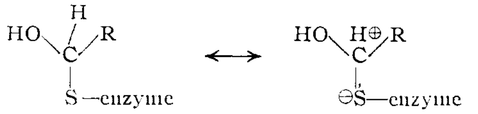
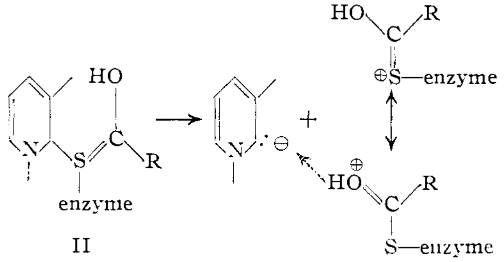
Consider, for example, reactions involving carbonyl groups under the influence of –SH groups either from an enzyme or a coenzyme. It is assumed that in certain cases, as a first step, a hemimercaptal Ia is formed. Contribution of a resonating structure Ib, in which the sulfur atom expands the octet, would give considerable proton-releasing effect on the attached carbon atom[7] and this may be of importance in relation to the mechanism of these reactions.



Ia Ib

For instance, one may conceive of removal of a proton from the hemimercaptal, followed by formation of an unstable intermediate II from DPN+ and the anion.[8] This intermediate would decompose forming DPNH and a thiolester



II

Experimental

The compounds were obtained by condensation of the phenol or thiophenol with acetyl chloride, extracted from the reaction mixture by current procedures and distilled (phenyl acetate, b.p. 189.5–191.5° at 701 mm.; phenyl thiolacetate, b.p. 117–118° at 21 mm.; anisyl acetate, b.p. 135–137° at 19 mm.; anisyl thiolacetate, b.p. 168–169° at 16 mm.). Anisyl acetate was also recrystallized from ether (m.p. 29–32°).

For absorption measurements, solutions in especially purified ethyl alcohol were prepared. Readings were taken with a Beckman D.U. quartz spectrophotometer at 2-mμ intervals, employing a constant band width of 10 Å.

Acknowledgments.—We wish to express our gratitude to the Rockefeller Foundation for the gift of the Beckman Spectrophotometer and to Prof. H. Hauptmann for his stimulating interest.

[7] (a) E. Rothstein, *J. Chem. Soc.*, 1550, 1553, 1558 (1940); (b) R. B. Woodward and R. H. Eastman, THIS JOURNAL, **68**, 2229 (1946).

[8] It is interesting that DPN+, in fact, forms dissociable addition complexes with cyanide and bisulfite (O. Meyerhof, P. Ohlmeyer and W. Möhle, *Biochem. Z.*, **297**, 113 (1938)).

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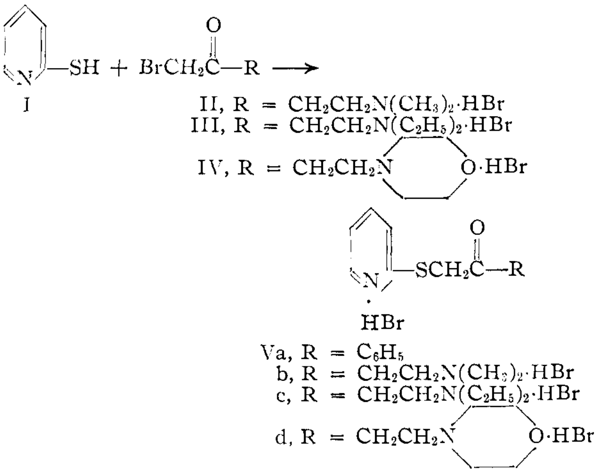
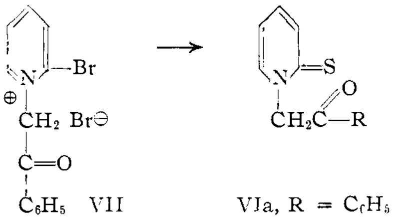
The Reaction of α-Halo Ketones with 2-Pyridinethiol[1]

