Derivatives of 4-Mercaptodipicolinic Acid[1]

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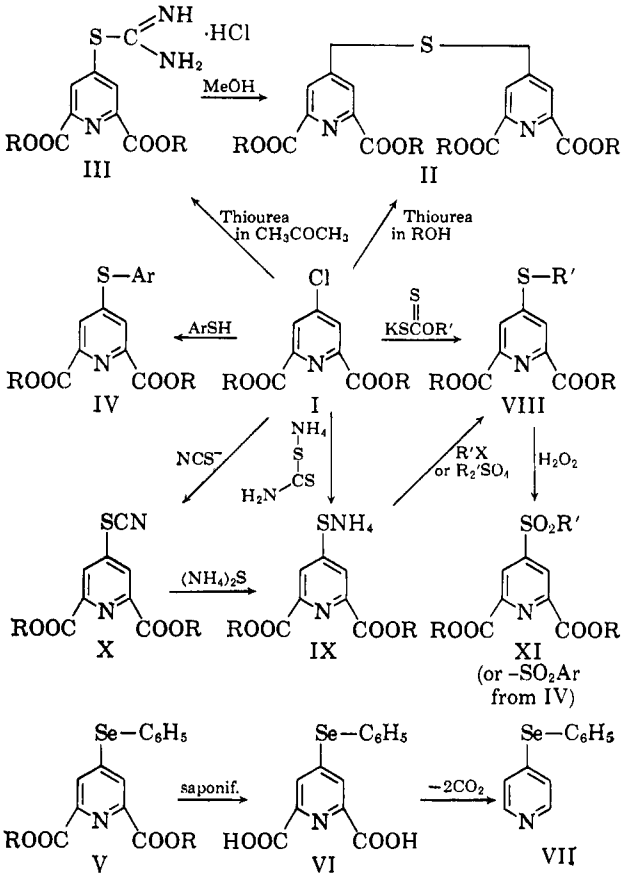
Reactions of various S-containing nucleophiles with dialkyl 4-chloropyridine-2,6-dicarboxylates are described. In some cases thioethers derived from 4-mercaptopyridine-2,6-dicarboxylic acid were obtained. Other reactions furnished products which could be converted readily to compounds of that type. The preparation of dimethyl 4-phenylselenopyridine-2,6-dicarboxylate and some related compounds is included. Oxidation of the thioethers with hydrogen peroxide led to the corresponding sulfones.

In connection with a biochemical project, esters of 4-alkyl-, 4-aralkyl-, and 4-arylthiopyridine-2,6-dicarboxylic acids were required. This paper deals with the synthesis of these materials.

It seemed likely that diethyl 4-mercaptopyridine-2,6-dicarboxylate could be substituted on the sulfur atom in a manner similar to the recently reported O-alkylation of diethyl 4-hydroxypyridine-2,6-dicarboxylate.[2] Since the preparation of diethyl 4-mercaptopyridine-2,6-dicarboxylate reported in the literature[3] did not appear attractive the synthesis of this thiol, as well as the corresponding dimethyl ester, was attempted by reaction of a dialkyl 4-chloropyridine-2,6-dicarboxylate with thiourea.[4] The only products which were isolated from these reactions, however, were the symmetrical thioethers II. The formation of this type of compound by reaction of thiourea with heterocyclic halides has been observed on various occasions,[5] and several schemes for its course have been proposed.[6] Usually it is assumed that a thiouronium salt is formed, which subsequently breaks down to thiol. This, in turn, may react quickly with more thiouronium salt or, alternatively, with still unconsumed halide to give the thioether. The first possibility was supported by the finding that the thiouronium salt III, prepared from diethyl 4-chloropyridine-2,6-dicarboxylate and thiourea in boiling acetone, was converted to thioether when refluxed in methanol. The alternate path was supported by the ready reaction of chlorodipicolinates with a variety of thiophenols to give dialkyl 4-arylthiopyridine-2,6-dicarboxylates (IV). Benzeneselenol was found to react analogously. Hydrolysis of the resulting dimethyl 4-phenylselenopyridine-2,6-dicarboxylate (V) gave the corresponding acid (VI), which could be decarboxylated to 4-phenylselenopyridine (VII).

