needles of mp 88.4–89.6°. The benzamide was gas chromatographically pure and had $[\alpha]^{27}D$ −15.6° (95% ethanol).

**Optical Purity Considerations.**—The optically active amine was regenerated by treatment of the (−)-benzamide with polyphosphoric acid. Recovered (*R*)-(−)-*sec*-butylamine was pure by vpc and had $[\alpha]^{27}D$ −3.83° (neat). Since the α-pinene utilized in the hydroboration reaction had an optical purity of 68%,[8] correction of the specific rotation of the (−)-amine for optically pure α-pinene gives $[\alpha]^{27}D$ −5.63° (neat). The optical activity data, corrected in this manner, are summarized in Table I.

TABLE I
OPTICAL ROTATION AND OPTICAL PURITY DATA

| | $[\alpha]D$, deg, optically pure material | *Via* hydroboration (present work), corrected for α-pinene, $[\alpha]D$, deg | % optical purity |
|---|---|---|---|
| *sec*-Butylamine | 7.44[a] | −5.63 | 76 |
| N-(*sec*-Butyl)benzamide | 30.65[b] | −23.0 | 75 |
| *sec*-Butyl alcohol | 13.5[c] | −10.3 | 76 |

[a] L. G. Thome, *Ber.*, **36**, 582 (1903). [b] N. J. Leonard and E. W. Nommensen, *J. Am. Chem. Soc.*, **71**, 2808 (1949). [c] P. J. Leroux and H. J. Lucas, *ibid.*, **73**, 41 (1951).

**Registry No.**—(*R*)-(−)-*sec*-Butylamine, 13250-12-9; (*R*)-(−)-N-(*sec*-butyl)benzamide, 13250-13-0.

**Acknowledgment.**—This work was supported in part by U. S. Public Health Service Grant GM 14068 from the National Institute of General Medical Sciences. We are grateful to Mr. R. Einhorn for preliminary experiments and to Professor C. E. Myers for a helpful discussion.

(8) The highest reported rotation for α-pinene is $[\alpha]D$ 51.1°: F. H. Thurber and R. C. Thielke, *J. Am. Chem. Soc.*, **53**, 1030 (1931).

## Protonation Effects on Cyclic Amine Nucleophilicities. Piperazine[1a]

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The over-all hydrolysis of methyl *o*-formylbenzoate (MOFB) in aqueous solution, reported in detail by Bender and co-workers,[2] has been utilized in this study to observe the effect of protonation of a single amine group on the nucleophilicity of the cyclic diamine piperazine. In particular, we have studied the kinetics of the hydrolysis using hydroxide ion, piperazine, piperazinium ion, and, to a lesser extent, morpholine as nucleophiles. The last three contain the groups >NH, $>NH_2^+$, and –O–, respectively, γ to the site of nucleophilic activity.

For runs in aqueous piperazine solutions, the over-all reaction may be expressed by eq 1 where OFBA is *o*-formylbenzoic acid and P and $PH^+$ are piperazine and the piperazinium ion, respectively. (The equivalent expression for aqueous morpholine solutions involves $k_M[M]$ in place of $k_P[P]$; $k_{PH}[PH^+]$ does not appear.) The disappearance of MOFB is given by

$$\text{MOFB} \xrightarrow[k_P[P]]{k_{OH}[OH^-]} \text{OFBA} \qquad (1)$$

$$\frac{-d[MOFB]}{dt} = (k_{OH}[OH^-] + k_P[P] + k_{PH}[PH^+])[MOFB] \qquad (2)$$

Equation 2 reduces to eq 3 when piperazine is present

$$\frac{-d[MOFB]}{dt} = k_0[MOFB] \qquad (3)$$

in sufficient excess ([piperazine]/[MOFB]) > 5) so as to remain essentially constant during a run. In this case $k_0$ is given by eq 4 where $k_{OH}$, $k_P$, and $k_{PH}$ are the second-order rate constants for catalysis by the subscript species and $k_0$ is the observed pseudo-first-order constant.

$$k_0 = k_{OH}[OH^-] + k_P[P] + k_{PH}[PH^+] \qquad (4)$$

The concentration of the three catalytic species will be dependent upon the pH of the solution and the total concentration of piperazine, $[P]_T$, given by eq 5.

