Condensations at the Methyl Groups of 6-, 4-, and 3-Methyl-2(1H)-pyridones and the Sulfur Analogs through Dilithio Salts Prepared by Means of *n*-Butyllithium[1]

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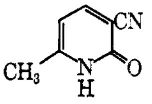
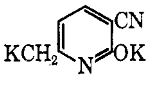
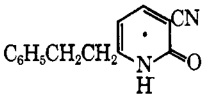
Electrophilic compounds were condensed with 6-, 4-, and 3-methyl-2(1H)-pyridones at the methyl groups through the dilithio salts, which were prepared by means of 2 mol equiv of *n*-butyllithium in tetrahydrofuran–hexane solutions. Similar condensations were effected at the methyl groups of 6- and 3-methyl-2-mercaptopyridines. The adduct from 2-mercapto-3-methylpyridine and benzophenone was cyclized to form 2,2-diphenyl-2,3-dihydrothieno[2,3-*b*]pyridine. The method furnishes a convenient route to the synthesis of many new compounds.

Recently[2] 6-methyl-3-cyano-2(1H)-pyridone (I) and certain related 6-methyl- and 4-methyl-3-cyanopyridones were shown to undergo primary ionization of the amide hydrogen and secondary ionization of a methyl hydrogen with 2 mol equiv of potassium amide in liquid ammonia to form their dipotassio salts, for example, I′. This was evidenced by C alkylation and other types of C condensations with electrophilic compounds. Thus I′ underwent C benzylation with benzyl chloride to give II.

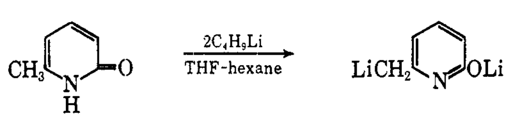

I


I′


II

However, the corresponding 6-methylpyridone having no 3-cyano group failed to undergo sufficient secondary ionization of a methyl hydrogen with potassium amide under similar conditions for C benzylation to occur with benzyl chloride; instead, the halide underwent self-condensation to form stilbene.[2]

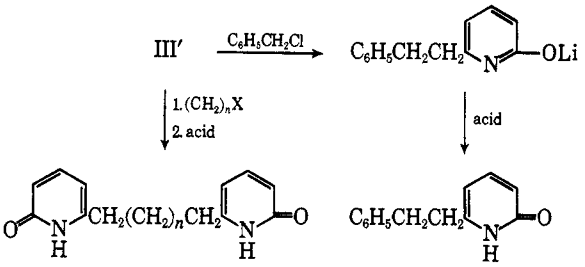
In the present investigation this 6-methylpyridone (III) having no cyano group was found to undergo apparently complete secondary ionization of a methyl hydrogen with 2 mol equiv of thes tronger base *n*-butyllithium in tetrahydrofuran (THF)–hexane (eq 1). This was evidenced by C condensations with electrophilic compounds. Also, the corresponding 4-methyl- and 3-methylpyridones, as well as the 6-methyl and 3-methyl sulfur analogs, were converted into dilithio salts suitable for such condensations.



III III′ (1)

Dilithio salt III′ underwent alkylation with benzyl chloride, and twofold alkylation with ethylene chloride and 1,4-dibromobutane, to form IV, Va, and Vb, respectively (Scheme I).

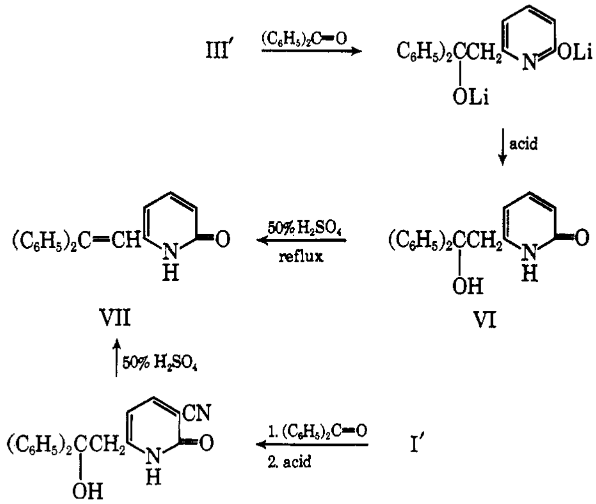
SCHEME I



Va, $n = 2$
b, $n = 4$
IV

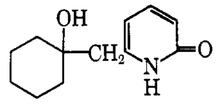
Dilithio salt III′ underwent an addition reaction with benzophenone to give alcohol-pyridone VI, which was dehydrated with refluxing 50% surfuric acid to afford unsaturated pyridone VII; VII was independently synthesized from the benzophenone adduct of dipotassio cyanopyridone I′ (Scheme II).[3]

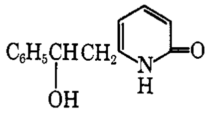
SCHEME II



VII VI

Also, dilithio salt III′ was condensed with cyclohexanone and benzaldehyde to form alcohol pyridones VIII and IX, respectively.


