**Spectral Data.**—Infrared absorption was at 5.75, 5.88, and 6.01 $\mu$. Nmr (neat) showed 1.15 (singlet), 1.30 (singlet), 1.43 (singlet), 1.63 (singlet), 3.45 (singlet), 3.55 (singlet), and 3.62 (singlet). Comparative areas (3.5:1) of peaks at 1.15 [$C(CH_3)_3$] and at 1.43 and 1.63 ppm [$>C=C(CH_3)_2$] indicated the presence of about 30% methyl 2,2,4,4-tetramethyl-3-oxovalerate and 70% methyl 3-methoxy-2,2,4-trimethyl-3-pentenoate.

The mixture was then heated for 39 hr in refluxing methanol in which 1.0 g of sodium had been dissolved. During this time the infrared absorption at 5.88 $\mu$ disappeared and a new absorption band at 5.83 $\mu$ appeared.

The solid was filtered off and the solvent was flashed off. Again solid was removed from the residue and the product was distilled through a Vigreux column, yielding methyl 3-methoxy-2,2,4-trimethyl-3-pentenoate, 42.3 g, bp 68–69° (5 mm), $n^{20}D$ 1.4460.

*Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.5; H, 9.7; mol wt, 186. Found: C, 64.4; H, 9.6; mol wt (ebullioscopic in acetone), 203.

Infrared absorption was at 5.75 and 6.01 $\mu$. Nmr (neat) showed 1.28 singlet (6 H), 1.41 singlet (3 H), 1.60 singlet (3 H), 3.45 singlet (3 H), and 3.57 singlet (3 H).

**Oxygen Acylation of 7.**—The reaction of **7** with acetyl chloride, cyclohexylcarbonyl chloride, and methyl chloroformate has been reported to give carbon acylation.[7] The products prepared by the published procedure were further analyzed.

The product of **7** and acetyl chloride is methyl 3-acetoxy-2,2,4-trimethyl-3-pentenoate.

*Anal.* Calcd for $C_{11}H_{18}O_4$: sapon equiv, 107. Found: sapon equiv, 107.

Infrared absorption was at 5.73, 5.80, and 5.98 $\mu$. Nmr (30% in carbon tetrachloride) showed 1.27 (6 H); 1.49 and 1.55 [$>C=C(CH_3)_2$], 2.11 (3 H), and 3.65 (3 H).

The product of **7** and cyclohexylcarbonyl chloride is methyl 3-(cyclohexylcarbonyloxy)-2,2,4-trimethyl-3-pentenoate.

*Anal.* Calcd for $C_{16}H_{26}O_4$: sapon equiv, 141. Found: sapon equiv, 146.

Infrared absorption was at 5.78, 5.88, and 6.00 $\mu$. Nmr (30% in carbon tetrachloride) showed 1.27 (6 H); 1.48 and 1.56 [$>C=C(CH_3)_2$], 3.65 (3 H), and broad absorption at 1.2–2.7.

The product of **7** and methyl chloroformate is methyl 3-(methoxycarbonyloxy)-2,2,4-trimethyl-3-pentenoate.

**Spectral Data.**—Infrared absorption was at 5.71, 5.82, and 5.91 $\mu$. Nmr (30% in carbon tetrachloride) showed 1.32 (6 H), 1.56 (6 H), 3.71 (3 H), and 3.83 (3 H).

This product apparently was *not* identical with that of Murin, *et al.*,[16] because its saponification by an identical procedure did not give 2,2,4,4-tetramethyl-3-oxoglutaric acid but rather carbon dioxide and diisopropyl ketone (35%), identified as its 2,4-dinitrophenylhydrazone, mp 93–95°.

Acylation of **7** with isobutyryl chloride was carried out by the published procedure.[7] The yield of methyl 3-isobutyryloxy-2,2,4-trimethyl-3-pentenoate was 48%, bp 93–96° (2.3 mm).

**Spectral Data.**—Infrared absorption was at 5.81, 5.92, and 6.00 $\mu$. Nmr (30% in carbon tetrachloride) showed 1.22 doublet and 2.64 septet [$CH(CH_3)_2$], 1.28 (3 H), 1.30 (3 H), 1.46 and 1.53 [$>C=C(CH_3)_2$], and 3.64 (3 H).

