in 1,2-dimethoxyethane (15–35 mL) was added to this solution and the mixture was refluxed for 8–12 h. The solution was cooled and filtered, and the filtrate was concentrated in vacuo. The crude product was treated with ether (150–200 mL) and filtered, and the filtrate was washed with equal volumes of water until the aqueous layer was colorless (three or four washings). The ether extract was dried ($MgSO_4$), percolated through a short column of Florisil (if necessary), and concentrated to give the pure desulfurized product.

General Procedure for Reaction of Thiones with Bis(triphenylphosphine)iminium Tetracarbonylcobaltate and Cyclopentadienyliron Dicarbonyl Dimer. The thioketone (2.5 mmol) and $(Ph_3P)_2N^+Co(CO)_4^-$ or $[C_5H_5Fe(CO)_2]_2$ (1.4 mmol) in benzene (5–7 mL) was heated in a Carius tube at 90–100 °C for 4 days. During this period, a large amount of black precipitate was formed. The tube was opened, the black material was filtered, and the filtrate was concentrated to 2–3 mL. The latter was chromatographed on silica gel using petroleum ether (bp 80–100 °C). Elution with benzene–petroleum ether (1:5 to 1:1) gave the olefin **3**.

General Procedure for the Reaction of Thiones with Dicobalt Octacarbonyl. A mixture of the thione (2.7 mmol) and dicobalt octacarbonyl (0.51 g, 1.5 mmol) in benzene (50 mL) was refluxed for 5 h. The solution was cooled and filtered, and evaporation of the filtrate gave **3**. Crystallization of the latter from benzene–petroleum ether gave the pure crystalline olefin **3**.

Acknowledgment. We are grateful to Imperial Oil Ltd. for support of this research.

Registry No.—$Fe(CO)_5$, 13463-40-6; $[(Ph_3P)_2N^+Co(CO)_4^-]$, 53433-12-8; $Co_2(CO)_8$, 10210-68-1; $[C_5H_5Fe(CO)_2]_2$, 12154-95-9; $HFe(CO)_4^-$, 18716-80-8.

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Chemistry of Heterocyclic Compounds. 25. Selective Metalation of the Pyridine Nucleus at the 3-Position[1]

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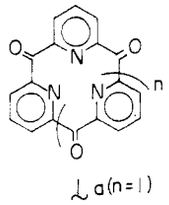
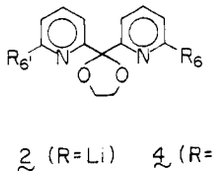
Treatment of bis(6-bromo-2-pyridyl) ketone ketal (**3**) with *n*-butyllithium in diethyl ether at −40 °C resulted in the isolation of pyridone **6** after normal hydrolytic workup. Selective metalation of the 3 position of **3** has been demonstrated by labeling studies. The formation of pyridone **6** is proposed to occur by first 1,4-elimination–fragmentation of one pyridine nucleus, followed by cyclization upon workup.

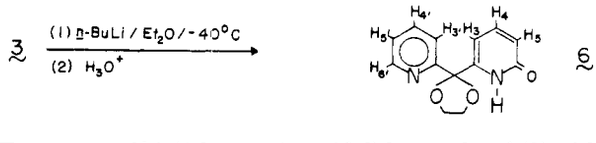
In one of our synthetic routes to trione **1a**,[3] as well as the related pyridine-based xanthoporphinogen model compounds (**1b**), the intermediary bis(6-lithio-2-pyridyl) ketone ketal (**2**) was of pivotal importance. Attempted conversion of **3**[4] to either diacid **4**, according to the standard metalation–carboxylation procedure of Gilman et al.,[5] or to 2,2-bis(2-pyridyl)-1,3-dioxolane (**5**) via metalation–hydrolysis, gave in both cases the undesired pyridone **6** as a major side product. We herein describe the directive metalation of the 3-position of the pyridine nucleus under normal metalation conditions[5] and propose procedures to circumvent, as well as a rationale for, pyridone formation.