The synthesis of diethyl 4-alkylthiopyridine-2,6-dicarboxylates (VIII) could be achieved by reaction of diethyl 4-chlorodipicolinate with potassium alkylxanthates. This reaction, which takes place by warming the reaction partners without a solvent, is reminiscent of the Leuckart thiophenol synthesis,[4] in which a diazotized arylamine is decomposed in presence of a potassium alkylxanthate. The intermediate aryl alkylxanthate then breaks down to thiophenol or aryl alkyl thioether depending on the conditions. No attempts were made to isolate any intermediates in the present case.



R = Methyl or ethyl in compounds I, II, IV
R = Methyl in compounds III, V
R = Ethyl in compounds VIII, IX, X, XI

A better and more flexible method for the preparation of diethyl 4-alkylthiopyridine-2,6-dicarboxylates consisted of alkylation of the ammonium salt of diethyl 4-mercaptopyridine-2,6-dicarboxylate (IX) which was originally prepared by reaction of diethyl 4-chlorodipicolinate (I) with ammonium dithiocarbamate in boiling water. It was unlikely that the dithiocarbamate itself acted as nucleophile in this condensation, but rather one of its decomposition products. Indeed, it was found that thiocyanate ion, a known decomposition product of dithiocarbamate[7] could be condensed with

(1) Presented before the Division of Organic Chemistry at the 142nd National Meeting of the Americal Chemical Society, Atlantic City, N. J., September, 1962.

(2) D. G. Markees, V. C. Dewey, and G. W. Kidder, paper presented before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(3) E. Koenigs and G. Kinne, *Ber.*, **54B**, 1357 (1921).

(4) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 779.

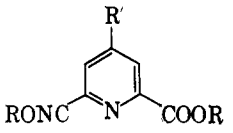
(5) A. G. Renfrew, *J. Am. Chem. Soc.*, **68**, 1433 (1946); M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, **1951**, (1218); E. A. Steck and R. P. Brundage, *J. Am. Chem. Soc.*, **81**, 6511 (1959).

(6) For a brief review see M. Polonovski and H. Schmitt, *Bull. soc. chim. France*, [5] **17**, 616 (1950).

(7) J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. 6, Longmans Green and Co., London, 1925, p. 133.

TABLE I

ESTERS OF 4-ARYLMERCAPTO- AND 4-ARYLSELENOPYRIDINE-2,6-DICARBOXYLIC ACIDS



R	R'	Formula	Yield, % crude	Recrystallization solvent	M.p., °C.	Calcd. C	Calcd. H	Found C	Found H	Calcd.	Found
Me	C_6H_5S—	$C_{15}H_{13}NO_4S$	74	MeOH	138–140	59.39	4.32	59.65	4.51		
Et	C_6H_5S—	$C_{17}H_{17}NO_4S$	42	EtOH–H_2O	78–81					N, 4.23	N, 3.98
Me	*p*-*t*-Bu-C_6H_4S—	$C_{19}H_{21}NO_4S$	69	MeOH–H_2O	117–118	63.48	5.89	63.82	5.97	S, 8.92	S, 9.03
Et	*p*-Cl-C_6H_4S—	$C_{17}H_{16}ClNO_4S$	68	EtOH	126	55.81	4.41	55.86	4.26	Cl, 9.69	Cl, 9.76
Et	*p*-Br-C_6H_4S—	$C_{17}H_{16}BrNO_4S$	88	EtOH–H_2O	118–120	49.76	3.93	49.72	3.88	Br, 19.5	Br, 19.8
Me	*o*-HOOC-C_6H_4S—[a]	$C_{16}H_{13}NO_6S$	85	MeOH	194–196	55.32	3.77	55.41	3.65	S, 9.31	S, 9.31
Me	*o*-MeOOC-C_6H_4S—[b]	$C_{17}H_{15}NO_6S$	83	MeOH	123–125	56.60	4.18	56.62	4.33	S, 8.87	S, 8.89
Me	C_6H_5Se—	$C_{15}H_{13}NO_4Se$	91	MeOH	142–143	51.42	3.74	51.55	4.03		

[a] Reaction carried out in presence of sodium acetate. [b] For Methyl *o*-mercaptobenzoate see L. Gattermann, *Ber.*, **32**, 1150 (1899).

diethyl 4-chloropyridine-2,6-dicarboxylate to give diethyl 4-thiocyanopyridine-2,6-dicarboxylate (X), which, in turn, was reduced to the ammonium salt of diethyl 4-mercaptopyridine-2,6-dicarboxylate (IX) by aqueous alcoholic ammonium sulfide.