**Reaction of 1 with Ammonia.**—A mixture of 20.0 g of **1** and 250 ml of 30% ammonium hydroxide was stirred vigorously for 3 hr. The solid was filtered off, washed with three 100-ml portions of water, and then dried in a forced-air oven at 100°, yielding 2,2,4,4,6-pentamethyl-3,5-dioxoheptanamide (**11**), 14.6 g (68%), mp 188–190°.

*Anal.* Calcd for $C_{12}H_{21}NO_3$: C, 63.4; H, 9.3. Found: C, 63.6; H, 9.3.

Infrared absorption was at 2.83, 3.11, 5.85, and 6.0 $\mu$. Nmr (10% in pyridine) showed 1.10 doublet (3 H), 1.25 singlet (3 H), 1.31 doublet (3 H), 1.47 singlet (3 H), 1.52 singlet (3 H), 1.58 singlet (3 H), 2.32 multiplet (1 H), and 7–8 broad general (pyridine).

A 5.0-g sample of **11** was boiled for 5 min in a test tube. The sample was cooled and recrystallized from ethanol; yield of 6-isopropylidene-3,3,5,5-tetramethyl-2,4-piperidinedione was 2.7 g (59%), mp 178–183°.

*Anal.* Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.2. Found: C, 69.4; H, 9.5.

Infrared absorption was at 3.17, 5.83, and 6.05 $\mu$. Nmr (10% in tetrachloroethane) showed 1.29 (6 H), 1.32 (6 H), 1.77 (3 H), 1.86 (3 H), and 7.99 (1 H). The only change in the nmr spectrum on heating to 140° was a very slight shift up field of the peak at 7.99 ppm.

**Reaction of 1 with Butylamine.**—A mixture of 100.0 g of **1** and 35.0 g of butylamine was heated at 200° for 30 min. The product was distilled; yield of N-butyl-2,2,4,4,6-pentamethyl-3,5-dioxoheptanamide was 93.4 g (69%), bp 143–144° (1 mm).

*Anal.* Calcd for $C_{16}H_{29}NO_3$: C, 67.8; H, 10.3; N, 4.9. Found: C, 67.6; H, 10.7; N, 4.8.

Infrared absorption was at 3.00 and 5.8–6.2 $\mu$. Nmr (25% in carbon tetrachloride) showed 1.07 doublet (6 H), 1.37 singlet (6 H), 1.43 singlet (6 H), 3.2 multiplet (3 H), 6.90 singlet (1 H), and 7 H obscured under peaks 1.43 and 1.07.

**Acknowledgment.**—The author is indebted to E. U. Elam for helpful discussions and to J. E. Poe for interpretation of the nmr spectra.

# Preparation of β-Ketoaldehydes by Acylation of Aldehyde Enamines[1]

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The reaction of 1-N-morpholinoisobutene (II) with acetyl chloride gives, after mild hydrolysis, α-acetylisobutyraldehyde. Direct acetylation, rather than cycloaddition of ketene followed by ring cleavage, is proposed as a probable mechanism. Benzoylation of 1-N-morpholinoisobutene (II) and 1-N-morpholinobutene (IX) gives α-benzoylaldehydes.

Acylation of the enamines derived from ketones, particularly cyclic ketones, is a well-known synthetic method for α acylation of ketones.[2] The acylation with acid halides bearing no α-hydrogen atom is straightforward, and the acylated enamines give, after hydrolysis, the α-acyl derivatives of the original ketones.[3] With an acid chloride that has an α-hydrogen atom, the enamine will take up hydrogen chloride to form a ketene *in situ*, which in turn adds to the enamine to give an aminocyclobutanone derivative.[4] The aminocyclobutanones derived from cyclic ketone enamines give on hydrolysis the α-acyl ketones gen-

(1) Presented in part at the 19th Annual Meeting of the Chemical Society of Japan, Yokohama, Japan, March 1966; Abstract, Section III, p 460.