$$[P]_T = [P] + [PH^+] + [PH_2^{2+}] \qquad (5)$$

Substitution of this quantity, along with $K_w$, the autoprotolysis constant for water, and the first and second ionization constants for piperazine, $K_1$ and $K_2$, into eq 4 yields

$$k_0 = \frac{k_{OH}K_w}{[H^+]} + \left[\frac{k_P}{f_P} + \frac{k_{PH}}{f_{PH}}\right][P]_T \qquad (6)$$

where

$$f_P = 1 + \frac{[H^+]}{K_2} + \frac{[H^+]^2}{K_1K_2} \qquad (7)$$

and

$$f_{PH} = \frac{K_2}{[H^+]} + 1 + \frac{[H^+]}{K_1} \qquad (8)$$

Two types of data were obtained at each temperature, one set at constant pH and variable $[P]_T$ and the other at constant $[P]_T$ and variable pH. For the data at constant pH and variable $[P]_T$, plots of $k_0$ *vs.* $[P]_T$ gave good straight lines as required by eq 6 with slopes equal to $[(k_P/f_P) + (k_{PH}/f_{PH})]$ and intercepts of $k_{OH}K_w/[H^+]$. (The values of $k_{OH}$ obtained from these intercepts were the same as those obtained from runs in which piperazine was absent.)

Simultaneous solution of eq 6, using the slopes of the above plots obtained at several pH's, gave the values of $k_P$ and $k_{PH}$ recorded in Table I. The factors $f_P$ and $f_{PH}$ were calculated from eq 7 and 8 using the $pK_a$ values for piperazine of Paoletti, *et al.*[3] The data obtained at constant $[P]_T$ and variable pH were used to assess the error in the rate constants reported in Table I.

It was observed that the rate constants obtained in this fashion obey the relation $k_P/k_{PH} = K_1/K_2$ at all temperatures. An examination of eq 6 showed that this result is not unexpected since $f_P/f_{PH} = [H^+]/K_2$ and

(1) (a) Supported by Grant No. P-272 from the American Cancer Society. (b) To whom all correspondence should be addressed at the Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221.

(2) (a) M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962); (b) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *ibid.*, **87**, 4545 (1965).

(3) P. Paoletti, M. Ciampolini, and A. Vacca, *J. Phys. Chem.*, **67**, 1065 (1963).

TABLE I

SECOND-ORDER RATE CONSTANTS[a] FOR THE HYDROLYSIS OF MOFB ($\mu$ = 0.2) AND THE p$K_a$ VALUES FOR PIPERAZINE

| $T$, °C | $k_{OH} \times 10^{-3}$ | $k_P$[b] | $k_{PH}$[c] $\times 10^3$ | p$K_{a1}$[d] | p$K_{a2}$[d] |
|---|---|---|---|---|---|
| 0 | 1.3 ± 0.2 | 21.2 | 1.0 | 6.078 | 10.403 |
| 15 | 1.8 ± 0.1 | 25.6 | 1.6 | 5.780 | 9.978 |
| 25 | 2.1 ± 0.2[e] | 27.3 | 2.1 | 5.600 | 9.720 |
| 35 | 2.4 ± 0.3 | 31.2 | 2.8 | 5.430 | 9.478 |

[a] See text, eq 4, units of $M^{-1}$ sec$^{-1}$. [b] Estimated error ±15–25%. [c] Estimated error < a factor of 2. [d] See ref 3. [e] Compared with 2.02 ± 0.08 × $10^3$ calculated from data in ref 2b over the same pH range and $\mu$ = 0.1.

substitution of this result into the slope of eq 6, after elimination of terms which are negligible below pH 9, yields the expression $k_{PH} = k_P K_2/K_1$.

In addition to runs with hydroxide ion, piperazine, and the piperazinium ion as nucleophiles, several rate determinations were made using morpholine. The second-order rate constant at 25° ($\mu$ = 0.2) was 4.10 × $10^{-2}$ $M^{-1}$ sec$^{-1}$. Also, runs were made using 0.2$M$ piperidine (p$K_a$ = 11.2,[4] 25°) as a nucleophile at pH 7. As expected, the rate was identical with that observed in the absence of piperidine since the concentration of unprotonated amine at pH 7 is negligibly small.

The specificity of the hydroxide ion as a nucleophile was verified in runs in which the total buffer concentrations were varied at constant pH with no differences in the rates observed. Runs in which the ionic strength was varied over a 20-fold range (0.1–2.0) gave hydrolysis rate constants which varied only slightly (±4%) over the entire range.