The formation of diethyl 4-thiocyanopyridine-2,6-dicarboxylate from the corresponding chloro ester and thiocyanate was unexpected insofar as Takahashi and Yamashita[8] reported that 3-bromo-4-chloro-5-nitropyridine reacts with thiourea to give the symmetrical thioether and with potassium thiocyanate to form 3-bromo-4-amino-5-nitropyridine.

A series of halides, ethylene dibromide and dimethyl sulfate were found to react within seconds with ammonium salt of diethyl 4-mercaptopyridine-2,6-dicarboxylate to form the expected alkyl thioethers (VIII) in good to excellent yields.

Various thioethers prepared by the reactions reported were oxidized with hydrogen peroxide in acetic acid. Since the oxidation of representative types with chromium trioxide led to the same products as the peroxide oxidation, it was concluded that the oxidation products were sulfones (XI) and that the ring nitrogen remained unaffected during these reactions.

Experimental[9]

Bis(2,6-dicarbomethoxy-4-pyridyl) Sulfide.—A mixture of 2.3 g. of dimethyl 4-chloropyridine-2,6-dicarboxylate,[10] 0.8 g. of thiourea, and 20 ml. of methanol was refluxed for 3 hr. After cooling 2.0 g. (95%) of crude product was filtered. A sample recrystallized from dioxane melted at 259–261°.

Anal. Calcd. for $C_{18}H_{16}N_2O_8S$: C, 51.42; H, 3.84; N, 6.66; S, 7.63. Found: C, 51.49; H, 3.87; N, 6.70; S, 7.55.

Bis(2,6-dicarbethoxy-4-pyridyl) Sulfide.—This compound was obtained similarly from diethyl 4-chloropyridine-2,6-dicarboxylate[10] and thiourea; yield, 72%. A sample recrystallized from ethanol melted at 152–153°.

Anal. Calcd. for $C_{22}H_{24}N_2O_8S$: C, 55.45; H, 5.08; N, 5.88. Found: C, 55.37; H, 4.86; N, 5.55.

2,6-Dicarbomethoxy-4-pyridylthiouronium Chloride.—Crystallization set in after about 2.5 hr. when a mixture of 2.3 g. of dimethyl 4-chloropyridine-2,6-dicarboxylate, 0.8 g. of thiourea, and 30 ml. of acetone was refluxed. After cooling 1.5 g. (49%) of crude product was filtered. A sample recrystallized from methanol melted at 178–180° dec.

Anal. Calcd. for $C_{10}H_{11}N_3O_4S\cdot HCl$: C, 39.28; H, 3.96; N, 13.74; Cl, 11.60; S, 10.49. Found: C, 39.12; H, 4.00; N, 13.67; Cl, 11.42; S, 10.60.

Dialkyl 4-Arylthiopyridine-2,6-dicarboxylates.—An equimolecular amount (or slight excess) of a thiophenol (or benzeneselenol) was added to a warm solution of a dialkyl 4-chloropyridine-2,6-dicarboxylate in about the eightfold amount of alcohol. The mixture was refluxed for 4–6 hr., poured into water, and the precipitated solid filtered, washed consecutively with dilute sodium hydroxide and water, and recrystallized. Additional preparative information, physical constants, and analytical data are summarized in Table I.

4-Phenylthiopyridine-2,6-dicarboxylic Acid.—A mixture of 1.0 g. of dimethyl 4-phenylthiopyridine-2,6-dicarboxylate and 20 ml. of 2 *M* sodium hydroxide was refluxed for 2 hr., filtered and the filtrate acidified with 3 *M* hydrochloric acid. The solid, 0.8 g. (86%) was collected and a sample recrystallized several times from water. A hemihydrate was obtained, m.p. 199–200° dec.

Anal. Calcd. for $C_{13}H_9NO_4S\cdot 0.5H_2O$: C, 54.92; H, 3.55; S, 11.28. Found: C, 54.85; H, 3.81; S, 11.15.