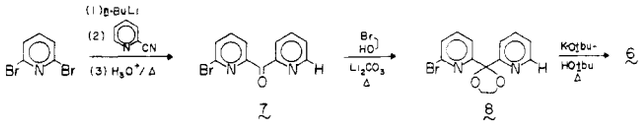
1 a (n = 1)
b (n = 2)



2 (R = Li) **4** (R = CO_2H)
3 (R = Br) **5** (R = H)



Treatment of bis(6-bromo-2-pyridyl) ketone ketal (**3**) with *n*-butyllithium (10% mol excess) in diethyl ether at −20 °C for 1 h, followed by carboxylation and mild hydrolysis, gave (30%) pyridone **6** along with the starting ketal as the major nonacidic components. Structure proof of **6** was achieved by reaction of methyl 2-pyridinecarboxylate and 2-bromo-6-lithiopyridine,[5,6] affording (70%) 2-pyridyl 6-bromo-2-pyridyl ketone (**7**), which upon base-catalyzed ketalization[4] gave (75%) ketal **8**. Treatment of **8** with potassium *tert*-butoxide

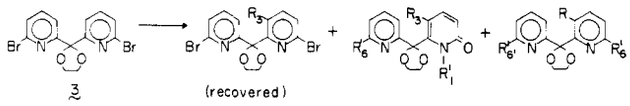


in anhydrous *tert*-butyl alcohol[7] afforded a 39% overall yield of pyridone **6**. In general, hydrolyses of these pyridyl ketals occur only under rigorous conditions (6 h in refluxing concentrated hydrochloric acid or 12–18 h in warm 80% acetic acid); thus, the ketals herein described would be unaffected by the hydrolytic workup procedure.

Pyridone **6** was isolated from **3** in comparable yield when the carboxylation step was eliminated. In order to assure the complete exclusion of oxygen, rigorous degassing procedures[8] were conducted and the reaction was conducted under an argon atmosphere; the yield of **6** remained virtually constant. However, either utilization of better anion stabilizing solvents, such as dimethoxyethane or tetrahydrofuran, or reduced reaction temperatures (−60 to −90 °C) suppressed pyridone formation, in favor of products arising from lithiated ketal. Table I summarizes the diversified reaction conditions vs. the product distribution.

In order to ascertain the position(s) of lithiation, ketal **3** was

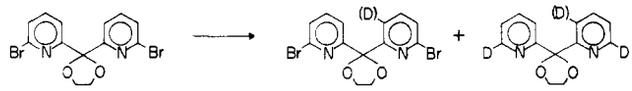
Table I



Reaction temp, °C	Solvent	Trapping agent	Isolated yields, %[a]		
−40 to −20	Et_2O	CO_2/H_3O^+	34 (R = H)	32 (R = R′ = H)	*b*
	THF	H_3O^+	51 (R = H)	<1 (R = R′ = H)	42 (R = R′ = H)
	DME	H_3O^+	50 (R = H)	<2 (R = R′ = H)	43 (R = R′ = H)
	Et_2O	D_3O^+	35 (R = H, D)	21 (R = R′ = >90% D)	Traces
−55 to −40	Et_2O	D_3O^+	30 (R = 26% D)	<2 (R′ = >90% D; R = H, D)[c]	52 (R′ = >95% D; R = 25% D)
−78 to −60	Et_2O	D_3O^+	48 (R = 23% D)	≪1[d]	47 (R′ = >95% D; R = 19% D)

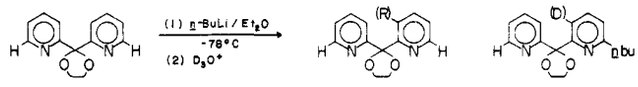
[a] Isolated, recrystallized product yields. [b] Traces of **5** were found; the diacid **4**, from the carboxylation step, was not isolated. [c] Isotopic distribution was not determined. [d] Insufficient sample to determine isotopic distribution.