BY CARL DJERASSI AND GEORGE R. PETTIT

RECEIVED APRIL 7, 1954

In connection with another project, it was necessary to determine the course of the reaction of 2-pyridinethiol (I) with certain α-halo ketones, notably brominated Mannich bases.[2] The condensation was carried out in glacial acetic acid solution with the following ketones: phenacyl bromide, 1-bromo-4-dimethylamino-2-butanone hydrobromide (II), 1-bromo-4-diethylamino-2-butanone hydrobromide (III) and 1-bromo-4-morpholino-2-butanone hydrobromide (IV). The solubility characteristics of the resulting products and especially the presence of a carbonyl function, detected by infrared and chemical means, excluded a cyclic (quaternary) pyridothioazole structure and indicated that the compounds must be the products of S- (V) or N-alkylation (VI). A decision in favor of structure V was arrived at as follows: The quaternary salt, 1-phenacyl-2-bromopyridinium bromide (VII), prepared from 2-bromopyridine and phenacyl bromide, was converted to 1-phenacyl-2-pyridinethione (VIa) with sodium hydrogen sulfide. The ultraviolet absorption spectrum (see Experimental) of this substance, though very similar to that of 1-ethyl-2-pyridinethione,[3,4] was completely different from that of the pyridinethiol–phenacyl bromide condensation product (as the free base), which is therefore assigned structure Va. The analogous condensation products with the Mannich bases II–IV exhibited essentially the same ultraviolet absorption spectra (see Experimental), as did 2-ethylthiopyridine[3,5] and it is clear, therefore, that all of these substances are the products of S-alkylation (V). This was confirmed further by the stability of Vd toward boiling 42% hydrobromic acid; 1-alkyl-2-pyridinethiones are converted to





VII VIa, R = C_6H_5

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[1] Taken in part from the M.S. thesis of G. R. P.

[2] For the reaction of thioamides with brominated Mannich bases, see C. Djerassi, R. H. Mizzoni and C. R. Scholz, *J. Org. Chem.*, **15**, 700 (1950).

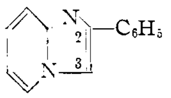
[3] D. J. Fry and J. D. Kendall, *J. Chem. Soc.*, 1716 (1951).

[4] The ultraviolet absorption spectrum of 2-pyridinethiol (I) is given for comparison and indicates that in ethanol solution it exists primarily in the thione form.

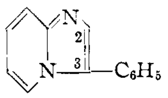
[5] H. J. Backer and J. A. K. Buisman, *Rec. trav. chim.*, **64**, 102 (1945).

the corresponding pyridones under such conditions.[6]

It is pertinent to mention that the condensation of phenacyl bromide with 2-aminopyridine has been carried out a number of times[7-9] and that the resulting product (m.p. 135°) has been assumed to be the 2-phenylimidazo-(1,2-a)-pyridine (VIII),[10] while the decarboxylated condensation product (m.p. 98°) of 2-aminopyridine and β-bromo-β-phenylpyruvic acid has been assigned[11] the isomeric 3-phenylimidazo-(1,2-a)pyridine (IX) structure. In neither instance is the evidence conclusive.



VIII



IX

We have obtained the higher melting isomer (m.p. 135°) by effecting the condensation in dimethylformamide solution[12] as well as by treatment of the lithium salt of 2-aminopyridine with phenacyl bromide. Since it is known[13] that condensation of 2-aminopyridine with alkyl halides in the presence of sodium or lithium amide leads to the 2-substituted aminopyridine, it would appear that the condensation product of m.p. 135°, hitherto assumed to be the 2-phenyl derivative VIII should in fact be assigned the 3-phenylimidazo-(1,2-a)pyridine structure (IX) unless alkylation of 2-aminopyridine with α-haloketones proceeds differently than with alkyl halides.

Experimental[14]

1-(2-Pyridylthio)-4-diethylamino-2-butanone Dihydrobromide (Vc).—The following procedure is typical of the preparation of the various 1-(2-pyridylthio)-ketones.

A solution of 3.5 g. of 1-bromo-4-diethylamino-2-butanone hydrobromide (III)[2] and 1.4 g. of 2-pyridinethiol (I)[15] in 20 cc. of glacial acetic acid was allowed to stand at room temperature for 1 hour. During this period, the product slowly separated as an oil and precipitation was completed by the addition of 100 cc. of ether. Removal of the solvent and trituration with boiling acetone furnished 4.1 g. (81%) of the tan **dihydrobromide monohydrate** of Vc with m.p. 121–124°. The analytical sample was obtained as colorless crystals from ethanol–acetone; m.p. 121–122°.

Anal. Calcd. for $C_{13}H_{22}Br_2N_2OS \cdot H_2O$: C, 36.13; H, 5.59. Found: C, 36.27; H, 5.85.

The anhydrous dihydrobromide (m.p. 162.5–163.5°) was obtained on drying the hydrate *in vacuo* at 100° for 8 hours.

Anal. Calcd. for $C_{13}H_{22}Br_2N_2OS$: C, 37.70; H, 5.35. Found: C, 37.62; H, 5.54.