4-Phenylthiopyridine-2,6-dicarboxamide was obtained on reaction of the dimethyl ester with a mixture of alcohol and aqueous ammonia. The yield was 72%, the analytical sample was obtained by recrystallization from dilute ethanol, m.p. 275–277°.

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: N, 15.38. Found: N, 15.27.

4-Phenylselenopyridine-2,6-dicarboxylic Acid.—Saponification of dimethyl 4-phenylselenopyridine-2,6-dicarboxylate followed by acidification of the reaction mixture gave this acid (94% yield, crude). The analytical sample (from water) melted at 203–205° dec.

Anal. Calcd. for $C_{13}H_9NO_4Se$: C, 48.46; H, 3.82. Found: C, 48.31; H, 3.28.

4-Phenylselenopyridine.—Heating of 5.0 g. of crude 4-phenylselenopyridine-2,6-dicarboxylic acid in an oil bath of 210° caused smooth decarboxylation, and 2.1 g. of crude material was obtained on distillation, boiling range 156–160° at 1.5 mm. Repeated distillation at reduced pressure gave the analytical sample, b.p. 143–145° (1.5 mm.).

Anal. Calcd. for $C_{11}H_9NSe$: C, 56.42; H, 3.87; N, 5.98; Se, 33.72. Found: C, 56.29; H, 4.14; N, 5.80; Se, 33.41.

Diethyl 4-Methylthiopyridine-2,6-dicarboxylate.—A mixture of 2.0 g. of diethyl 4-chloropyridine-2,6-dicarboxylate and 4.0 g. of potassium methylxanthate was immersed in a boiling water bath. Reaction took place promptly and, after the evolution of gases had ceased, water was added. A sample of the solid crude ester (1.6 g., 73%) was purified by recrystallization from aqueous alcohol, once with charcoal, and sublimation at 1.5 mm., bath temp., 130°. Its melting point was 102–104°.

Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.51; H, 5.61; S, 11.91. Found: C, 53.60; H, 5.73; S, 12.05.

Diethyl 4-Ethylthiopyridine-2,6-dicarboxylate.—This ester was prepared similarly from 2.0 g. of diethyl 4-chloropyridine-2,6-dicarboxylate and 2.5 g. of potassium ethylxanthate. An oil separating upon addition of water to the reduction mixture was extracted with ether, the ether solution was washed with water and dried, and the solvent removed. The residue, 1.4 g. (64%),

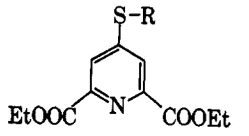
(8) T. Takahsashi and J. Yamashita, *Pharm. Bull. Japan*, **4**, 20 (1956).

(9) The melting points reported were taken on a Mel-Temp apparatus and are corrected. The boiling points are uncorrected.

(10) D. G. Markees and G. W. Kidder, *J. Am. Chem. Soc.*, **78**, 4130 (1956).

TABLE II

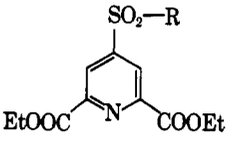
DIETHYL 4-ALKYLTHIOPYRIDINE-2,6-DICARBOXYLATES



R	Alkylating agent	Formula	Yield, % crude	Recrystallization solvent	M.p. or b.p., °C.	Calcd. C	Calcd. H	Found C	Found H	Calcd.	Found
CH_3	$(CH_3)_2SO_4$	$C_{12}H_{15}NO_4S$	86	EtOH[a]	102–104	[b]	[b]				
C_2H_5	C_2H_5I	$C_{13}H_{17}NO_4S$	94	Pet. ether	47–49	[b]	[b]				
i-C_3H_7	*i*-C_3H_7Br	$C_{14}H_{19}NO_4S$	73		Oil	[c]	[c]				
n-C_4H_9	*n*-C_4H_9Br	$C_{15}H_{21}NO_4S$[d]	90		189–199 (1.3 mm.)	57.88	6.79	57.89	6.78	N, 4.50	N, 4.72
s-C_4H_9	*s*-C_4H_9Br	$C_{15}H_{21}NO_4S$	86		Oil	[c]	[c]				
i-C_5H_{11}	*i*-$C_5H_{11}Br$	$C_{16}H_{23}NO_4S$	79		205–206 (1.3 mm.)	59.05	7.12	59.00	7.08	S, 9.85	S, 10.00
$C_6H_5CH_2$	$C_6H_5CH_2Cl$	$C_{18}H_{19}NO_4S$	97	EtOH	95	62.59	5.55	62.51	5.52	S, 9.28	S, 9.41
$—CH_2CH_2—$	$BrCH_2CH_2Br$	$C_{24}H_{28}N_2O_8S_2$	93	EtOH	126–127	53.71	5.26	53.95	5.42	S, 11.95	S, 11.95