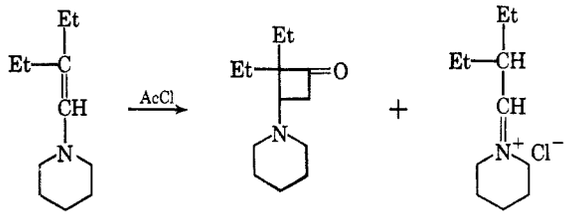
(2) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(3) *Cf. inter alia*, (a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); (b) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 798 (1964); (c) R. D. Campbell and W. L. Harmer, *ibid.*, **28**, 379 (1963); (d) R. D. Campbell and J. A. Jung, *ibid.*, **30**, 3711 (1965); (e) M. Mühlstädt and J. Riemer, *Z. Chem.*, **4** (2), 70 (1964).

(4) Cycloaddition of ketenes to the enamines derived from ketones and aldehydes has been reported by various workers; see, for example, (a) G. Opitz, H. Adolph, M. Kleemann, and F. Zimmermann, *Angew. Chem.*, **73**, 654 (1961); (b) G. Opitz, M. Kleemann, and F. Zimmermann, *ibid.*, **74**, 32 (1962); (c) G. Opitz and F. Zimmermann, *Ann.*, **662**, 178 (1963); ref 5–8.

erally.[5,9] Therefore many of the reported α acylations of enamines[3a,10] may have proceeded, at least partly, *via* cycloaddition of ketenes rather than direct acylation.

With aldehyde enamines the direct acylation has not been exploited as a synthetic means for α-acylaldehydes. Opitz and Zimmermann[4c] reported that the attempted acetylation of the enamine I afforded no

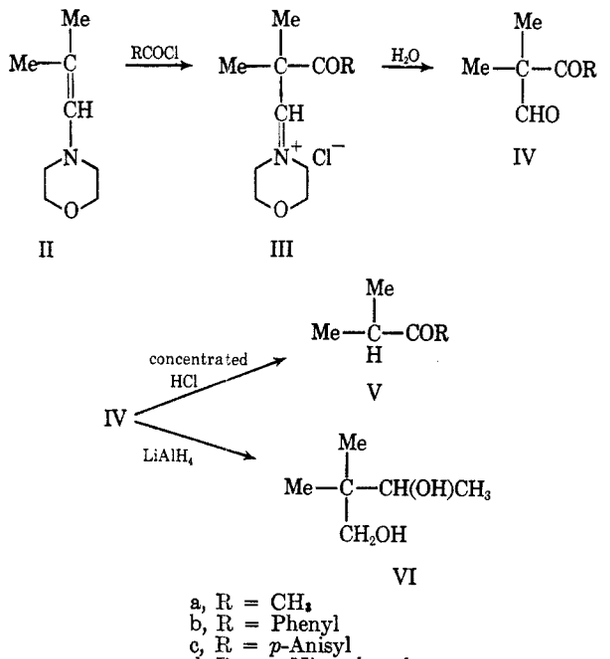


I

acyl derivative but an aminocyclobutanone. The present paper reports some observations on direct acetylation of the aldehyde enamine II where α-acetylisobutyraldehyde (IVa) is prepared in a fair yield. Benzoylations of enamines II and IX are also described.

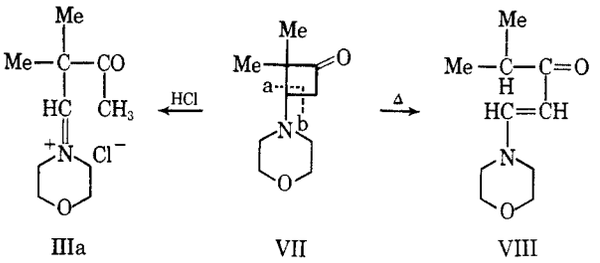
When 1 mole of II was added to 1 mole of acetyl chloride in ether, precipitates of the immonium salt IIIa were formed. Compound IIIa was isolated and hydrolyzed under mild conditions to afford α-acetylisobutyraldehyde (IVa) in 66% yield. Small amount of isobutyraldehyde was also obtained suggesting that the precipitates contained II hydrochloride. The structure of IVa was confirmed by nmr spectrum, decarbonylation to isopropylmethyl ketone (Va), and by lithium aluminum hydride reduction to the diol VI (see Scheme I).