The thermodynamic functions of activation for the process described by eq 1, recorded in Table II, were determined in the usual fashion.

TABLE II

THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR THE HYDROLYSIS OF MOFB, CATALYZED BY HYDROXIDE ION, PIPERAZINE, AND PIPERAZINIUM ION[a]

| Nucleophile | $\Delta H^{\pm}$, kcal/mole | $\Delta G^{\pm}$, kcal/mole | $\Delta S^{\pm}$, eu |
|---|---|---|---|
| Hydroxide ion | +2.3 ± 0.2 | +12.9 ± 0.0 | −35.6 ± 0.6 |
| Piperazine | +1.3 ± 0.1 | +15.5 ± 0.0 | −47.6 ± 0.3 |
| Piperazinium ion | +3.8 ± 0.4 | +21.1 ± 0.5 | −58 ± 3 |

[a] $\Delta G^{\pm}$ and $\Delta S^{\pm}$ calculated at 25°.

The kinetics of the over-all hydrolysis of MOFB to OFBA in aqueous piperazine solution can be explained on the basis of catalysis by hydroxide ion, piperazine, and the piperazinium ion. A comparison of the catalytic constants for hydroxide ion and piperazine ($k_{OH}/k_P$) shows that hydroxide ion is about 100 times more effective as a catalyst than piperazine and approximately $10^6$ more effective than the piperazinium ion. Morpholine is about three orders of magnitude less effective than piperazine as a nucleophile ($k_P/k_M$ = $27.3/4.10 \times 10^{-2}$). The direction of this latter behavior is expected on the basis of the comparative base strengths. (At 25°, p$K_{a2}$ for piperazine is 9.72,[3] while p$K_a$ for morpholine is 8.36.[4]) However, the magnitude is somewhat surprising and reflects more than the small statistical factor for the double-ended nitrogen base. In terms of inductive effects, we may conclude that substitution at the $\gamma$ position affects the rate, NH > O > $NH_2^+$.

Piperazine and piperazinium ion catalyses follow the simple form of the Brønsted catalysis law, log $k_B$ = log $K_B$ + 5.72, where $k_B$ is the second-order catalysis constant and $K_B$ the constant for the association of piperazine, or the piperazinium ion, with water. A similar expression for morpholine gives a constant term of 6.97. The fact that the rate constants for piperazine catalysis can be correlated with its ionization constants is evidence that no major changes in the mode of addition of the nucleophile to MOFB occur upon protonation of the nucleophile.

In catalysis reactions of the type described in this work, it is important to bear in mind that over-all nucleophilic effectiveness is a function of both the nucleophilicity and concentration of the catalyst. A guide to the relative efficacy of a catalyst may be found by comparing the pH at which a given concentration of nucleophile and the hydroxide ion contribute equally to the over-all reaction rate. At 25°, hydroxide ion is isocatalytic with piperazine at pH 11.4, with piperazinium ion at pH 7.3 in solutions 0.2 $M$ in total piperazine, and with morpholine at pH 8.2 in 0.2 $M$ morpholine. Thus morpholine is more like the piperazinium ion in over-all effect than like piperazine as one would normally predict from a comparison of p$K_a$ values. It is interesting to note that the "isocatalytic" values for piperazine and piperazinium ion are almost identical with the concentration-independent $H$ values of the Edwards equation,[5] but differ appreciably in the case of morpholine. More work is contemplated in this area.

### Experimental Section

**Materials.**—Eastman practical grade piperazine was sublimed under reduced pressure: mp 108–109.5° (lit.[6] mp 104.4–107.7°). *o*-Formylbenzoic acid (phthalaldehydic acid) was prepared in 40% yield from naphthalene and alkaline potassium permanganate according to the procedure of Gardner and Naylor:[7] mp 96–97° (lit. mp 99.8–100.5°,[2b] 96–96.5°[7]). Methyl *o*-formylbenzoate was prepared from monomethylphthaloyl chloride[8] by a modification of the procedure of Eliel and Burgstahler.[8] A mixture of toluene (200 ml, dried over sodium sand), palladium–barium sulfate catalyst[9] (6.0 g), and thiourea[10] (20 mg, catalyst poison) were heated until toluene vapors emerged from the top of an air condenser. The condenser water was started and a slow stream of dry hydrogen gas passed through the mixture. Crude monomethylphthaloyl chloride (0.33 mole, based on methyl hydrogen phthalate) was added carefully through the condenser and immediately a tube was connected between the condenser top and a beaker of standardized sodium hydroxide. The reaction was continued until about 90% of the theoretical amount of hydrogen chloride was evolved. The reaction mixture was cooled, filtered, and distilled. The fraction (29 g, 44% of theory) boiling at 135–136° (12 mm) was collected: $n^{20}D$ 1.5412 (lit. $n^{20}D$ 1.5412,[8] 1.5426[2b]). The ultraviolet spectrum of the hydrolyzed product was identical with that of the previously prepared *o*-formylbenzoic acid. In contrast, phthalic anhydride was obtained as the product in repeated attempts of the literature procedure.[8]