[a] Also sublimed *in vacuo*. [b] Identified by mixture melting point with authentic sample, no depression. [c] Not further purified. Crude material was oxidized to sulfone, which was analyzed. See Table III. [d] Saponification of this ester gave the corresponding acid, 59% yield, crystallized as hydrate from aqueous alcohol, m.p. 156–158° dec. *Anal.* Calcd. for $C_{11}H_{13}NO_4S \cdot H_2O$: C, 48.34; H, 5.53; S, 11.73. Found: C, 48.17, H, 5.52, S, 11.78.

TABLE III



ESTERS OF 4-ALKYLSULFONYL- AND 4-ARYLSULFONYLPYRIDINE-2,6-DICARBOXYLIC ACIDS[a]

R	Formula	Yield, % crude	M.p., °C.	Recrystallization solvent	Calcd. C	Calcd. H	Found C	Found H	Calcd.	Found
C_2H_5	$C_{13}H_{17}NO_6S$	90	131–132	EtOH–H_2O	49.51	5.43	49.76	5.14	S, 10.07	S, 10.08
i-C_3H_7	$C_{14}H_{19}NO_6S$	40	112–114	EtOH–H_2O H_2O	51.05	5.81	51.20	5.96	S, 9.73	S, 9.62
n-C_4H_9	$C_{15}H_{21}NO_6S$	61	101–102	EtOH–H_2O	52.46	6.16	52.67	6.08	S, 9.34	S, 9.45
s-C_4H_9	$C_{15}H_{21}NO_6S$	58	106–108	EtOH	52.46	6.16	52.56	6.28	S, 9.34	S, 9.41
i-C_5H_{11}	$C_{16}H_{23}NO_6S$	73	138–140	EtOH–H_2O	53.76	6.49	54.02	6.67	S, 8.97	S, 8.97
$—CH_2CH_2—$	$C_{24}H_{28}N_2O_{12}S_2$	83	235–239	$CH_3OC_2H_4OH$	47.99	4.70	48.09	4.79	S, 10.68	S, 10.51
$C_6H_5CH_2$	$C_{18}H_{19}NO_6S$	61	139–140	EtOH	57.28	5.08	57.15	4.87	S, 8.50	S, 8.08
C_6H_5	$C_{15}H_{13}NO_6S$[b]	97	205–206	MeOH	[c]	[c]				
C_6H_5	$C_{17}H_{17}NO_6S$	73	155–157	EtOH	56.19	4.72	56.31	4.88	S, 8.82	S, 8.72
p-ClC_6H_4	$C_{17}H_{16}ClNO_6S$	59	112.5–114.5	EtOH	51.32	4.05	51.25	4.10	S, 8.06	S, 8.12
p-BrC_6H_4	$C_{17}H_{16}BrNO_6S$	59	113.5–114.5	EtOH	46.16	3.65	46.32	3.77	Br, 18.32	Br, 18.00

[a] Diethyl esters unless stated otherwise. [b] Dimethyl ester. [c] Identified by mixture melting point with authentic sample, no depression.

solidified; recrystallization from hexane gave the analytical sample, m.p. 49–50°.

Anal. Calcd. for $C_{13}H_{17}NO_4S$: C, 55.10; H, 6.05; N, 4.94; S, 11.32. Found: C, 55.06; H, 6.00; N, 4.94; S, 11.38.

Ammonium 2,6-Dicarbethoxypyridine-4-thiolate.—A mixture of 2.6 g. of diethyl 4-chloropyridine-2,6-dicarboxylate, 5.0 g. of ammonium dithiocarbamate,[11] and 8 ml. of water was refluxed for 2 hr. The solid material was filtered after cooling and the analytical sample of indefinite melting point was obtained by recrystallization from methanol.[12]

Anal. Calcd. for $C_{11}H_{16}N_2O_4S$: C, 48.51; H, 5.92; N, 10.26; S, 11.77. Found: C, 48.61; H, 6.38; N, 10.09; S, 11.59.

