones **1** and **2** (nmr): bp 35–40° (0.1 mm); vpc (2-ft TCEP and 6-ft silicon gum rubber) 1 peak; ir ($CHCl_3$) 1650, 1670, 1695, 3430 cm^{-1}; uv (EtOH) 308 nm (ϵ 2450); uv (pentane) 312 nm (ϵ 3360); nmr (100 MHz, C_6D_6) enamine tautomer δ 1.5 (2 H, m), 1.9 (2 H, m), 2.0 (3 H, s), 2.8 (2 H, t, J = 2.5 Hz), 4.3 (1 H, broad, disappears on exchange with D_2O), 5.2 (1 H, t, J = 2.5 Hz); nmr imine tautomer δ 1.2 (4 H, m), 2.2 (2 H, m), 2.3 (3 H, s), 3.4 (2 H, m); mass spectrum (70 eV) m/e (rel intensity) 125 (58), 43 (100).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 67.25; H, 9.29.

Hydrochloride of 1 and 2.—To an ice-cold solution of 603 mg (4.8 mmol) of the amines **1** and **2** in 20 ml of dry ether was added dropwise a slight excess of HCl in dry ether. The solid was filtered, washed with ether, and dried in a desiccator at 10 mm to give 664 mg (86%) of the hydrochloride: mp 112–119°; ir ($CHCl_3$) 1675, 1690, 1735, 2000–3600 cm^{-1}.

Regeneration of the Free Base.—A mixture of 427 mg (2.64 mmol) of the hydrochloride, 20 ml of methylene chloride, and 2 g of sodium bicarbonate was stirred at room temperature for 20 min. Filtration followed by evaporation and distillation of the residue yielded 217 mg (66%) of the amines **1** and **2**, bp ~35° (0.1 mm).

Registry No.—**1**, 25343-57-1; **1** HCl, 27300-26-1; **2**, 27300-27-2; **2** HCl, 27300-28-3.

Acknowledgment.—We are indebted to Firmenich et Cie., Geneva, for generous financial support.

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Further Evidence for the Validity of the Overlap Indicator Method. Correlation of pK_a's of Corresponding Aniline and 2-Nitroaniline Derivatives

MORTIMER J. KAMLET* AND RICHARD R. MINESINGER

Advanced Chemistry Division, U. S. Naval Ordnance Laboratory, White Oak, Silver Spring, Maryland 20910

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Katritzky and coworkers[1] and Arnett and coworkers[2,3] have recently reported that good linear enthalpy–free-energy correlations serve to support the validity of the Hammett overlap indicator method[4] for estimating pK_a's of very weak bases. In the former instance,[1] ionization constants of a number of aniline indicators were determined over a range of temperatures,[5] and ΔF values were shown to be linear with enthalpies of ionization. The latter reports[2,3] involved comparisons of pK_a's for a variety of amine types with partial molal heats of transfer from carbon tetrachloride or tetrachloroethane to fluorosulfuric or sulfuric acid solvents.

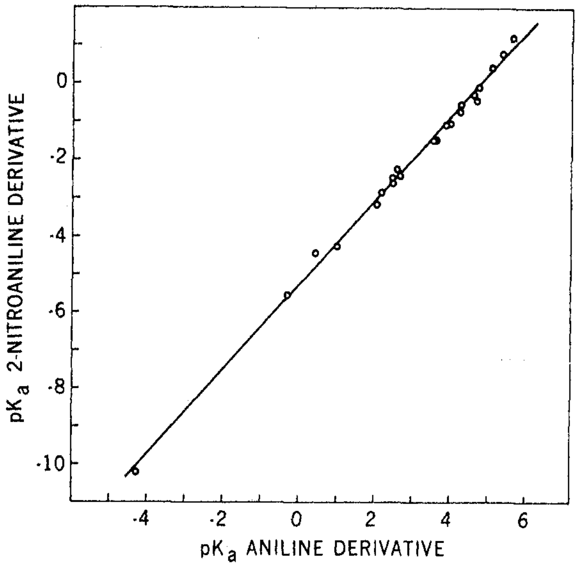

Figure 1.—Variation in pK_a's of 2-nitroaniline derivatives with those of correspondingly substituted anilines.

We wish now to describe an extended pK_a range linear free-energy correlation which serves as additional supporting evidence to confirm the reliability of more recent H_0 acidity function extrapolations for primary aniline indicators and therefore the overlap indicator method in general. Our evidence differs in nature from Arnett's and Katritzky's in that they compared related thermodynamic properties of same materials, whereas we correlate same properties of related materials.[6]

We have compared literature values for pK_a's of ortho- meta-, para-, and polysubstituted anilines (reaction series A) with those of corresponding 2- (or 6-) nitroaniline derivatives (series B) in water at 25 ± 3°; the data are listed in Table I. A plot (Figure 1) shows excellent linear correlation between the two series; least-squares analysis leads to the equation

$$\text{p}K_a\ (\text{series B}) = -5.32 + 1.11\ \text{p}K_a\ (\text{series A}) \qquad (1)$$

$$r\ (\text{correlation coefficient}) = 0.998$$
$$s\ (\text{standard deviation}) = 0.16\ \text{p}K\ \text{unit}$$

For the more basic compounds, the pK_a determinations in both series were carried out in standard buffer solutions; at intermediate basicities, the pK_a's in

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