**Experimental Procedure.**—The following procedure was used for all runs. Anhydrous methanol (4–5 drops) was added to a small sample of methyl *o*-formylbenzoate contained in a weighing boat. (The methanol was used to expedite the dissolution of the

(4) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

(5) J. O. Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954): piperazine, $H$ = 11.46; piperazinium ion, $H$ = 7.34; morpholine, $H$ = 10.10.

(6) Charles Pfizer and Co., Inc., British Patent 816,037 (1959).

(7) G. H. Gardner and C. A. Naylor, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 523.

(8) E. L. Eliel and A. W. Burgstahler, *J. Am. Chem. Soc.*, **71**, 2251 (1949).

(9) E. Mosettig and R. Mozingo, *Org. Reactions*, **IV**, 362 (1948).

(10) C. Weygand and W. Meusel, *Ber.*, **76B**, 503 (1943).

ester in the hydrolyzing solution and was found not to effect the kinetics of the reaction.) The alcoholic mixture was placed in a dry 25-ml volumetric flask immersed in a constant-temperature bath. A hydrolyzing solution of the desired pH (borate, phosphate, or acetate buffers when necessary), concentration of nucleophile, and ionic strength (adjusted with sodium nitrate) was also immersed in the bath. After reaching bath temperature, a measured quantity of hydrolyzing solution (to give a solution $2.5 \times 10^{-3}$ $M$ in MOFB) was injected vigorously into the sample flask. The time of injection was taken as the initial reaction time. At intervals over three half-lives, samples were taken from the reaction mixture and quenched in a hydrochloric acid solution at a pH ~2. (Investigation had shown that the hydrolysis essentially is stopped at this pH.)[11] The absorbances of the quenched solutions were read on a Beckman DU spectrophotometer using a blank of hydrolyzing solution at pH 2. The very rapid runs were sampled using a Cornwall continuous pipettor immersed in the bath.

The large difference in the ultraviolet absorption at 260 mμ between methyl *o*-formylbenzoate and its hydrolysis product, *o*-formylbenzoic acid, in acid media was used in determining the concentrations of the reactants as a function of time. Using standard equations,[12] excellent pseudo-first-order plots were obtained. In a study of the reproducibility of duplicate runs, a variation of less than 2% in the rate constants was observed for a test group of runs. All pH measurements were made using a Beckman Model 76 expanded-scale pH meter. The error in pH, including buffer standardizations, was assumed to be no greater than ±0.07 pH units.

**Registry No.**—Piperazine, 110-85-0.

(11) Reference 2b gives a difference of $10^7$ in the rate constants for hydroxide ion and hydronium ion catalyzed reactions.

(12) A. Frost and R. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, p 28.