subjected to a 10% mol excess of *n*-butyllithium in diethyl ether at −78 °C, then quenched with 10% D_2SO_4. Two partially deuterated ketals were isolated and characterized by NMR and confirmed with mass spectral data: the recovered starting material (**3**) had incorporated (23%) a deuterium atom at position 3 of one pyridine ring as determined by the decreased integration of the doublet of doublets at δ 7.82. The second major product, deuterated **5**, showed nearly complete absence of the characteristic broad doublet at δ 8.65 for the 6-pyridyl hydrogen and a 19% decrease in the aromatic region as compared to the ketal singlet. Under these conditions pyridone **6** was not detected. Isolation of partially deuterated starting ketal **3** from the reaction suggests directive lithiation at the 3 position being a result of the proximity of the ketal or



pyridyl moiety. There are numerous examples of ethereal directivity in metalation in aromatic nuclei;[9a] however, this is the first example of selective metalation of the normally unreactive (toward metalation) 3 position of a pyridine ring. Reaction temperatures above −55 °C resulted in marginal increases in both label incorporation as well as isolable pyridone. At −40 °C, pyridone **6** has deuterons incorporated in positions 1, 3, and 6′ to the extent of >90% based upon its NMR spectral data, which show complete absence of both the broad, 6-pyridyl doublet (δ 8.65) and doublet of doublet at δ 6.51. The pyridone nucleus shows only two doublets at δ 7.35 (H_4) and 6.42 (H_5); this pattern does not change upon hydrolysis; however, a new broad peak at δ 10.45 appears for the NH group. To confirm the exchangeability of the 3 position, pyridone **6** was dissolved in 10% deuteriosulfuric acid and the exchange rate monitored via NMR. After 40 h at 38 °C, negligible, if any, deuterium incorporation was observed; at increased temperatures, hydrolysis of the ketal moiety resulted.

Further confirmation of this selective metalation was demonstrated by treatment of **5** with *n*-butyllithium (10% mol excess) in diethyl ether at −78 °C, followed by quenching with 10% D_2SO_4. The recovered "starting" ketal has deuterium incorporation (ca. 18%) predominantly at the 3 position as determined by NMR spectral integration and mass spectral data [*m/e* 228–229 (18%); $M^+ - C_5H_4N \rightarrow C_8H_8NO_2$ (*m/e* 150) *m/e* 150 → 151 (~10%)]; as expected upon more rigorous conditions, alkylation at the 6 and/or 6′ position(s) afforded the *n*-butyl incorporation products (e.g. **9**). Giam et al. have adequately demonstrated the enamine character of the 1,2-dihydro intermediates, which afford these 2-alkylpyridines;[10]

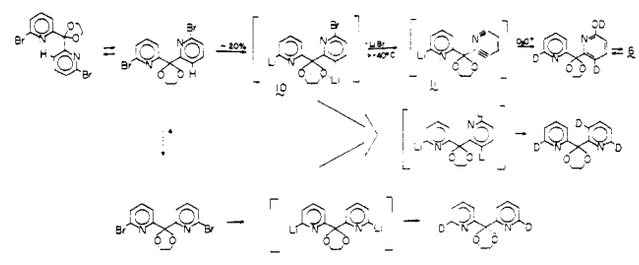


thus, deuterium incorporation in the 3 and/or 5 positions would be expected in any alkylated products. Longer reaction times, different temperatures, and numerous other factors will alter the percentage of label incorporation; these variables were not investigated.

The proposed explanation of the formation of pyridone **6** from ketal **3** is shown in Scheme I. Ketal **3** undergoes (ca. 20–30%) selective metalation at the 3 position of a single pyridine ring under these reaction conditions. This directivity of metalation results from both initial complexation of the organolithium reagent with either the 1,3-dioxolane group[9a,b] or other nitrogen atom[9c] as well as a conformational preference about the sp^3–sp^2 bond.[11] This is further substantiated by the above labeling studies and the observation that good complexing solvents retard the directive metalation, since the intramolecular solvation cannot compete with the solvent–metal interactions.

At reduced temperatures (<−60 °C), the dilithiated ketal **5**-d_2 can be generated by normal metal–halogen exchange along with approximately 20% of the trilithiated ketal **5**-d_3, which arose by both metal–halogen exchange and directive metalation. At −40 to −20 °C, the partially metalated intermediate **10** can fragment at the elevated temperatures via 1,4-elimination of lithium bromide to generate ynenenitrile **11**. Similar fragmentations of the pyrimidine nucleus have been reported[12] and recently Utimoto et al.[13] have described a related cleavage of the pyridine ring to give dienenitriles. No attempts have been made to isolate the ynenenitrile intermediate.[14] Cyclization of **11** under the workup conditions affords pyridone **6** in approximately the same isolated percentages as that of the selective deuterium incorporation studies. Although there is no exact precedence for the cyclization step, Perveev and co-workers[15] have demonstrated the facile cyclization of alkyl-substituted ynenenitriles in the

Scheme I



presence of alkyl- and dialkylamines at room temperature to generate (70–80%) the pyridine nucleus. Related dienenitriles have been shown[16] to give dihydropyridines when subjected to mild acidic conditions, such as the typical workup (dilute mineral acid at room temperature for several minutes). Directive protonation may also facilitate this cyclization.

