The Reaction of 2-Acetoacetamidopyridines with Phosgene. A Route to Novel 3-Acetyl-2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

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2-(Acetoacetamido)pyridine, **1**, and its 5-methyl derivative, **2**, with phosgene, gave 3-acetyl-2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **5**, and 3-acetyl-2-chloro-7-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one, **6**, respectively. The structures of these compounds followed from their elemental analyses, and interpretations of their uv, ir, pmr, and X-ray spectra. An alternative route to **5** and **6**, which sought first to react **1** and **2** with methyl - and benzyl chloroformates, was unsuccessful, and led, instead, to elimination of the acetoacetyl group with concomitant formation of the carbamate derivatives, **10** and **11**.

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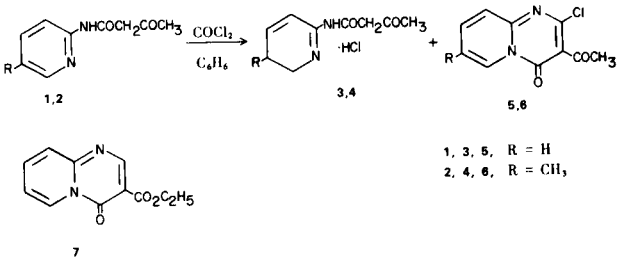
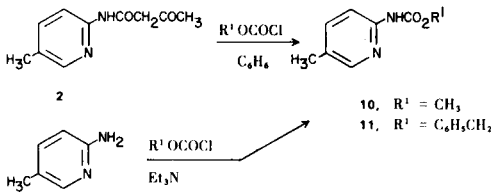
In recent papers, we have reported the intramolecular cyclization of a variety of substituted 2-(acetoacetamido)-pyridines, reactions which led to the formation of derivatives of the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one heterocycle (**2a-d**). During those investigations, several by-products of unknown structure were isolated, and it was in an effort to elucidate the structure of one of these, that we examined the behavior of 2-(acetoacetamido)-pyridine, **1**, and its 5-methyl derivative, **2**, toward phosgene (3). In benzene solution at ambient temperature, reaction was prompt in each instance, and, gave as the major product, the benzene insoluble hydrochlorides of **1** and **2**, **3** and **4**, respectively. The minor products from each reaction, **5** and **6**, were isolated *via* recrystallization of the solids recovered by concentration of the benzene filtrates from **3** and **4**. The structures assigned to **5** and **6** developed from a consideration of several criteria. Each compound was shown to be homogeneous by tlc and elemental analyses indicated that their molecular formulas were $C_{10}H_7ClN_2O_2$ and $C_{11}H_9ClN_2O_2$, respectively. Their uv spectra were similar, showing three maxima at 256, 317, and 355 mμ and 260, 315, and 359 mμ. That these absorptions were strikingly similar to those reported (4) for the 3-carboethoxy derivative, **7**, *i.e.*, three maxima at 260, 310, and 360 mμ, represented presumptive evidence that **5** and **6** had the structures designated below (5); subsequently, these assignments were confirmed by an analysis of other spectral data. Thus, the ir spectra of **5** and **6** showed no NH or OH



absorptions and revealed the anticipated two carbonyl bands at *ca.* 1690 and 1670 cm^{-1} that could be assigned, respectively, to the carbonyl group of the substituent at position-3 and the cyclic amide carbonyl group at position-4. The pmr spectrum of **5** showed the absence of a singlet at *ca.* δ 6.25, revealing the absence of a proton at position-3 (2a, 6), as well as a three-proton singlet at δ 2.64, attributable to the methyl group of the 3-acetyl substituent. Similarly, the pmr spectrum of **6** revealed no resonance at *ca.* δ 6.25, a three-proton singlet at δ 2.62, and a second three-proton singlet, a signal associated with the 7-methyl group, upfield at δ 2.50 (6). The mass spectra of **5** and **6** offered additional support for the assigned structures: the molecular ions were observed at m/e 222 and 236, respectively, and the presence of fragments of M^+-15 and M^+-43 in both spectra suggested that an acetyl group was present in each compound (7). Finally, X-ray analysis of a single crystal of **5** established the structure proposed for that compound, and indirectly, that suggested for **6** (8).