SCHEME I



a, R = $CH_3$
b, R = Phenyl
c, R = *p*-Anisyl
d, R = *p*-Nitrophenyl

The actual route to IIIa may be supposed to be *via* cycloaddition product VII, since aminocyclobutanones are known to undergo thermal rearrangement with bond fissions at a and/or b depending on their structure.[5,7,8] Although it is reported[5,8] that VII rearranged to VIII on heating (fission at a), the other mode of rearrange-



IIIa VII VIII

ment (fission at b) remains as a possibility under our experimental conditions. This is because VII, if it is formed, is to be in a salt form. This possibility, however, was ruled out because VII hydrochloride prepared by the known method[4c] did not rearrange to IIIa by heat treatment (*i.e.*, 2-hr reflux in its ether suspension) which is an approximate reproduction of environment to which VII hydrochloride would have been subjected if it were formed in the preparation of IIIa. Consequently IIIa is assumed not to be formed through VII hydrochloride, and a direct acetylation may be assumed. The reason we obtained the acetylation product, rather than the aminocyclobutanone, is probably that the enamine was added *to* acetyl chloride.

Benzoylation, *p*-methoxybenzoylation, and *p*-nitrobenzoylation of II proceeded to give the immonium salts IIIb, IIIc, and IIId in 86, 72, and 58% yields, respectively. Hydrolyses of these salts under mild conditions afforded α-aroylisobutyraldehydes IVb, IVc, and IVd in 72, 69, and 63% yields, respectively. The structures of IVb–d were proved by the nmr and by decarbonylation to Vb–d.

The nonenolizable aldehyde group of β-ketoaldehydes is quite easily lost under alkaline and acidic conditions.[11] This is probably the reason for the failure of formylation of isobutyrophenone with ethyl formate under basic conditions reported by Claisen and Meyerowitz.[12,13] The reaction under present study is therefore a convenient way of preparing this type of β-ketoaldehydes.

It is of interest to note an apparent difference observed in benzoylations of II and IX. The former reaction is not affected by the presence of added triethylamine; *i.e.*, IIIb precipitates out as in the absence of the triethylamine. In the reaction of IX with benzoyl chloride in the presence of triethylamine, however, the precipitates formed were triethylammonium chloride instead of X. This difference is obviously explained by noting that X has an acidic hydrogen atom α to the acyl group while IIIb has none. 1-N-Morpholino-2-benzoyl-1-butene (XI) is as-

(5) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, Jr., *J. Org. Chem.*, **26**, 4776 (1961); **30**, 2642 (1965).

(6) A. Kirrmann and C. Wakselman, *Compt. Rend.*, **261**, 759 (1965).

(7) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **28**, 1468 (1963).

(8) G. Opitz and M. Kleemann, *Ann.*, **665**, 114 (1963).

(9) See, however, ref 6 for exceptional cases of 12- or 15-membered cyclic ketone enamines, which give 14- or 17-membered cyclic 1,3-diketones, respectively.

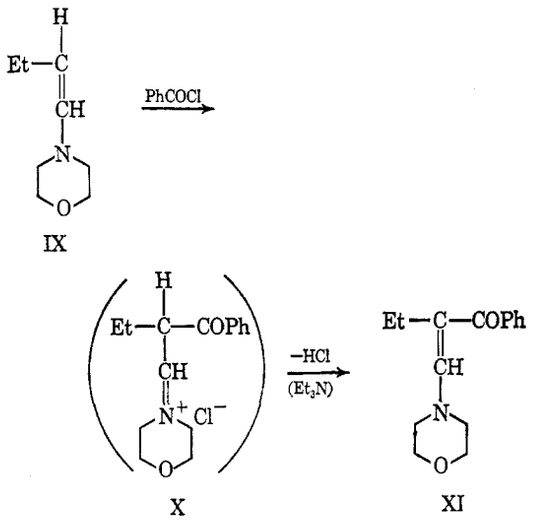
(10) S. Hünig and M. Salzwedel, *Chem. Ber.*, **99**, 823 (1966), and previous papers of this series.