In order to dispel the obvious reactions which could conceivably convert **3** into **6**, ketal **3** was subjected to conditions in excess of normal workup procedures: (a) refluxed **3** in 5% HCl for 12 h; (b) refluxed **3** in 12 N HCl in methanol for 24 h; or (c) heated **3** in alcoholic potassium hydroxide at 60 °C for 4 h resulting in isolation of either recovered starting ketal **3** (100%), bis(6-bromo-2-pyridyl) ketone (>90%), or **3** (100%), respectively.

This directive metalation and novel fragmentation of the pyridine nucleus are currently being evaluated as a convenient synthon for polyfunctional C_5 and C_6 units.

Experimental Section

All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared and ultraviolet spectra were recorded on a Beckmann IR-7 and Cary 14 spectrophotometers, respectively. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and are recorded in parts per million downfield of the internal standard of tetramethylsilane. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMS-4 spectrometer by Ms. Paula Moses. Elemental analyses were performed by Mr. R. Seab in these laboratories.

The recorded R_f values were determined by a standardized thin-layer chromatograph (TLC) procedure: 0.025-mm Brinkmann silica gel HF eluting with the stipulated solvent system. For preparative thick-layer chromatography (ThLC), 2-mm silica gel (Brinkmann PF-254-366) plates were used, eluting with the stated solvents.

Bis(6-bromo-2-pyridyl) ketone was prepared, according to the procedure of Holm et al.,[6] from 2,6-dibromopyridine and ethyl chloroformate: mp 155–156 °C (lit.[6] mp 155–156.5 °C).

2-Pyridyl 6-bromo-2-pyridyl ketone (7) was synthesized from 2-bromo-6-lithiopyridine and methyl 2-pyridinecarboxylate by standard procedures: mp 85–86 °C (lit.[6] mp 84.5–86.5 °C).

2,2-Bis(6′-bromo-2′-pyridyl)-1,3-dioxolane (3) was prepared[4] (75–85%) from the corresponding ketone by treatment with 2-bromoethanol and sodium carbonate: mp 146–148 °C; R_f 0.41 [cyclohexane–ethyl acetate (1:1)]; NMR ($CDCl_3$) δ 4.14 (s, OCH_2CH_2O, 4 H), 7.35 (dd, 5-pyr-H, J = 7, 2 Hz, 2 H), 7.58 (dd, 4-pyr-H, J = 7, 7.7 Hz, 2 H), 7.82 (dd, 3-pyr-H, J = 7.7, 2 Hz, 2 H).

Treatment of 2,2-Bis(6′-bromo-2′-pyridyl)-1,3-dioxolane (3) with *n*-Butyllithium. Method A. Ether Solvent at −40 to −20 °C. A solution of **3** (100 mg, 0.26 mmol) in anhydrous diethyl ether (100 mL; distilled from lithium aluminum hydride under argon) was cooled to −40 °C and *n*-butyllithium (0.3 mL, 2 M in hexane, 0.6 mmol) was added slowly. The reaction was conducted under an argon atmosphere with *complete* exclusion of oxygen. After the addition was complete, the solution was allowed to warm slowly to −20 °C and then maintained at −20 °C for 1 h. Dry ice was added to the solution and the mixture was hydrolyzed by addition of cold 5 N hydrochloric acid (30 mL). The organic solvents were removed at reduced pressure, then the aqueous slurry was extracted with chloroform (10 × 50 mL). The combined extract was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a beige solid, which was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:1) to give 20 mg (32%) of pyridone **6**: mp 185–187 °C; R_f 0.04 [cyclohexane–ethyl acetate (1:1)]; NMR ($CDCl_3$) δ 4.16 (s, OCH_2CH_2O, 4 H), 6.42 (dd, H_5, J = 7, 1 Hz, 1 H), 6.51 (dd, H_3, J = 9, 1 Hz, 1 H), 7.37 (dd, H_4, J = 9, 7 Hz, 1 H), 7.30 (ddd, $H_{5'}$, J = 6, 5, 2 Hz, 1 H), 7.76 (ddd, $H_{3'}$, J = 5, 2, 0.9 Hz, 1 H), 7.78 (ddd, $H_{4'}$, J = 5, 6, 1.5 Hz, 1 H), 8.63 (ddd, $H_{6'}$, J = 5, 1.5, 0.9 Hz, 1 H), and 10.45 [brs, NH (exchanged with D_2O), 1 H]; IR ($CHCl_3$) 3350 (amide), 3000, 1670 (amide), 1630, 1440, 1200, 1150, 1090, 1040, 950 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.96; N, 11.47. Found: C, 64.11; H, 5.03; N, 11.38.