In an attempt to elaborate the mechanism of the above reaction, and, possibly to improve the yields of **5** and **6**, **2** was reacted with methyl-, **8**, and benzyl chloroformate, **9**, under the same conditions as those employed with phosgene. Unexpectedly, the products from these reactions were shown to be the urethanes, **10** and **11**, respectively, and **4**; the formation of the former, involved a most unusual elimination of the acetoacetyl substituent. These anomalous products were identified by their elemental analyses, ir and pmr spectra, and by comparison with authentic samples prepared by the reactions of 2-amino-5-methylpyridine, **12**, with **8** and **9** (10). Thus, the mechanism by which **5** and **6** were formed remains



obscure, particularly, since 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with 3-acetyl and 2-chloro substituents are unknown. Uncertainty exists, also, as to the mechanism for the cleavage of the acetoacetyl group in **2** by **8** and **9** (11), under the mild experimental conditions employed.

EXPERIMENTAL

The analytical data and spectra were obtained by the staff of the Analytical Department of this Institute as described in our earlier papers (1a-d). The melting points were determined in capillary tubes in an electrically heated oil bath and are not corrected.

3-Acetyl-2-chloro-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **6**.

To a solution of 12.0 g. (0.06 mole) of **2** in 1.5 l. of reagent grade benzene at *ca.* 20° was added dropwise in 0.67 hour, 6.8 g. (0.07 mole) of phosgene in 55 ml. of the same solvent. The reaction mixture turned orange immediately, and, after several minutes, that color formation was followed by the separation of a flocculent orange solid. Subsequently, the mixture was stirred for 72 hours at ambient temperature and the solid filtered to give 12.3 g. of crude **4**, m.p. 170-175° (turbid). Recrystallization of an analytical sample from acetonitrile gave pure **4**, m.p. 174-176° dec. A mixture m.p. with authentic **4** (see below) was 174-176° dec., and their ir and pmr spectra were superimposable.

Anal. Calcd. for $C_{10}H_{12}N_2O_2 \cdot HCl$: C, 52.62; H, 5.73; N, 12.25; Cl, 15.50. Found: C, 52.55; H, 5.77; N, 12.30; Cl, 15.57.

The above crude product, 10.0 g., was dissolved in 100 ml. of cold water and the *p*H of the solution was adjusted to 7.5 with solid sodium bicarbonate. The solid that separated was filtered and dried to give 5.50 g. (69% recovery) of **2**, m.p. and mixture m.p. 140-142°.

The benzene filtrate from the crude **4** was concentrated to dryness to give 1.0 g. of crude **6**, m.p. 138-144°. Recrystallization from 600 ml. of cyclohexane gave 0.80 g. (6% yield) of pure **6**, m.p. 150-152°; uv λ max (methanol): 260, 315, 359 mμ [ε (x 10^3) 10.0, 4.0, 16.0]; ir (mull): ν 1700(s), 1675(s), 1630(s), 1550(s), 1520(s), 1460(broad s), 1420(s) cm^{-1}; pmr (deuteriochloroform): δ 2.50 (s, 3H, C*H*$_3$ at position-7), 2.62 (s, 3H, C*H*$_3$CO), 7.53-8.00 (m, 2H, 2 Py-*H*), 8.90 [d (J = 1.5 Hz), 1H, *H* at position-6]; R_f (one spot), *ca.* 0.86 [C_6H_6:CH_3OH (9:1)].

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.84; H, 3.83; N, 11.84; Cl, 14.98; M^+, 236. Found: C, 55.63; H, 3.55; N, 11.97; Cl, 15.15; M^+, 236.