VIII


IX

Alcohol–pyridone IX was dehydrated with refluxing 6 *N* hydrochloric acid to form unsaturated pyridone X. Surprisingly, treatment of alcohol-pyridone IX with

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[1] This investigation was supported by U. S. Public Health Service Research Grant No. CA-04455 from the National Cancer Institute and by the National Science Foundation.

[2] S. Boatman, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 3593 (1965).

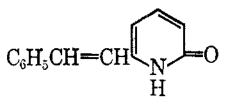
[3] A preliminary report on this reaction has appeared in a communication: R. L. Gay, S. Boatman, and C. R. Hauser, *Chem. Ind.* (London), 1789 (1965). For details of the independent synthesis of VII from I, see S. Boatman, T. M Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 5198 (1965).

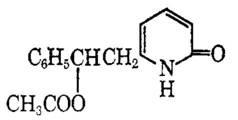
TABLE I

DERIVATIVES OF 6-, 4- AND 3-METHYL-2(1H)-PYRIDONES AND CERTAIN SULFUR ANALOGS

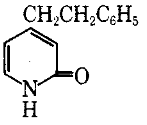
Product		Yield,		
No.	Name	%	Mp, °C	Recrystn solvent
IV	6-(2-Phenylethyl)-2(1H)-pyridone	79	155–156	Methanol–water
Va	1,4-Bis{6-[2-oxo(1H)pyridyl]}butane	60	283	Acetonitrile
Vb	1,6-Bis{6-[2-oxo(1H)pyridyl]}hexane	41	239–241	Ethanol
VIII	6-(1-Hydroxycyclohexylmethyl)-2(1H)-pyridone	50	165–167	Ethanol
IX	6-(2-Hydroxy-2-phenylethyl)-2(1H)-pyridone	69	148–149	Ethanol–hexane
X	6-Styryl-2(1H)-pyridone	90	215–216	Ethanol
XI	6-(2-Phenylethyl-2-acetate)-2(1H)-pyridone	60	197–198	Ethanol–water
XII	4-(2-Phenylethyl)-2(1H)-pyridone	37	168–169	Benzene
XIII	4-(2-Hydroxy-2,2-diphenylethyl)-2(1H)-pyridone	40	259–260	Acetic acid
XIV	4-(2,2-Diphenylvinyl)-2(1H)-pyridone	80	168–170	Ethanol
XV	3-(2-Phenylethyl)-2(1H)-pyridone	75	188	Benzene
XVI	3-(2-Hydroxy-2,2-diphenylethyl)-2(1H)-pyridone	55	294–295	Acetonitrile
XVII	3-(2,2-Diphenylvinyl)-2(1H)-pyridone	75	225–226	Benzene
XIX	2-Mercapto-6-(2-phenylethyl)pyridine	59.5	145–149	Benzene
XX	2-Mercapto-6-(2-hydroxy-2,2-diphenylethyl)pyridine	80	231–232	Ethanol
XXIIa	2-Mercapto-3-(2-phenylethyl)pyridine	18.5	177–179	Benzene–hexane
XXIIb	2-Mercapto-3-(2-*p*-chlorophenylethyl)pyridine	70	185–186	Benzene–hexane
XXIII	2-Mercapto-3-(2-hydroxy-2,2-diphenylethyl)pyridine	80	240–241	Benzene–ethanol
XXIV	2,2-Diphenyl-2,3-dihydrothieno[2,3-*b*]pyridine	75	117–118	Hexane

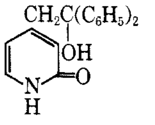
acetic anhydride and sulfuric acid afforded the acetyl derivative XI, which eliminated acetic acid on heating with dilute sulfuric acid to give unsaturated pyridone X.

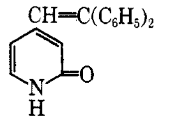

X

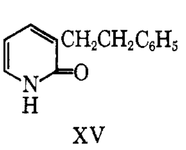

XI

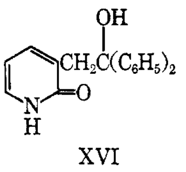
Similarly, the corresponding 4-methyl- and 3-methylpyridones were condensed (through their dilithio salts) with benzyl chloride and benzophenone to form XII and XIII and XV and XVI, respectively. Alcohol-pyridones XIII and XVI were dehydrated with cold, concentrated sulfuric acid to give unsaturated pyridones XIV and XVII, respectively. The structure of XVII was supported by its nmr spectrum which showed only vinyl and aromatic protons.