This compound was also obtained when 2.2 g. of diethyl 4-thiocyanopyridine-2,6-dicarboxylate was refluxed with 10 ml. of 20% aqueous ammonium sulfide and 20 ml. of ethanol. The initially dark solution became lighter and, after removal of some insoluble material, 2.0 g. (95%) of large yellow crystals were deposited on cooling. This compound was identified by its reaction with ethyl iodide which produced diethyl 4-ethylmercaptopyridine-2,6-dicarboxylate.

Diethyl 4-Thiocyanopyridine-2,6-dicarboxylate.—A solution of 3.0 g. of ammonium thiocyanate in 3 ml. of water was added to 5.2 g. of diethyl 4-chloropyridine-2,6-dicarboxylate dissolved in 10 ml. of warm acetic acid and the mixture boiled for a few minutes. Some yellow solid was formed, but disregarded. Water was added to the mixture after slight cooling and the precipitate, 4.5 g. (83%), filtered. The analytical sample, m.p. 162.5–164.5°, was obtained upon repeated recrystallization from aqueous acetic acid.

Anal. Calcd. for $C_{12}H_{12}N_2O_4S$: C, 51.41; H, 4.32; S, 11.44. Found: C, 51.58; H, 4.52; S, 11.35.

This compound was also obtained when a mixture of the diethy 4-chloropyridine-2,6-dicarboxylate and excess potassium thiocyanate in acetic acid was allowed to stand for 15 hr.,[8] but the yield was inferior.

Dimethyl 4-thiocyanopyridine-2,6-dicarboxylate was obtained when a mixture of 2.3 g. of dimethyl 4-chloropyridine-2,6-dicarboxylate, 1.5 g. of potassium thiocyanate, and 30 ml. of acetic acid was allowed to stand at room temperature for 60 hr. It was filtered and combined with a second crop, which was obtained on adding water to the mother liquor, bringing the total

(11) C. E. Redemann, R. N. Icke, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 763.

(12) This reaction was found to be somewhat unreliable; therefore, no yield is indicated.

yield to 1.5 g. (62%). The analytical sample (from aqueous dioxane melted at 207–209°.

Anal. Calcd. for $C_{10}H_8N_2O_4S$: C, 47.61; H, 3.20; N, 11.11; S, 12.71. Found: C, 47.83; H, 3.08; N, 10.96; S, 12.75.

Diethyl 4-Alkylthiopyridine-2,6-dicarboxylate.—A slight excess of alkyl halide (or dimethyl sulfate) was added to a warm solution of ammonium 2,6-dicarbethoxypyridine-4-thiolate in a fivefold amount of dimethylformamide. The mixture, filtered when necessary, was diluted with water. The solid thioethers were filtered, washed and dried, while liquid ones were taken up with ether; the ether solutions were washed with water and sodium carbonate solution, dried, the solvent removed, and the residue distilled *in vacuo*. Additional preparative information, physical constants, and analytical data are summarized in Table II.

Oxidation of Thioethers with Hydrogen Peroxide.—The sample of thioether was dissolved in a fivefold amount of acetic acid and an equal volume of hydrogen peroxide (30%) was added. The mixture then was allowed to stand for several days. In some cases starting material was precipitated upon addition of the oxidizing agent, but dissolved slowly on standing, and, upon further standing, a new solid was formed. In other cases a clear solution was obtained and the sulfone was precipitated by addition of water. The crude products were filtered and recrystallized. Further experimental information, physical constants, and analytical data are summarized in Table III.

Diethyl 4-Ethylsulfonylpyridine-2,6-dicarboxylate.—A solution of 3.0 g. of diethyl 4-ethylthiopyridine-2,6-dicarboxylate in 15 ml. of acetic acid was oxidized by gradual addition of 4.0 g. of chromium trioxide. The dark reaction mixture was poured into water and 1.4 g. (42%) of the crystalline sulfone was filtered and recrystallized from water containing a little ethanol. It had m.p. 131–132° and no depression was observed when a sample was mixed with material obtained by oxidation of the same thioether with hydrogen peroxide.