3-Acetyl-2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **5**.

The reaction between 17.2 g. (0.1 mole) of **1** in 1.0 l. of reagent grade benzene and 9.6 g. (0.1 mole) of phosgene in 80 ml. of the same solvent (1 hour addition) as above gave 16.9 g. of crude **3**, m.p. 140-150° (turbid). An analytical sample from acetonitrile gave pure **3**, m.p. 153-154° dec.; a mixture m.p. with authentic **3** (see below) was 153-154°, and their ir and pmr spectra were superimposable.

Anal. Calcd. for $C_9H_{10}N_2O_2 \cdot HCl$: C, 50.37; H, 5.17; N, 13.05; Cl, 16.52. Found: C, 50.10; H, 4.96; N, 13.00; Cl, 16.54.

When the filtrate from **3** was concentrated to dryness, there was obtained 1.8 g. of crude **5**, m.p. 145-155°; recrystallization from 40 ml. of ethyl acetate gave 0.94 g. (5% yield) of pure **5**, m.p. 145-155°; recrystallization from 40 ml. of ethyl acetate gave 0.94 g. (5% yield) of pure **5**, m.p. 161-163°; uv λ max m.p. 161-163°; uv λ max (methanol): 256, 317, 355 mμ [ε (x 10^3) 9.0, 5.0, 13.0]; ir (mull): ν 1690(s), 1670(s), 1620(s), 1550(s), 1460(s), 1420(s) cm^{-1}; pmr (deuteriochloroform): δ 2.64 (s, 3H, C*H*$_3$CO), 7.20-8.20 (m, 3H, 3 Py-*H*), 9,10 [q (J = 1.5, 6.0 Hz) H at postition-6], R_f (one spot), *ca.* 0.80 [C_6H_6:$(CH_3)_2CO$ (1:1)].

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.96; H, 3.17; N, 12.58; Cl, 15.93; M^+, 222. Found: C, 53.69; H, 2.92; N, 12.34; Cl, 15.97; M^+, 222.

Reaction Between **2** and Methyl Chloroformate, **8**. Formation of **10**.

To a solution of 3.9 g. (0.02 mole) of **2** in 500 ml. of reagent grade benzene at ambient temperature, was added in 0.5 hour, 2.00 g. (0.02 mole) of **8** (97% pure) in 40 ml. of the same solvent. The mixture was subsequently stirred for 72 hours at *ca.* 20° and filtered to give 2.3 g. of crude **4**; recrystallization from 300 ml. of acetonitrile gave 2.0 g. of pure **4**. The benzene filtrate from the crude **4** was concentrated to dryness to give 2.3 g. of solid, m.p. 105-132°. This was dissolved in 50 ml. of dichloromethane, the solution was washed with water, then with 5% aqueous sodium bicarbonate until the washings were at *p*H 7.5, dried, and concentrated to give 1.6 g. of solid, m.p. 125-135°. Recrystallization from 15 ml. of acetonitrile gave 1.1 g. (33% yield) of **10**, m.p. 145-147°; ir (potassium bromide): ν 3200(s), 1725(s), 1600(s), 1540(s), 1480(m, 1430(m) cm^{-1}; pmr (deuteriochloroform): δ 2.38 (s, 3H, C*H*$_3$ at position-5), 3.88 (s, 3H, COC*H*$_3$), 7.40-8.30 (m, 3H, 3 Py-*H*), 9.55-9.80 [m, 1H, N*H*- (exchanges with deuterium oxide)]; R_f *ca.* 0.75 [C_6H_6:$(CH_3)_2CO$ (4:1)].

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.16; N, 16.86; N.E., 166. Found: C, 57.84; H, 6.03; N, 16.92; N.E. (perchloric acid), 163.