## On the Structure of N-Acyl-α-amino Ketones Obtained from 2-Alkylidenepseudoxazolones

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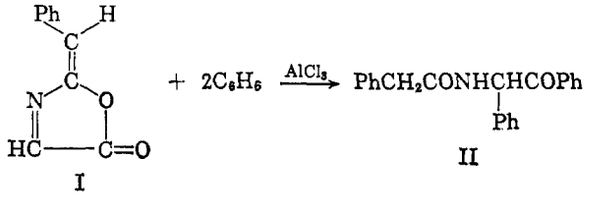
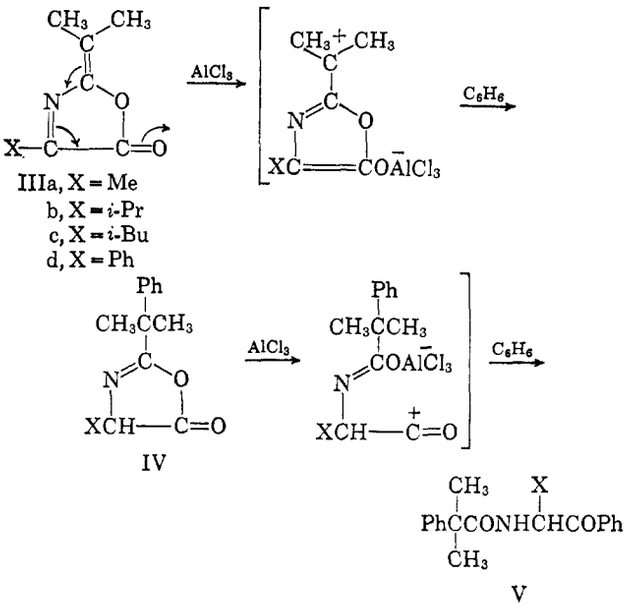
Filler[1] reported that 2-benzylidene-3-oxazolin-5-one (I) reacts with 2 equiv of benzene to give N-phenylacetyl-α-amino ketone II under Friedel–Crafts reaction conditions by the addition to C-4 and then ring opening at C-5 position. However, we have found that



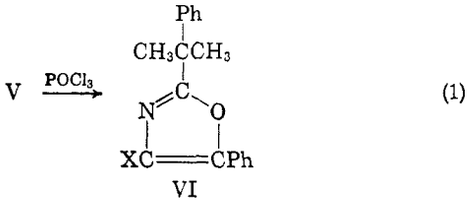

I II

2-isopropylidene-4-substituted 3-oxazolin-5-ones[2] (III) also reacted with benzene to give 1:2 adducts, N-(α-phenylisobutyryl)-α-amino ketones (V), by a reverse mode of 1,4-addition reaction at both C-5 and the isopropylidene *exo* double bond in the presence of anhydrous aluminum chloride. In III, the replacement of the hydrogen at C-4 could be the reason for lack of reaction at C-4. A suggested mechanism for the formation of V is *via* the formation of 1:1 adduct intermediate IV by increased electrophilic character of the isopropylidene substituent caused by the coordination of aluminum chloride to the carbonyl group, followed by its subsequent ring opening with benzene[3,4] (Scheme I).

SCHEME I




Elemental analyses and yields are summarized in Table I. The structure of V was confirmed by the infrared and the nmr spectral data as shown in Table II. The fact that V was readily cyclized to oxazole VI[5] (eq 1) by the treatment of dehydrating agent such as phosphorus oxychloride and to thiazole by phosphorus pentasulfide[6] is more convincing evidence of the structure V. The elemental analyse sand yields are shown in Table III.




### Experimental Section

**Reaction of 3-Oxazolin-5-ones with Benzene.**—A sample of IIIb[2] (6.7 g, 0.04 mole) in 200 ml of dry benzene was added dropwise to a stirred slurry of 23.2 g (0.175 mole) of anhydrous aluminum chloride in 50 ml of dry benzene.[1] After the solution had been stirred for 2 hr, 120 ml of 18% HCl was added. The benzene layer was separated and washed twice with 100-ml portions of water and dried over anhydrous sodium sulfate. After removal of benzene, the resulting solid was recrystallized from ethanolic water to give N-(α-phenylisobutyryl)-α-aminoisobutyrophenone (Vb, 8 g), mp 78–81°, mol wt 290 (calcd 323.4) measured by vapor pressure osmometer in benzene. 2,4-Dinitrophenylhydrazone was obtained by refluxing with 1 equiv of 2,4-dinitrophenylhydrazine in ethanol: mp 125–127°.

(1) R. Filler and E. J. Piasek, *J. Org. Chem.*, **29**, 2205 (1964).

(2) Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron Letters*, 4427 (1966).

(3) R. Filler, *Advan. Heterocyclic Chem.*, **4**, 82 (1965).

(4) R. Filler and Y. S. Rao, *J. Org. Chem.*, **27**, 2403 (1962); A. Mustafa, A. E. Sammour, M. M. N. Eldeen, T. Salama, and M. K. Hilmy, *Ann.*, **689**, 189 (1965); A. Mustafa, A. E. Sammour, M. M. M. Eldeen, T. Salama, and H. K. Hilmy, *ibid.*, **689**, 189 (1965).

(5) P. T. Frangopol, A. T. Balaban, L. Birladeanu, and E. Cioranescu, *Tetrahedron*, **16**, 59 (1961).

(6) R. P. Kurkjy and E. V. Brown, *J. Am. Chem. Soc.*, **74**, 5778 (1952).