For spectroscopic purposes, all of the dihydrobromides were converted to the corresponding free base with ammonia and the infrared and ultraviolet spectra determined immediately. Compounds Vb–d all exhibited an infrared band ($CHCl_3$ soln.) at 5.87 μ.

The semicarbazone monohydrobromide was prepared by allowing a solution of 0.5 g. of the dihydrobromide of Vc, 0.3 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate to stand at room temperature for 15 minutes in 5 cc. of water. The product was collected and recrystallized from ethanol, m.p. 172.5–173°.

Anal. Calcd. for $C_{14}H_{24}BrN_5OS$: C, 43.09; H, 6.19; S, 8.21. Found: C, 42.85; H, 6.67; S, 7.65.

1-(2-Pyridylthio)-4-dimethylamino-2-butanone Dihydrobromide (Vb).—This salt was obtained in 85% yield and melted at 161.5–162.5° after recrystallization from methanol–hexane.

Anal. Calcd. for $C_{11}H_{18}Br_2N_2OS$: C, 34.22; H, 4.69. Found: C, 33.92; H, 4.83.

The semicarbazone monohydrobromide exhibited m.p. 163–163.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{20}BrN_5OS$: C, 39.78; H, 5.56. Found: C, 39.78; H, 5.77.

1-(2-Pyridylthio)-4-morpholino-2-butanone Dihydrobromide (Vd).—The dihydrobromide with m.p. 196–199° was isolated in 81% yield.[16] The analytical sample showed m.p. 205–207° after three recrystallizations from methanol.

Anal. Calcd. for $C_{13}H_{20}Br_2N_2O_2S$: C, 36.46; H, 4.70. Found: C, 35.93; H, 5.19.

The semicarbazone monohydrobromide melted at 183.5–184°.

Anal. Calcd. for $C_{14}H_{22}BrN_5O_2S$: C, 41.60; H, 5.48; N, 17.33; Br, 19.77. Found: C, 41.91; H, 5.65; N, 17.43; Br, 19.58.

2-(2-Pyridylthio)-acetophenone Hydrobromide (Va).—Upon mixing the reactants in acetic acid solution, a colorless crystalline product was obtained in 96% yield; m.p. 184.5–185.5° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{13}H_{12}BrNOS$: C, 50.34; H, 3.90. Found: C, 50.18; H, 3.76.

The oily base, obtained on making an aqueous solution of the dihydrobromide basic with ammonia, exhibited an infrared carbonyl band ($CHCl_3$ soln.) at 5.95 μ.

1-Phenacyl-2-bromopyridinium Bromide (VII).—A solution of 11.1 g. of phenacyl bromide and 4.4 g. of 2-bromopyridine in 40 cc. of benzene was refluxed for 8 days. The tan precipitate was collected (6.5 g.), washed with benzene and recrystallized from dimethylformamide–ether; colorless crystals, m.p. 177–177.5°.

Anal. Calcd. for $C_{13}H_{11}Br_2NO$: C, 43.73; H, 3.10. Found: C, 44.15; H, 2.91.

1-Phenacyl-2-pyridinethione (VIa).—A solution of 3.0 g. of sodium hydrogen sulfide and 4.3 g. of 1-phenacyl-2-bromopyridinium bromide (VII) in 100 cc. of water was heated on the steam-bath for 2 hours. The product (2.5 g. m.p. 169–179°) was collected and recrystallized from ethanol and from ethyl acetate; pale yellow needles, m.p. 180.5–181.5°.

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.13; H, 4.83. Found: C, 67.84; H, 4.68.

3-Phenylimidazo-(1,2-a)-pyridine (IX). (a) **In Dimethylformamide.**—A mixture of 3.7 g. of 2-aminopyridine, 7.9 g. of phenacyl bromide, 3.7 g. of sodium bicarbonate and 25 cc. of dimethylformamide was heated for 1 hour at 150° after moderation of the initial exothermic reaction. Dilution with water liberated an oil which solidified on cooling. Collection of the solid furnished 5.2 g. (67%) of crystals with m.p. 134–136°, raised to 135–136° upon recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19. Found: C, 80.38; H, 5.35.

(b) **With Lithium Amide.**—2-Aminopyridine (6.6 g.) was converted into the lithium salt by refluxing with 1.6 g. of lithium amide in 150 cc. of dry toluene for 2 hours. At the end of this period, a solution of 14 g. of phenacyl bromide in 50 cc. of toluene was added dropwise over a period of 1 hour and refluxing was continued for an additional 21 hours. After addition of dilute hydrochloric acid, separation

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(6) J. Renault, *Compt. rend.*, **232**, 77 (1951).