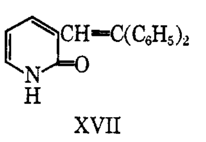

XII


XIII

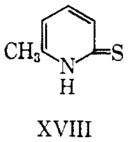

XIV

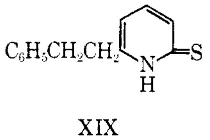

XV

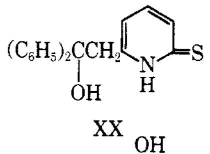

XVI

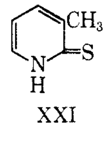

XVII

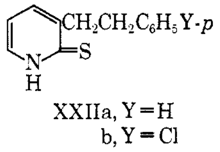
Likewise, the 6-methyl sulfur analog XVIII and the 3-methyl analog XXI were condensed (through their dilithio salts) with benzyl chloride and benzophenone to form XIX and XX and XXIIa and XXIII, respectively. Also, the dilithio salt of XXI was alkylated with *p*-chlorobenzyl chloride to give XXIIb.


XVIII

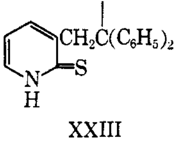

XIX


XX

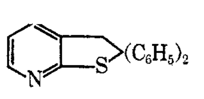

XXI


XXIIa, Y = H

b, Y = Cl


XXIII

In contrast to the alcohol-pyridone XVI from 3-methylpyridone, the sulfur analog XXIII underwent cyclization with cold, concentrated sulfuric acid to give XXIV. This structure was supported by its nmr spectrum which showed peaks at 4.43 (2, methylene singlet) and 7.2–8.7 ppm (13, aromatic multiplet).


XXIV

These results are summarized in Tables I and II. The yields were generally good (see Table I), and the products afforded satisfactory analyses and characteristic infrared spectra (see Table II).

Experimental Section[4]

Preparation of Starting Materials.—The methylpyridones were prepared by diazotization of the corresponding methyl-2-aminopyridines.[5] The mercaptopyridines were prepared by treating the corresponding pyridones with phosphorus pentasulfide in pyridine.[6]

Conversion to the Dilithio Salts.[7]—To a solution of 0.025 mol of the pyridone or mercaptopyridine in 35 ml of tetrahydrofuran (freshly distilled from $LiAlH_4$) in an ice bath was added 0.055 mol of *n*-butyllithium in hexane.[8] The solution was stirred at ice-bath temperature for 20 min during which time a reddish brown color developed.

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[4] Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 137 Infracord with potassium bromide pellets. Nmr spectra were measured in deuteriochloroform solutions on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and by M-H-W Laboratories, Garden City, Mich.

[5] R. Adams and H. W. Schrecker, *J. Amer. Chem. Soc.*, **71**, 1186 (1949).

[6] M. Guthzeit and W. Epstein, *Ber.*, **B20**, 2111 (1887).

[7] Reactions were run in three-necked, round-bottom flasks equipped with magnetic stirrers, nitrogen inlet, and dropping funnels stoppered with a dry tube. The reaction vessels were swept with dry nitrogen while drying with a flame.

[8] Used as obtained from Foote Mineral Co., New Johnsonville, Tenn.