Unreacted starting material [34 mg (34%)] was also isolated from the ThLC plate, mp 146–148 °C.

Any carboxylated products, specifically **5**, neither moved nor could be easily extracted from the baseline of the chromatography plate.

Method B. Tetrahydrofuran Solvent. Repetition of method A, except for the substitution of tetrahydrofuran as solvent and omission of the carboxylation step, resulted in the isolation of **3** [51 mg (51%)] and **5**: mp 164–165 °C; 24 mg (42%).

Method C. Dimethoxyethane Solvent. Repetition of method A without the carboxylation stage and utilizing dimethoxyethane as solvent afforded 50 mg (50%) of **3** and 25 mg (43%) of **5**.

Method D. Quenching with Deuterated Sulfuric Acid. Method A was repeated without the carboxylation step, and quenched with 10% deuterated sulfuric acid (10 mL, 98% d_2). Purification (ThLC) afforded, along with starting material [35 mg, (35%)], 13.5 mg (21%) of the deuterated pyridone (**6-*1,3,6′*-d_3**): mp 185–187 °C; R_f 0.04; NMR ($CDCl_3$) δ 4.16 (s, OCH_2CH_2O, 4 H), 6.42 (d, H_5, J = 8.0 Hz, 1 H), 7.35 (d, H_4, J = 8.0 Hz, 1 H), 7.30 (dd, $H_{5'}$, J = 5, 2 Hz, 1 H), 7.76 (dd, $H_{3'}$, J = 6, 2 Hz, 1 H), 7.78 (dd, $H_{4'}$, J = 6, 5 Hz, 1 H), and 10.65 (brs, NH (exchanged with H_2O), 1 H]; MS (60 eV) m/e 247 (M^+, d_3).

Method E. Temperature Range (−55 to −40 °C). Repetition of method D, except that the initial addition of *n*-butyllithium was at −55 °C and then maintained for 3 h at −40 °C, afforded only a trace (<2%) of pyridone **6**, recovered 3-deuterio ketal **3** [33 mg (33%); mp 145–147 °C; NMR ($CDCl_3$) δ 4.16 (s, OCH_2CH_2O, 4 H), 7.35 (dd, 5-pyr-H, J = 7, 2 Hz, 2 H), 7.58 (brdd, 4-pyr-H, J = 7, ~7 Hz, 2 H), 7.82 (brdd, 3-pyr-H, J = 7.7, 2 Hz; MS (60 eV) m/e 389 (M^+, 36% d_1)], and the "trideuterated" ketal [31 mg (52%); mp 163–165 °C; NMR ($CDCl_3$) δ 4.10 (s, OCH_2CH_2O, 4 H), 7.0–8.0 (m, 3,4,5-pyr-H, 5.8 H), 8.65 (m, 6-pyr-H, 0.05 H); MS m/e 228 (1% d_0), 229 (2% d_1), 230 (72% d_2), 231 (25% d_3)].