When the reaction was repeated, with the modification that 2.0 g. (0.02 mole) of triethylamine was added to the **2** in benzene, triethylamine hydrochloride was formed instead of **4**, and the yield of **10** was 2.2 g. (66%).

Reaction Between **2** and Benzyl Chloroformate, **9**. Formation of **11**.

To a solution of 3.9 g. (0.02 mole) of **2** and 2.2 g. (0.02 mole) of triethylamine in 500 ml. of reagent benzene was added in 0.75 hour, 3.4 g. (0.02 mole) of **9** in 50 ml. of benzene, while maintaining the reaction temperature at 10-15°. Subsequently, the mixture was stirred at ambient temperature for 72 hours. The insoluble material was filtered to give 2.5 g. (quantitative yield) of triethylamine hydrochloride. The benzene filtrate was concentrated to dryness and the solid residue, 3.8 g., was recrystallized from 60 ml. of acetonitrile to give 2.8 g. (58% yield) of **11**, m.p. 148-150°; uv λ max (methanol): 231, 280 mμ [ε (x 10^3) 18.5, 5.2]; ir (potassium bromide): ν 3200(m), 1730(s), 1615(s), 1605(s), 1545(s), 1500(m), 1490(m), 1460(m), 1450(m), 1390(s) cm^{-1}; pmr (deuteriochloroform): δ 2.10 (s, 3H, C*H*$_3$ at position-5), 5.25 (s, 2H, C*H*$_2$), 6.10-7.10 (m, 8H, 5 Ar-*H* plus 3 Py-*H*), 9.05-9.35 [m, 1H, N*H* (exchanges with deuterium oxide)]; R_f *ca.* 0.94 [C_6H_6:$(CH_3)_2CO$ (1:1)].

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.39; H, 5.81; N, 11.56; N.E., 242. Found: C, 69.22; H, 5.84; N, 11.76; N.E. (perchloric acid), 242.

Reaction Between 2-Amino-5-methylpyridine, **12**, and **8**. Preparation of Authentic **10**, along with 1,3-*bis*(2-pyridyl)urea, **13**.

To a solution of 6.5 g. (0.06 mole) of **12** and 6.6 g. (0.06 mole) of triethylamine in 500 ml. of reagent grade benzene was added in 0.5 hour a solution of 6.0 g. (0.06 mole) of **8** (97% pure) in 40 ml. of the same solvent. The reaction mixture was kept at 10-15° during the addition, and then stirred at ambient temperature for 18 hours. The insoluble material was filtered to give 9.7 g. of solid, m.p. 233-250°; when suspended in 200 ml. of cold water and refiltered, there was obtained 1.1 g. of solid, m.p. 220-221°. The aqueous filtrate was concentrated to dryness, and the residue, 7.20 g., m.p. 123-140°, was extracted with 200 ml. of boiling diisopropyl ether, and filtered hot from 1.0 g. of insoluble material, m.p. 212-218° (see below for diisopropyl ether filtrate). The combined 1.1 g. and 1.0 g., 2.1 g., was recrystallized from 75 ml. of benzene to give 1.70 g. (20% yield) of **13**, m.p. 218-220°; λ max (methanol): 232, 283 mμ [ε (x 10^3) 15.1, 4.7]; ir (potassium bromide): ν 3210(w), 1680(s), 1615(m), 1580(s), 1540(broad s), 1490(s), 1475(s) cm^{-1}; pmr (deuteriochloroform): δ 2.28 (s, 6H, 2(C*H*$_3$) at position-5), 7.54 [s, 4H, 2(Py-*H*) at positions-3 and -4]; 8.20 [s, 2H, 2(Py-*H*) at position-6], R_f *ca.* 0.4 [C_6H_6:$(CH_3)_2CO$ (4:1)].

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.77; N, 23.14. Found: C, 64.35; H, 5.84; N, 22.94.