(11) *Cf.* H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957); G. D. Ryerson, R. L. Wasson, and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 957; A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1715 (1946).

(12) (a) L. Claisen and L. Meyerowitz, *Ber.*, **22**, 3273 (1889). (b) We reconfirmed the failure in an attempted preparation of authentic IVb.

(13) Compound IVb could not be recovered from its solution in ethanolic sodium ethoxide even with quick and careful work-up, since IVb so readily decarbonylates to Vb.

SCHEME II



sumed to be present in the solution because α-benzoyl-*n*-butyraldehyde was obtained on hydrolysis. (See Scheme II.)

## Experimental Section[14]

**1-N-Morpholinoisobutene (II)** was prepared by the method of Benzing[15] and had bp 55.5–57.5° (11 mm) [lit.[15] bp 56–57° (11 mm)].

**1-N-Morpholinobutene (IX)** was prepared by the published procedure[16] and had bp 73.5–74.5° (10 mm) [lit.[16] bp 72–74° (12 mm)].

**Reaction of 1-N-Morpholinoisobutene (II) with Acetyl Chloride.**—A solution of 28.2 g (0.2 mole) of II in 50 ml of ether was added dropwise in 45 min to a stirred solution of 15.7 g (0.2 mole) of acetyl chloride in 50 ml of ether in an iced water bath. The resulting mixture was gently refluxed for 2 hr and was allowed to stand overnight at room temperature. The white precipitates were filtered under exclusion of moisture, washed with ether, and dried under vacuum to a constant weight of 28.2 g (64% yield based on the formula IIIa). The precipitates were dissolved in 30 ml of water and the pH of the solution was adjusted to 5 by adding sodium bicarbonate. The solution was stirred with 30 ml of ether overnight at room temperature. The aqueous layer was extracted with ether and the combined ether layers were washed with water and dried with anhydrous sodium sulfate. Distillation afforded 1 g of isobutyraldehyde and 9.7 g (66% yield based on IIIa) of α-acetylisobutyraldehyde (IVa), bp 43–44° (8 mm), $n^{20}D$ 1.4230.

*Anal.* Calcd for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Found: C, 62.7; H, 9.0.

The nmr spectrum had three singlets at τ 8.70 (6 H, *gem*-$CH_3$), 7.86 (3 H, $COCH_3$), and 0.45 (1 H, CHO).

The bis-2,4-dinitrophenylhydrazone was prepared and showed mp 223–225° dec.

*Anal.* Calcd for $C_{18}H_{18}N_8O_8$: N, 23.6. Found: N, 23.8.

Another 3.6 g of isobutyraldehyde was obtained from the filtrate and ether washings of IIIa.

**Reduction of IVa to 2,2-Dimethyl-1,3-butanediol (VI).**—A solution of IVa (2.85 g, 25 mmoles) in 10 ml of ether was added dropwise in 30 min to a suspension of lithium aluminum hydride (1.75 g, 46 mmoles) in 60 ml of ether at −10°. After stirring for 1 hr at this temperature, the mixture was allowed to stand overnight at room temperature. By usual work-up, 2.1 g (72% yield) of VI was obtained by distillation: a viscous oil, bp 71–72° (0.5 mm), $n^{20}D$ 1.4475 [lit.[17] bp 121° (20 mm), $n^{20}D$ 1.4408]. The infrared spectrum was identical with the published one.[18]

**α-Benzoylisobutyraldehyde (IVb).**—To an ice-cold solution of 14 g (0.1 mole) of the enamine II in 50 ml of *p*-dioxane was added dropwise a solution of 14 g (0.1 mole) of benzoyl chloride in 50 ml of *p*-dioxane, and the resulting mixture was allowed to stand overnight at room temperature. After refluxing for 1 hr, the mixture was cooled and the precipitates (IIIb) were filtered, washed with ether, and dried under vacuum, yielding 24.3 g (86% from II). Fifteen grams of IIIb was stirred with 30 ml of water and 30 ml of ether overnight at room temperature. From the ether layer was obtained 10.9 g (72% based on IIIb) of α-benzoylisobutyraldehyde, bp 87–89° (1 mm), $n^{20}D$ 1.5291. It had two nmr singlets at τ 8.58 (6 H, *gem*-Me) and 0.34 (1 H, CHO), with a complex multiplet in the region 2.2–2.8 (5 H, aromatic CH).