Method F. Temperature Range (−78 to −60 °C). Repetition of method D, except that the initial addition of *n*-butyllithium was at −78 °C and the reaction was maintained for 3 h at −60 °C, afforded deuterated starting material **3** [50 mg (50%); mp 146–147 °C; NMR ($CDCl_3$) identical with sample isolated from method E, except for δ 7.81 (3-pyr-H, 1.55 H (77% H))] and the trideuterated ketal [mp 164–166 °C; 30 mg (50%); NMR ($CDCl_3$) identical with sample derived from method E; MS m/e 228 (1% d_0), 229 (1% d_1), 230 (78% d_2), 231 (19% d_3)].

Treatment of 2,2-Bis(2′-pyridyl)-1,3-dioxolane (5) with *n*-Butyllithium. A solution of **5** (180 mg, 0.8 mmol) in diethyl ether (50 mL) was cooled to −78 °C and *n*-butyllithium (1 mL, 2 M in hexane, 2 mmol) was added dropwise. After 3 h at −70 °C, 10% deuterated sulfuric acid (10 mL, 98% d_2) was added. After neutralization with sodium carbonate, the suspension was extracted with chloroform (5 × 50 mL), then the combined extract was dried over anhydrous sodium sulfate and concentrated to afford a gummy residue, which was chromatographed (ThLC), eluting two times with diethyl ether to give starting **5** [110 mg (60%), mp 164–165 °C (needles, petroleum ether); NMR ($CDCl_3$) δ 4.12 (s, OCH_2CH_2O, 4 H), 7.0–8.0 (m, 3,4,5-pyr-H, 5.8 H), 8.66 (ddd, 6-pyr-H, 2 H); MS m/e 228 (81% d_0), 229 (19% d_1)] and 2-(2′-pyridyl)-2-(6′-*n*-butyl-2′-pyridyl)-1,3-dioxolane [20 mg (8%); bp 100 °C (0.1 mm, microdistillation); R_f 0.3; NMR ($CDCl_3$) δ 1.0–1.7 (m, *n*-Pr, 7 H), 2.8 (t, pyr-CH_2, J = 8 Hz, 2 H), 4.18 (s, OCH_2CH_2O, 4 H), 7.0–7.8 (m, pyr-H, 6 H), 8.65 (ddd, 6-pyr-H, J = 4.5, 2, 1 Hz, 1 H).

Attempted Deuterium Exchange of Pyridone 6. A sample of **6** (50 mg, 0.2 mmol) was dissolved in 10% deuteriosulfuric acid (0.3 mL, 98% d_2) and the incorporation was monitored via NMR analysis at 38 °C. After 40 h at 38 °C, negligible, if any, incorporation was observed. The ketal singlet at δ 4.16 was used as the internal standard.

Independent Synthesis of Pyridone 6. A. 2-(2′-Pyridyl)-2-(6′-bromo-2′-pyridyl)-1,3-dioxolane (8). A suspension of **7** (1.03 g, 3.5 mmol), lithium carbonate (15 g, 200 mmol), and 2-bromoethanol (25 mL) was refluxed gently with stirring for 6 h. After cooling, the mixture was poured into 10% aqueous sodium bicarbonate (150 mL). The undissolved solids were filtered and the filtrate was extracted with chloroform (10 × 50 mL). The combined organic extract was dried over anhydrous potassium carbonate and concentrated to afford a pale amber yellow liquid. The attendent 2-bromoethanol was removed via vacuum distillation and the residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to afford **8** as colorless rhombohedron crystals: mp 117–117.5 °C (recrystallized from ethyl acetate–cyclohexane); 800 mg (75%); NMR ($CDCl_3$) δ 4.12 (s, OCH_2CH_2O, 4 H), 7.0–7.85 (m, pyr-H, 6 H), 8.47–8.52 (ddd, 6-pyr-H, J = 5, 5, 2, 1 Hz, 1 H); IR ($CHCl_3$) 3000, 1650, 1620, 1575, 1390, 1280, 1160, 995 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}N_2O_2Br$: C, 50.86; H, 3.61; N, 9.13. Found: C, 50.62; H, 3.83; N, 9.23.

B. Pyridone Synthesis. A mixture of **8** (130 mg, 0.425 mmol), anhydrous *tert*-butyl alcohol (8 mL), and potassium *tert*-butoxide (4 g) was refluxed for 12 h. After cooling, the solvent was removed in vacuo, ice water was slowly added, and the solution was extracted with

methylene chloride. The combined extract was dried over anhydrous sodium sulfate, concentrated, and chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (3:1) to afford 72.7 mg (75%) of pure pyridone **6**, mp 185–187 °C. This sample was identical in all respects with the sample isolated from method A.