Dimethyl 4-Phenylsulfonylpyridine-2,6-dicarboxylate.—This compound was obtained similarly in a yield of 36%. A sample recrystallized from methanol melted at 202–202.5°.

Anal. Calcd. for $C_{15}H_{13}NO_6S$: C, 53.78; H, 3.91; N, 4.18; S, 9.56. Found: C, 53.67; H, 3.88; N, 4.46; S, 9.66.

Diethyl 4-phenylsulfonylpyridine-2,6-dicarboxylate was isolated in 2.3% yield when diethyl 4-phenylthiopyridine-2,6-dicarboxylate was oxidized with chromium trioxate, m.p. 155–157°; there was no depression when mixed with a sample obtained by oxidation with hydrogen peroxide.

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Syntheses of Reduced Lipoic Acid and Analogs of Lipoic Acid

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Methyl 8-chloro-6-keto-7-octenoate has been prepared by condensation of methyl δ-chloroformylvalerate with acetylene. This β-chlorovinyl ketone has been converted to reduced lipoic acid by various routes. It also has served as an intermediate to the lipoic acid analogs 3-pyrazolevaleric acid and 5-isoxazolevaleric acid.

Lipoic acid, 1,2-dithiolane-3-valeric acid, has been the subject of many investigations directed to the clarification of its role in biological processes.[1] It has been reported to be useful in the treatment of various disorders,[2,3] although, a recent indication of liver cell damage following intraperitoneal administration has been reported.[4] This interest has led to much research[5] to make lipoic acid and related compounds available for experimental purposes.

In the course of our studies on lipoic acid, we investigated the utility of appropriately substituted chlorovinyl ketones[6] as intermediates for synthesis of lipoic acid and its analogs. Condensation of methyl δ-chloroformylvalerate with acetylene in tetrachloroethane solution gave methyl 8-chloro-6-keto-7-octenoate (I) in high yields.

$$CH_3O_2C(CH_2)_4COCl \xrightarrow[AlCl_3]{CH\equiv CH} CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH{=}CHCl$$

I

This β-chlorovinyl ketone is a skin irritant; extreme care must be exercised to prevent exposure. The material can be readily distilled under reduced pressure and is conveniently recrystallized from heptane. The pure compound, m.p. 51–52°, can be stored indefinitely at −80° but decomposes in a few days to a red oil if allowed to stand at room temperature.

Methyl 8-chloro-6-keto-7-octenoate possesses, and is readily transformed into other structures which possess, the proper functionality for conversion into lipoic acid type compounds. Reduction of this chlorovinyl ketone

$$I + NaBH_4 \longrightarrow CH_3O_2C(CH_2)_4\underset{\underset{OH}{|}}{CH}{-}CH{=}CHCl$$

II

$$I + CH_3\overset{\overset{O}{\|}}{C}SH \longrightarrow CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH_2CH(S\overset{\overset{O}{\|}}{C}CH_3)_2$$

III

$$I + C_2H_5SH \longrightarrow CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH{=}CHSC_2H_5$$

IV

$$I + NaOCH_3 \longrightarrow CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH_2CH(OCH_3)_2 + CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH{=}CHOCH_3$$

V VI

with sodium borohydride gave the chlorovinyl alcohol II. Reaction of I with thiolacetic acid in the presence of pyridine gave methyl 8,8-bis(acetylthio)-6-ketooctanoate (III) in very good yields. With ethyl mercaptan, the only product isolated was methyl 8-ethylthio-6-keto-7-octenoate (IV). When chlorovinyl ketone I reacted with sodium methoxide, both the ketoacetal V

(1) For a review of the early work with lipoic acid, see L. J. Reed, *Advan. Enzymol.*, **18**, 319 (1957).

(2) F. Rausch, *Arzneimittel-Forsch.*, **5**, 32 (1955).

(3) A. Segre, *Nature*, **177**, 75 (1956).

(4) Z. T. Wirtschafter and F. W. Smith, *J. Lab. Clin. Med.*, **60**, 649 (1962).

(5) For a list of references to prior synthetic work, see D. S. Acker and W. J. Wayne, *J. Am. Chem. Soc.*, **79**, 6483 (1957).

(6) For a review of the synthesis and chemistry of chlorovinyl ketones, see N. K. Kochetkov, *Usp. Khim.*, **24**, 32 (1955).