*Anal.* Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 74.8; H, 7.0.

The mono-2,4-dinitrophenylhydrazone, mp 147–149° (from ethanol), was prepared.

*Anal.* Calcd for $C_{17}H_{16}N_4O_5$: N, 15.7. Found: N, 15.9.

**α-(*p*-Anisoyl)isobutyraldehyde (IVc).**—Compound IIIc was prepared in 72% yield from II in a similar way. The ketoaldehyde IVc, bp 115–120° (0.5 mm), $n^{20}D$ 1.5473, was obtained in 69% yield based on IIIc. It had three singlets at τ 8.60 (6 H, *gem*-Me), 6.18 (3 H, $OCH_3$), and 0.33 (1 H, CHO) with two multiplets in the regions τ 2.1–2.4 (2 H, aromatic CH) and 3.0–3.3 (2 H, aromatic CH).

*Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8. Found: C, 69.7; H, 7.0.

The mono-2,4-dinitrophenylhydrazone, mp 161–162° (from ethanol–benzene), was prepared.

*Anal.* Calcd for $C_{18}H_{18}N_4O_6$: N, 14.5. Found: N, 14.4.

**α-(*p*-Nitrobenzoyl)isobutyraldehyde (IVd).**—A solution of 19.1 g (0.135 mole) of the enamine II in 50 ml of *p*-dioxane was added dropwise to a stirred solution of 25 g (0.135 mole) of *p*-nitrobenzoyl chloride in 50 ml of *p*-dioxane. When evolution of heat subsided the mixture was refluxed for 1 hr and was allowed to stand overnight at room temperature. The precipitates IIId, 25.4 g (58% yield), were treated in the usual way to yield 10.9 g (63% based on IIId) of crude IVd, bp 122–125° (0.05 mm). Small amount of crystals of *p*-nitroisobutyrophenone (Vd) appeared on standing. The elemental analysis of the liquid portion was satisfactory for IVd.

*Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.3. Found: C, 59.6; H, 5.3; N, 6.6.

The nmr spectrum exhibited two singlets at τ 8.51 (6 H, *gem*-Me) and 0.26 (1 H, CHO) and two multiplets in the regions 2.0–2.3 (2 H, aromatic CH) and 1.6–1.9 (2 H, aromatic CH), together with weak absorptions ascribable to *p*-nitroisobutyrophenone impurity. The monoxime of IVd melted at 151–152° (from dilute ethanol).

*Anal.* Calcd for $C_{11}H_{12}N_2O_4$: N, 11.9. Found: N, 11.7.

**Decarbonylation of β-Ketoaldehydes to Ketones Va–Vd.**—The β-ketoaldehyde (3 g) was stirred with 10 ml of ether and 5 ml of concentrated hydrochloric acid overnight at room temperature. The ketones Va–Vd were obtained in 60–70% yields and were identified in the following way.

**Isopropylmethyl ketone**, bp 90–93°, gave a 2,4-dinitrophenylhydrazone, mp 122.8–123.3° (from ethanol) (lit.[19] mp 122.5–123°).

*Anal.* Calcd for $C_{11}H_{14}N_4O_4$: N, 21.0. Found: N, 21.1.

**Isobutyrophenone**, bp 60–61° (1 mm), had a nmr doublet ($J$ = 6.9 cps) at τ 8.82 (6 H, *gem*-Me), a septet ($J$ = 6.9 cps) at 6.52 (1 H, *t*-CH), and two multiplets in the regions 2.0–2.2 (2 H, aromatic CH) and 2.4–2.8 (3 H, aromatic CH). The infrared spectrum was identical with the published one.[20] The 2,4-dinitrophenylhydrazone, mp 164–165° (from ethanol) (lit.[21] mp 163°), was obtained.