Acknowledgments. The authors gratefully acknowledge partial support of this work by Public Health Service grant from the National Institutes of Health and the Dr. Charles E. Coates Memorial Fund of the L.S.U. Foundation for financial aid (J.D.S.). We also wish to thank Professor Van der Plas for his helpful comments.

Registry No.—**3**, 42772-88-3; **3**-*3*-d_1, 63449-27-4; **3**-*3,6,6'*-d_3, 63449-28-5; **5**, 42772-86-1; **6**, 63449-29-6; **6**-*1,3,6'*-d_3, 63449-30-9; **7**, 49669-19-4; **8**, 63449-31-0; bis(6-bromo-2-pyridyl) ketone, 42772-87-2; 2-bromo-6-lithiopyridine, 37709-60-7; methyl 2-pyridinecarboxylate, 2459-07-6; 2-bromoethanol, 540-41-2.

References and Notes

(1) Presented in part at the 27th Southeast–31st Southwest Combined Regional Meeting of the American Chemical Society, Memphis, Tenn., Oct. 1975.
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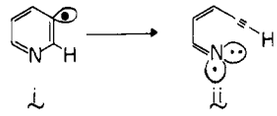

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α-Halogenation of Certain Ketones

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A variety of α-halo and α-*gem*-dihalo ketones, including the fluoro and iodo compounds, have been prepared. The scope and limitations of their syntheses have been studied. Every attempt at the preparation of 3,3-difluoro-2-butanone gave biacetyl as the only product, although the analogous *gem*-difluoropropiophenone was conveniently obtained. The synthesis of the difluorobutanone could, however, be effected with the introduction of an electronegative atom such as chlorine on the 1 position.

In the course of our stereochemical studies, the need for a number of ketones possessing a halogenated chiral carbon atom led us to investigate the halogenation, in particular fluorination, of one or both methylene hydrogens of 2-butanone, propiophenone, and 1-phenyl-2-propanone. None of the required *gem*-dihalo ketones possessing two different halogens has been previously reported.

α-Chloro or α-fluoro ketones were conveniently converted to their corresponding *gem*-bromohalo analogues by irradiation in the presence of NBS.[1] Table I lists the products with yields. Several alternate reported routes[2,3] were found to be ineffective, leading to bromoform (for methyl ketones) or polybrominated products. Bromination of monofluoroacetone with NBS gave a complex mixture.

Results and Discussion

Preparation of the Fluoro Ketones Although indirect routes have frequently been used for the preparation of fluoro methyl ketones,[4–7] direct exchange of bromine or chlorine for fluorine using metallic fluorides was used in the present work. This method, although preferred, often meets with difficulty due to the marked tendency of bromo and chloro ketones to decompose during the course of fluorination, particularly at high temperatures. The task was in finding a metal fluoride which would exchange its fluorine for halogen at a temperature low enough so as to minimize side reactions and decomposition of both the reactant and product. Mercuric fluoride was found to be a suitable metallic fluoride for the fluorination of most of the bromo ketones. These reactions are presented in Table II.

In the fluorination of **1a** with mercuric fluoride, under absolutely anhydrous conditions, a smooth exchange of bromine took place, leaving the chlorine intact and giving 3-chloro-3-fluoro-2-butanone (**1c**) together with some biacetyl. With antimony trifluoride, thallous fluoride, potassium fluoride, and potassium hydrogen difluoride, either no reaction occurred or extensive polymerization and charring resulted. Efforts to inhibit the formation of biacetyl, in the exchange reaction with mercuric fluoride, met with no success. The fluoro ketone formed an azeotropic mixture with the biacetyl and had to be purified by GLC. Pure **1c** was not hydrolyzed when boiled with water.

1c was also obtained in poor yield by the chlorination of 3-fluoro-2-butanone using *N*-chlorosuccinimide.

2-Bromo-2-chloro-1-phenyl-1-propanone (**3a**) reacted with mercuric fluoride at 85 °C to give, under optimum conditions,