(7) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(8) I. A. Kaye, C. L. Parris and W. J. Burlant, THIS JOURNAL, **75,** 746 (1953).

(9) V. K. Matveev, *Bull. acad. sci. U. R. S. S. Classe sci. math. nat. Ser. chim.*, 533 (1936); *C. A.*, **31**, 6654 (1937).

(10) L. Schmid and B. Bangler, *Ber.*, **59**, 1360 (1926).

(11) L. Goldfarb and M. S. Kondakova, *J. Applied Chem. (U.S.S.R.)*, **15,** 151 (1942).

(12) *Cf.* H. L. Rice and G. R. Pettit, THIS JOURNAL, **76,** 302 (1954).

(13) *Cf.* C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, *ibid.*, **68**, 1999 (1946); I. A. Kaye, I. C. Kogon and C. L. Parris, *ibid.*, **74**, 403 (1952).

(14) Melting points are uncorrected. We are indebted to Miss Phyllis Tocco (Wayne University) and Geller Laboratories (Hackensack, N. J.) for the microanalyses.

(15) J. R. Thirtle, THIS JOURNAL, **68**, 342 (1946).

(16) The reported (ref. 2) m.p. for 1-bromo-4-morpholino-2-butanone hydrobromide (IV) is 164–165°. In the present investigation, this salt had m.p. 174–175° after recrystallization from ethanol–acetone. *Anal.* Calcd. for $C_8H_{16}Br_2NO_2$: C, 30.31; H, 4.77. Found: C, 30.37; H, 4.81.

of the layers, addition of potassium carbonate to the acid solution and extraction with chloroform, the washed and dried chloroform solution was distilled *in vacuo*. After a fore-run of unreacted 2-aminopyridine, the fraction boiling at 185–205° and 0.5 mm. was collected and crystallized from ligroin; yield 3.4 g. (42% based on recovered 2-aminopyridine), m.p. 131–133°. Recrystallization raised the m.p. to 133–135°, undepressed upon admixture with a specimen prepared by procedure a; identity was confirmed by infrared comparison.

Ultraviolet Absorption Spectra.—All spectra were determined in 95% ethanol solution: 1-phenacyl-2-pyridinethione (VIa)—$\lambda_{max.}$ 243, 285 and 365 mμ (log ε 4.20, 4.12 and 3.78); $\lambda_{min.}$ 265 and 315 mμ (log ε 3.75 and 3.43).

2-Pyridinethiol: $\lambda_{max.}$ 285 and 363 mμ (log ε 3.94 and 3.64); $\lambda_{min.}$ 245 and 315 mμ (log ε 2.89 and 3.07).

1-Ethyl-2-pyridinethione: $\lambda_{max.}$ 287 and 360 mμ (log ε 4.12 and 3.86); $\lambda_{min.}$ 245 and 315 mμ (log ε 2.70 and 3.37).

2-(2-Pyridylthio)-acetophenone (**Va**): $\lambda_{max.}$ 247 and 288 mμ (log ε 4.36 and 3.76); $\lambda_{min.}$ 270 mμ (log ε 3.59).

1-(**2-Pyridylthio**)-**4-dialkylamino-2-butanones** (**Vb–d**): λ_{max} 245 and 290 mμ (log ε 4.03 and 3.67); $\lambda_{min.}$ 265 mμ (log ε 3.28).

2-Ethylthiopyridine: $\lambda_{max.}$ 250 and 293 mμ (log ε 3.90 and 3.54); $\lambda_{min.}$ 270 mμ (log ε 3.16).

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Lauraldehyde. Hemiacetal Formation

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RECEIVED FEBRUARY 18, 1954

Lauraldehyde has been reported to exist in two crystalline forms, m.p. 11° and 44.5°. It is shown in this report that the higher melting form is identical with the hemiacetal of lauraldehyde and lauryl alcohol.

Krafft[1] decomposed thermally a mixture of the barium salts of lauric and formic acids and obtained a substance which he described as lauraldehyde, m.p. 44.5°. Many years later Zaar[2] employed the same reaction and found that the product contained lauryl alcohol which was shown to form with lauraldehyde a crystalline substance which melted at 44.5–45.5° and had the composition of the hemiacetal. It was stated, however, that this product was not identical with the one obtained by Krafft. The lauraldehyde prepared by Zaar was a liquid, m.p. 11°, which deposited a quantity of crystals, m.p. 44.5°, on standing, and this substance was considered to be identical with Krafft's lauraldehyde. It was converted in part into the liquid aldehyde by vacuum distillation. The molecular weights of both solid and liquid aldehydes were found to be in good agreement with the theoretical value for lauraldehyde. Both gave the same oxime and semicarbazone, and from such convincing evidence Zaar concluded that lauraldehyde existed in two monomeric forms, differing only in physical properties.