***p*-Methoxyisobutyrophenone**, bp 102–103.5° (0.5 mm) [lit.[22] bp 188–190° (40 mm)], $n^{20}D$ 1.5371, had a nmr doublet ($J$ =

(14) All melting points are corrected. Infrared absorption spectra were determined with a Nihon Bunko Model IR-S spectrophotometer. Nmr spectra were taken using a Varian A-60A spectrometer on *ca.* 20 wt % carbon tetrachloride solutions containing tetramethylsilane as internal standard.

(15) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(16) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. France*, 967 (1960).

(17) R. G. Kelso, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **74**, 287 (1952).

(18) "Sadtler Standard Infrared Spectra," Midget ed, Sadtler Research Laboratories, Philadelphia, Pa., 1959, Spectrum No. 14518.

(19) S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc.*, **74**, 1160 (1952).

(20) Reference 18, 1962, Spectrum No. 5773.

(21) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 317.

(22) X. A. Dominguez, B. Gómez, J. Slim, D. Giesecke, and B. E. Ureta, *J. Am. Chem. Soc.*, **76**, 5150 (1954).

6.9 cps) at $\tau$ 8.85 (6 H, *gem*-Me), a septet ($J$ = 6.9 cps) at 6.57 (1 H, *t*-CH), a singlet at 6.18 (3 H, $OCH_3$), and two multiplets in the regions 2.0–2.3 (2 H, aromatic CH) and 3.0–3.3 (2 H, aromatic CH).

*Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.2; H, 7.7.

The 2,4-dinitrophenylhydrazone, mp 122–123° (from ethanol), was obtained.

*Anal.* Calcd for $C_{17}H_{18}N_4O_5$: N, 15.6. Found: N, 15.7.

**p-Nitroisobutyrophenone**, mp 51.8–52.3° (from dilute ethanol), had a nmr doublet ($J$ = *ca.* 7 cps) at $\tau$ 8.76 (6 H, *gem*-Me), a septet ($J$ = 6.9 cps) at 6.43 (1 H, *t*-CH), and a complex multiplet in the region 1.6–2.1 (4 H, aromatic CH). The doublet had a symmetrically spaced further pair of peaklets inside.

*Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.2; H, 5.7; N, 7.3. Found: C, 62.2; H, 6.2; N, 7.1.

The 2,4-dinitrophenylhydrazone melted at 147–149° (from ethanol–benzene).

*Anal.* Calcd for $C_{16}H_{13}N_5O_6$: N, 18.8. Found: N, 18.7.

**Reaction of 1-N-Morpholinobutene (IX) with Benzoyl Chloride.**—A solution of 14.1 g (0.1 mole) of benzoyl chloride in 50 ml of *p*-dioxane was added dropwise in 45 min to a stirred solution of 14.0 g (0.1 mole) of the enamine IX and 11 g (0.11 mole) of triethylamine in 50 ml of *p*-dioxane on an iced water bath. The mixture was allowed to stand overnight at room temperature. Triethylammonium chloride (14 g) was filtered and the filtrate was stirred with 10 ml of concentrated hydrochloric acid overnight at room temperature. Crude α-benzoyl-*n*-butyraldehyde, 9.5 g (54% yield), bp 110–130° (4 mm), was obtained by usual work-up. Analytical sample was obtained by repeated recrystallization from ether, mp 109–112°.[23]

*Anal.* Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 75.5; H, 6.9.

1-(2,4-Dinitrophenyl)-4-ethyl-5-phenylpyrazole, mp 130–131° (from ethanol), was prepared.

*Anal.* Calcd for $C_{17}H_{14}N_4O_4$: N, 16.6. Found: N, 16.3.

The copper chelate compound (green needles) melted at 172–175° (from ethanol). From the ethereal mother liquor of recrystallization of α-benzoyl-*n*-butyraldehyde was obtained 1.0 g of *n*-butyrophenone, bp 62–64° (0.5 mm); the 2,4-dinitrophenylhydrazone had mp and mmp 188–190° (from ethanol–benzene) (lit.[25] mp 187–189°).