The cooled diisopropyl ether filtrate from the above extraction deposited a crystalline solid; this was filtered to give 3.4 g. of crude **10**, m.p. 142-145°. Recrystallization from 100 ml. of diisopropyl ether gave 2.0 g. (40% yield) of pure **10**, m.p. 145-147°. Its uv, ir, and pmr spectra were identical with the product isolated from the reaction of **2** with methyl chloroformate, and a mixture m.p. of both samples showed no depression.

Reaction Between **12** and **9**. Preparation of Authentic **11** and **13**.

The reaction was carried out between 6.5 g. of **12** and 6.6 g. of triethylamine in 500 ml. of reagent grade benzene and 10.2 g. (0.06 mole) of **9** in 40 ml. of the same solvent, as described directly above. The yield of recrystallized **13** was 1.0 g., m.p. 218-220°. The benzene filtrate from the crude **13** was concentrated to dryness; tlc of the residual solid, 6.3 g., showed it to be a complex mixture. A portion, 3.0 g., dissolved in 30 ml. of dichloromethane, was chromatographed on a column of 90 g. of silica gel (Grace-Davison, grade 923, 100-200 mesh) and eluted first with 200 ml. of benzene and then with 3-100 ml. portions of benzene-acetone (4:1). The combined eluates were concentrated to dryness, and the solid, 2.2 g., m.p. 125-132° was recrystallized from 200 ml. of diisopropyl ether to give 1.3 g. (43% yield) of **11**, m.p. 148-150°. A mixture m.p. with the product obtained from **2** and **9** showed no depression, and their uv, ir, and pmr spectra were identical.

Preparation of Authentic **3**.

To a solution of 0.5 g. of **1** in 30 ml. of 2-propanol at *ca.* 20° was added 0.6 ml. of 4.8 *N* ethereal hydrogen chloride, with thorough mixing. The solution was cooled to 0° and the precipitated solid filtered and dried *in vacuo* to give 0.5 g. (83% yield) of **3**, m.p. 153-154° dec.; ir (potassium bromide): ν 3430(w), 1700(s), 1610(s), 1560(s), 1495(s) cm^{-1}; pmr (trifluoroacetic acid): δ 2.55 (s, 3H, C*H*$_3$CO), 4.16 (s, 2H, C*H*$_2$), 7.40-8.75 (m, 3H, 3 Py-*H*), 14.30-15.25 (m, 2H, N*H*$_2^+$).

Anal. Calcd. for $C_9H_{10}N_2O_2$·HCl: C, 50.37; H, 5.17; N, 13.05; Cl, 16.52. Found: C, 50.16; H, 4.99; N, 13.02; Cl, 16.54.

Preparation of Authentic **4**.

To a solution of 1.0 g. of **2** in 50 ml. of acetonitrile at *ca.* 20° was added 1.2 ml. of 4.8 *N* 2-propanolic hydrogen chloride. The salt separated directly. The suspension was cooled to 0° and the solid filtered and dried *in vacuo* to give 1.1 g. (quantitative yield) of **4**, m.p. 174-176° dec.; ir (potassium bromide): ν 3410(w), 1705(s), 1630(s), 1580(m), 1520(s), 1475(m), 1450(m) cm^{-1}; pmr (trifluoroacetic acid): δ 2.54 (s, 3H, C*H*$_3$ at position-5), 2.60 (s, 3H, C*H*$_3$CO), 4.18 (s, 2H, C*H*$_2$), 7.15-8.45 (m, 3H, 3 Py-*H*), 14.40-15.50 (m, 2H, N*H*$_2^+$).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$·HCl: C, 52.62; H, 5.73; N, 12.25; Cl, 15.49. Found: C, 52.96; H, 5.51; N, 12.52; Cl, 15.44.

2-Acetoacetamido-5-methylpyridine, **2**.