TABLE II

ANALYSES AND INFRARED SPECTRA OF PRODUCTS

Compound no.	Infrared spectrum	Formula	Calcd, % C	H	N	Found, % C	H	N
IV	6.04 (s), 6.15, 6.46, 6.94, 8.58, 10.2	$C_{13}H_{13}NO$	78.35	6.57	7.03	78.12	6.68	6.91
Va	2.9 (m), 3.05 (m), 3.5 broad, 6.0 (s), 6.45, 6.9	$C_{14}H_{16}N_2O_2$	68.8	6.61	11.48	68.87	6.58	11.27
Vb		$C_{16}H_{20}N_2O_2$	70.5	7.39	10.28	70.18	7.49	9.80
VIII	6.06 (s), 6.20 (m), 6.85 (m), 2.92 (m)	$C_{12}H_{17}NO_2$	69.54	8.27	6.76	69.30	8.30	6.92
IX	6.04 (s), 6.20, 6.84, 9.52, 2.91, 3.06	$C_{13}H_{13}NO_2$	72.54	6.09	6.51	72.25	6.18	6.48
X	6.04 (s), 6.23, 6.47, 10.16	$C_{13}H_{11}NO$	79.16	5.62	7.10	78.91	5.81	7.06
XI	5.80 (s), 6.05 (s), 8.10	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	69.83	5.86	5.49
XII	6.05 (s), 6.46, 6.9	$C_{13}H_{13}NO$	78.35	6.57	7.03	78.30	6.56	7.06
XIII	2.98 (s), 6.05 (s), 6.19, 6.58, 9.52	$C_{19}H_{17}NO_2$	78.33	5.88	4.81	77.28	5.95	4.70
XIV	6.06 (s), 6.22	$C_{19}H_{15}NO$	83.49	5.53	5.13	83.32	5.75	5.00
XV	6.5 (s), 6.75 (s), 6.04 (s), 6.44, 6.85	$C_{13}H_{13}NO$	78.35	6.57	7.03	78.71	6.57	6.75
XVI	3.05 (s), 3.4 (s), 3.55 (s), 6.05 (s), 6.15 (s), 6.4	$C_{19}H_{17}NO_2$	78.33	5.88	4.81	78.29	5.97	4.90
XVII	2.9 (m), 3.05 (m), 6.5 broad, 6.1 (s)	$C_{19}H_{15}NO$	83.49	5.53	5.13	83.64	5.58	5.04
XIX		$C_{13}H_{13}NS$[a]	72.5	6.08	6.51	72.37	6.15	6.42
XX	3.1 (s), 6.25 (s), 6.7 (s)	$C_{19}H_{17}NSO$	74.3	5.58	4.56	74.52	5.78	4.83
XXIIa	3.5 (s), broad, 6.2 (s), 6.3 (s), 6.7	$C_{13}H_{13}NS$	72.5	6.08	6.51	72.05	6.10	6.47
XXIIb		$C_{13}H_{12}NSCl$	62.5	4.85	5.61	62.88	5.01	5.56
XXIII	3.05 (s), 3.4 (s) broad, 6.2 (s), 6.25 (s), 6.35 (s), 6.7 (s), 6.9 (s), 7.4 (s)	$C_{19}H_{17}NSO$[b]	74.3	5.58	4.56	73.94	5.65	4.52
XXIV	3.27 (s), 6.3 (s), 6.4 (s), 6.7 (s), 6.95 (s), 7.2 (s)	$C_{19}H_{15}NS$[c]	78.9	5.22	4.84	79.14	5.38	4.63

[a] Calcd for S, 14.90. Found: S, 15.01. [b] Calcd for S, 10.44. Found: 10.55. [c] Calcd for S, 11.09. Found: 11.14.

Reactions of the Dilithio Salts with Electrophiles.—To the cold dilithio salt solution was added slowly 0.025 mol of the appropriate electrophile in 15 ml of tetrahydrofuran. The resulting solution was stirred at room temperature for 30 min, and 0.075 mol of acetic acid in 25 ml of water was added. After mixing thoroughly, the excess acid was neutralized by adding solid sodium bicarbonate. In a few cases a precipitate formed and was collected. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The product was recrystallized from the appropriate solvent. The results are summarized in Tables I and II, which also include results of the following reactions.

Acetylation of IX to give XI.—A mixture of 0.5 g of IX, 5 ml of acetic anhydride, and 5 drops of concentrated sulfuric acid was heated on the steam bath for 1 hr, then cooled. Sodium bicarbonate (0.5 g) was added, and the acetic anhydride was evaporated. Water was added to the residue, and the solid was collected and recrystallized from ethanol–water to give 0.3 g (60%) of the product XI, mp 197–198°.

Dehydration of the Benzophenone Condensation Products.—The alcohol–pyridone was dissolved in 20 times its weight of cold, concentrated sulfuric acid and stirred for 10–15 min. Ice-water was added, and the solution was then neutralized with sodium bicarbonate. The precipitate was collected and recrystallized from the appropriate solvent (see Table I).

Cyclization of XXIII to Give XXIV.—To 2 g of cold, concentrated sulfuric acid was added 0.1 g of XXV. The resulting solution was stirred for 15 min, and ice–water was added. An oily precipitate formed and remained after neutralization with solid sodium bicarbonate. The mixture was thoroughly extracted with ether, and the combined ether extracts were dried over magnesium sulfate. Evaporation of the ether gave 0.09 g of white solid, mp 115–117°. Recrystallization from hexane gave 0.07 g of white needles of XXIV, mp 117–118°.

Registry No.—IV, 16097-09-9; Va, 16097-10-2; Vb, 16097-11-3; VIII, 16097-12-4; IX, 16097-13-5; X, 16097-14-6; XI, 16097-15-7; XII, 16097-16-8; XIII, 16097-17-9; XIV, 16097-18-0; XV, 16097-19-1; XVI, 16097-20-4; XVII, 16097-21-5; XIX, 16097-22-6; XX, 16097-23-7; XXIIa, 16097-24-8; XXIIb, 16097-25-9; XXIII, 16097-26-0; XXIV, 16097-27-1; *n*-butyllithium, 109-72-8.