Our experiments show that lauraldehyde and lauryl alcohol readily combine to form the hemiacetal which corresponds in analysis, molecular weight, physical properties and chemical behavior to the substance, m.p. 44.5°, reported by Zaar. This hemiacetal yields lauraldehyde semicarbazone and a phenylurethan which is identical with that obtained from lauryl alcohol.

It seems very probable from these results and from the failure of a number of methods to convert lauraldehyde, m.p. 11°, into a higher melting form, that the higher melting form reported by earlier workers was in fact the hemiacetal of lauraldehyde and lauryl alcohol.

The hemiacetal is soluble in acetone and ether in which it is apparently highly dissociated, while it has a limited solubility in lauraldehyde where, owing to the high concentration of aldehyde, the equilibrium favors the hemiacetal. The molecular weight of the hemiacetal, determined cryoscopically in benzene, indicates nearly complete dissociation. Upon distillation of the hemiacetal, the forerun is very rich in lauraldehyde and as distillation continues the distillate becomes richer in lauryl alcohol. Experiments were conducted to determine the conditions for precipitation of the hemiacetal, and it was found that no more than 5.0 g. of lauryl alcohol may be added to 100 g. of lauraldehyde (aldehyde content 99.8%) without precipitation of the hemiacetal at temperatures below 19°, and that no more than 7.2 g. of the alcohol may be added at temperatures below 24°.

The infrared spectrum of the hemiacetal in carbon tetrachloride has the following discernible features: –OH absorption at 3350 and 1060 cm.$^{-1}$, C=O absorption at 1735 and 2740 cm.$^{-1}$, C–O–C absorption at 1120 cm.$^{-1}$, and suggests an equilibrium between the hemiacetal and its dissociation products, lauraldehyde and lauryl alcohol.

Experimental Part

Hemiacetal Formation.—Lauraldehyde (Givaudan–Delawanna, Inc.), b.p. 104–109° (6 mm.), aldehyde content (hydroxylamine method) 95.98%, acid value 4.01, was shaken with a saturated solution of sodium bisulfite for one hour. The resulting addition product was collected, washed with cold water, ethyl alcohol and ether. The bisulfite compound was decomposed with sodium carbonate, and the aldehyde was extracted with ether. Concentration of the dried extracts gave an oil which was fractionated to yield a main fraction, b.p. 99.5–100.0° (3.5 mm.), $n^{24.7}\text{D}$ 1.4328, aldehyde content 99.8%, acid value 0.57. A mixture of 10 g. of this aldehyde and 10 g. of lauryl alcohol was heated at 50° for a period of 30 minutes. Upon cooling, immediate precipitation of a white, waxy solid occurred. After recrystallization from acetone the product melted at 43.7–44.0°; yield 15.9 g. (80%). Bases strongly catalyze the formation of the hemiacetal at room temperature.

Anal. Calcd. for $C_{24}H_{50}O_2$: C, 77.77; H, 13.60; mol. wt., 370.6. Found: C, 77.68; H, 13.72; mol. wt. (benzene), 204.4, 196.7, 195.1.

The hemiacetal gave lauraldehyde semicarbazone, m.p. 102–104°, and a phenylurethan, m.p. 76°, which was identical with the phenylurethan prepared from lauryl alcohol.

Thermal Decomposition of the Hemiacetal.—A small quantity of the hemiacetal (16.5 g.) was fractionated under reduced pressure. The fractions obtained were analyzed for lauraldehyde content by the hydroxylamine method.

Fraction, b.p., °C. (mm.)	Grams	Lauraldehyde, %	Lauraldehyde, Wt., g.
102.4–107.2 (4.5)	5.7	73.4	4.18
107.2–113.1	3.9	55.1	2.15
113.1–116.0	3.9	31.9	1.24
Residue (above 116°)	3.0	17.1	0.51
Total	16.5		8.08

Solubility of the Hemiacetal in Lauraldehyde.—To 5.0 g. of lauraldehyde (aldehyde content 99.8%) was added 0.25 g. of lauryl alcohol. The reaction mixture was warmed at 40° for a few minutes and upon cooling to 15° gave a heavy precipitate of the hemiacetal, which dissolved upon warming to 20°. Upon cooling to 19.0° and inoculating the solu-

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(1) F. Krafft, *Ber.*, **13**, 1413 (1880); **23**, 2360 (1890).

(2) B. Zaar, *J. prakt. Chem.*, **132**, 163 (1931).