**α-Benzoyl-*n*-butyraldehyde by Formylation of *n*-Butyrophenone.**—The formylation was carried out by the procedure of Claisen and Meyerowitz.[12a] The product was recrystallized from ether, mp 107–110°.[23] The infrared absorption spectrum was identical with that of α-benzoyl-*n*-butyrophenone prepared by the enamine method, and the 2,4-dinitrophenylhydrazine derivative showed no melting point depression on admixture with 1-(2,4-dinitrophenyl)-4-ethyl-5-phenylpyrazole described above.

(23) The melting point of α-benzoyl-*n*-butyraldehyde has been reported to be 86–87°,[12a,24] but this melting point was not realized in our experiment. The enolizable 1,3-dicarbonyl compound may have a tendency to form polymorphs; see B. Eistert, F. Weygand and E. Csendes, *Chem. Ber.*, **84**, 745 (1951).

(24) S. Takagi and H. Yasuda, *Yakugaku Zasshi*, **79**, 467 (1959).

(25) M. S. Newman and A. Kutner, *J. Am. Chem. Soc.*, **73**, 4199 (1951).

# Hydrogen Bonding of Methanol with Pyridine Derivatives[1]

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Infrared spectroscopic studies in the 3000–4000-$cm^{-1}$ region were carried out in $CCl_4$ solution of nine hydrogen-bonding systems, in which methanol was a common proton donor. The proton acceptors were pyridine, 2-picoline, 2-ethylpyridine, 2-isopropylpyridine, 2-*t*-butylpyridine, 2,6-lutidine, 2-ethyl-6-methylpyridine, 2,6-diethylpyridine, and 2,6-diisopropylpyridine. Equilibrium constants for the formation of 1:1 complexes were determined. The enthalpies of complex formation were calculated from the temperature dependence of the spectra and are approximately 4 kcal/mole. The values of $\Delta\nu$, the difference in frequency for methanol monomer and the complex, were found to be temperature dependent. A linear relationship was found to exist between $\Delta\nu$ and pyridine base strength. The presence of bulky substituents at positions 2 or 2,6 was noted to impede the hydrogen-bonding reaction.

Interest in hydrogen bonding as an important parameter in drug pharmacodynamics originates in its participation in the complex events collectively termed "biological activity." Of particular concern to us have been the effects of steric hindrance on the thermodynamic properties of various simple hydrogen-bonding systems which may relate to the vastly more complicated chemistry of biophase reactions. To that end we have found pyridine to be a good proton acceptor model. Existing data on the thermodynamic properties of hydrogen-bonding reactions between pyridine derivatives and proton donors, especially alcohols, are scant.[4] Especially lacking have been studies on the way substituent groups adjacent to the heterocyclic nitrogen atom can alter its reactivity.

To further the development of a better understanding of hydrogen-bonding stereochemistry and to assist in the development of a working hypothesis on the mode of action of some drugs, it was desirable to determine the thermodynamic constants for several alcohol–pyridine systems. It was thought that the restricted access of a proton donor to a hindered pyridine could limit the degree of complexion in a manner similar to the steric inhibition of salt formation[5] and cause the equilibrium constants for complex formation to exhibit a dependence upon the size of pyridine substituent groups. Such a dependence has been inferred from nmr studies of hydrogen bonding in hindered phenols.[6]

This report concerns infrared spectroscopic studies carried out in the region of the fundamental OH stretching vibration. It covers reactions of pyridine, 2-picoline, 2-ethylpyridine, 2-isopropylpyridine, 2-*t*-butylpyridine, 2,6-lutidine, 2-ethyl-6-methylpyridine, 2,6-diisopropylpyridine, and 2,6-diethylpyridine with methanol at 18, 30, and 40°. The work was carried out at concentrations where only a 1:1 alcohol–base complex would be expected and methanol self-association would be prohibited. The equilibrium constants were determined by neglecting the contribution of

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(4) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960.

(5) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 65.

(6) B. G. Somers and H. S. Gutowsky, *J. Am. Chem. Soc.*, **85**, 3065 (1963).