To a stirred solution of 55.0 g. (0.5 mole) of **12** in 500 ml. of reagent grade toluene, preheated to 95°, was added, dropwise, 46.0 g. (0.55 mole) of diketene at a rate that maintained the internal temperature at 95-100°. Subsequently, the solution was heated under reflux for 1 hour and then cooled to 0°. The crystalline product that separated was filtered to give 68.6 g. of solid, m.p. 139-141°. Recrystallization from 4.5 l. of heptane gave 61.0 g. (63% yield) of **2**, m.p. unchanged at 139-141°; uv λ max (methanol): 240, 282 mμ [ε (x 10^3) 13.6, 8.4]; ir (potassium bromide): ν 3240(m), 1725(s), 1690(s), 1670(s), 1600(s), 1550(s), 1480(s) cm^{-1}; pmr (deuteriochloroform): δ 2.38 (s, 3H, C*H*$_3$ at position-5), 2.40 (s, 3H, C*H*$_3$CO), 3.60 (s, 2H, C*H*$_2$COCH$_3$), 7.45-8.25 (m, 3H, 3 Py-*H*), 9.30-9.85 (m, 1H, N*H*).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.58. Found; C, 62.46; H, 6.16; N, 14.77.

REFERENCES AND NOTES

(1) To whom all correspondence should be addressed.

(2a) H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, **10**, 123 (1973); (b) H. L. Yale and J. T. Sheehan, *ibid.*, **10**, 143 (1973); (c) H. L. Yale, *ibid.*, **11**, 739 (1974); (d) H. L. Yale, *ibid.*, **12**, 427 (1975).

(3) There are no reports in the literature of these or related reactions.

(4) R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 4906, 5491 (1952).

(5) 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones with 3-acetyl-2-chloro substituents are unknown in the literature.

(6) H. L. Yale and E. R. Spitzmiller, *J. Heterocyclic Chem.*, **13**, 797 (1976).

(7) The authors are indebted to Dr. M. S. Puar for the pmr spectra and to Dr. P. T. Funke for the mass spectra.

(8) The single crystal X-ray structural analysis of **5** was carried out by Mrs. B. Toeplitz and Dr. J. Z. Gougoutas. They reported that needle-like crystals of **5**, obtained by recrystallization from diisopropyl ether were used; these belonged to the monoclinic space group $P_{2\ 1/c}$, with unit cell constants, α = 3.865, β = 14.8699, c = 16.4167 A, and β = 93.5°. The crystals had a density, measured by flotation, of 1.628 g./cm^3. Intensities on 1074 reflections were obtained on a Syntex automated diffractometer. A Patterson map did not clearly indicate the position of the chlorine atom, hence, a direct phasing approach for centrosymmetric space groups was tried. The chlorine atom and all but one of the other atoms were located on an E map using 118 reflections with highest E value. Subsequent Fourier maps, using the full data set, located the remaining atom and a final R factor of 0.18 was reached without least squares refinement.

(9) This is the procedure of R. L. Shriner and R. G. Child, *J. Am. Chem. Soc.*, **74**, 549 (1952); these authors reported that 2-aminopyridine and methyl chloroformate in benzene at ambient temperature gave a mixture of 2-pyridylcarbamic acid, methyl ester and 1,3-*bis*(2-pyridyl)urea. N. P. Buu-Hoi, R. Rips, and C. Derappe, *J. Med. Chem.*, **7**, 364 (1964) prepared **10** by a different procedure and reported a m.p. of 215°.

(10) Although symmetrically *N*,*N*-disubstituted 2-(diacylamido)pyridines are known [J. J. den Hertog, C. R. Kolder, and W. P. Combe, *Rec. Trav. Chim.*, **70**, 591 (1951); German Patent 406,206 (*Chem. Zentr.*, I, 1534 (1925); E. H. Huntress and H. C. Walter, *J. Org. Chem.*, **13**, 735 (1948); H. L. Yale, *ibid.*, **35**, 4254 (1970)], unsymmetrical *N*-acylated-2-pyridylcarbamic acid esters are unknown in the literature.