TABLE I

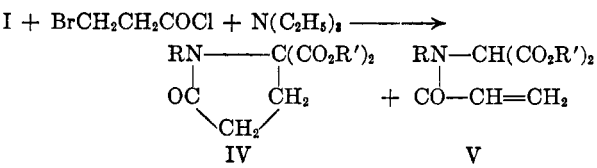
α-Halo Acid Halide	R	R′	R″	M.P.	Yield, %
$ClCH_2COCl$	C_6H_5	C_2H_5	H	38–39[a]	72
$BrCH_2COBr$	C_6H_5	C_2H_5	H	"	75
$ClCH_2COCl$	p-$CH_3C_6H_4$	C_2H_5	H	89–91[a]	83
$ClCH_2COCl$	$C_{10}H_7$	C_2H_5	H	75–76[a]	79
$C_6H_5CHClCOCl$	C_6H_5	C_2H_5	C_6H_5	87–88	74

[a] See ref. 2.

about three hours. The product from this reaction is the β-lactam III in about 70–80% yield (based on I).

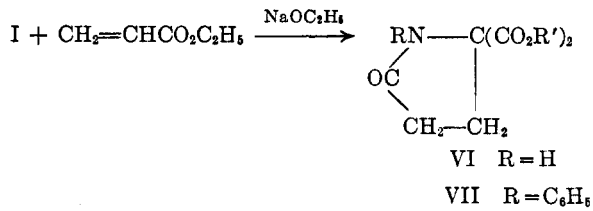
The preparation of several β-lactams (III) obtained by this one-step method is summarized in Table I.

Bose, Ghosh-Mazumdar, and Chatterji[4] have shown that γ-lactams of type IV can also be prepared by a two-step sequence similar to that used for the synthesis of the β-lactam III. When the conversion of I to IV in one operation was attempted using a β-halo acid halide and triethylamine, the yield of the γ-lactam IV was very poor. On the basis of infrared and proton magnetic resonance spectra, it was found that the major by-product was the substituted acrylamide V.



Cocolas and Hartung[5] have observed that the prolonged reaction of diethyl acetamidomalonate with ethyl acrylate in presence of sodium ethoxide leads to the γ-lactam VI.

When we allowed I (R = phenyl) to react with ethyl acrylate in presence of sodium ethoxide, the γ-lactam VII[4] was obtained in one operation in high yield.



EXPERIMENTAL

A typical procedure for the one-step synthesis of β-lactams of type III is illustrated by the following preparation.

1,3-Diphenyl-4,4′-dicarbethoxyazetidin-2-one. To a solution of 2.5 g. of diethyl anilinomalonate in 25 ml. of benzene were added 2.0 g. of α-chlorophenylacetyl chloride and 3 g. of triethylamine. A white solid separated out and the reaction mixture became warm. The mixture was allowed to stand at room temperature for 3 days and then filtered. The filtrate was washed with dilute hydrochloric acid and with water. After drying the washed filtrate over anhydrous magnesium sulfate, the solvent was removed under reduced pressure when 7.6 g. of a brown, semisolid mass was obtained. Recrystallization from a mixture of petroleum ether and ethyl acetate afforded 6 g. (74% yield) of colorless needles, m.p. 87–88°, λ_{max}^{Nujol} 5.62 μ (1783 cm.$^{-1}$, β-lactam carbonyl), 5.68 μ and 5.72 μ (1761 cm.$^{-1}$ and 1748 cm.$^{-1}$, ester groups).

Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 69.14; H, 6.54; N, 3.85.

1-Phenyl-5,5-dicarbethoxypyrrolidin-2-one.[4] A solution of 5 g. of diethyl anilinomalonate in 50 ml. of absolute ethanol was added to a solution of 78 mg. of sodium in 5 ml. of absolute ethanol taking the usual precautions for precluding moisture. Three grams of ethyl acrylate was then added with stirring over a period of 30 min., and the mixture was heated under reflux for 10 hr. After cooling the reaction mixture was neutralized with glacial acetic acid and then stripped of solvent by distillation under reduced pressure. The residue was taken up in ether and washed successively with sodium bicarbonate solution, dilute hydrochloric acid, and water. The ethereal layer was dried over anhydrous magnesium sulfate and the solvent removed from it under reduced pressure; 4.7 g. (81% yield) of a viscous liquid was obtained. After purification by evaporative distillation the product, n_D^{20} 1.5183, λ_{max} 5.72 μ (1749 cm.$^{-1}$, ester), 5.83 μ (1715 cm.$^{-1}$, γ-lactam) was found to be identical with the sample of the γ-lactam prepared by the two-step sequence.[4]

Acknowledgment. This work was supported in part by a research grant (MY-3930) from the National Institutes of Health, U. S. Public Health Services. Thanks are due to Dr. E. R. Malinowski for the NMR data and to R. I. Gluck[6] and F. Chasalow[6] for technical assistance.

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(4) A. K. Bose, B. N. Ghosh-Mazumdar, and B. G. Chatterji, *J. Am. Chem. Soc.*, **82**, 2382 (1960).

(5) G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, **79**, 5203 (1957); G. H. Cocolas, S. Avakian, and G. J. Martin, *J. Org. Chem.*, **26**, 1313 (1961).

(6) National Science Foundation undergraduate research participant.

A Study of the Chlorination of 2-Thenylamines with Sulfuryl Chloride[1]

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The purpose of this paper is to describe a novel general method for introducing chlorine into the

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5- position of 2-thenylamines in relatively high yields.

Although considerable study has been given to the chlorination of thiophene and to a lesser extent the alkylthiophenes, no detailed work on the chlorination of 2-thenylamines has been reported.

Reaction of thiophene and chlorine in equimolar amounts gives 2-chlorothiophene as the main product (37%).[2] A considerable amount of 2,5-dichlorothiophene (27%) and other di- and trichloro derivatives (20%) are formed. These latter products arise from direct substitution of the nucleus as well as addition of chlorine across the double bonds followed by dehydrochlorination of these addition products. A somewhat higher yield of 2-chlorothiophene (43%) along with the 2,5-dichloro derivative has been obtained using sulfuryl chloride as the chlorinating agent.[3] Other chlorinating agents, such as nitrosyl chloride, hypochlorous acid, and *N*-chloroacetamide, have received only minor attention.

Concerning the chlorination of alkylthiophenes, nuclear substitution definitely predominates over side chain chlorination with either chlorine or sulfuryl chloride. Multiple substitution in the nucleus is the general rule when using chlorine; however, a high yield (79%) of 2-chloro-3-methylthiophene has been obtained from 3-methylthiophene employing sulfuryl chloride.[3,4]

In our laboratory, we have found that sulfuryl chloride is an excellent reagent for selectively chlorinating 2-thenylamines in the 5- position. As a prime example, a chloroform solution of the complex antihistaminic compound 2-[(2-dimethylaminoethyl)-2-thenylamino]pyridine (Methapyrilene)[5] in the form of its trihydrochloride can be chlorinated with sulfuryl chloride to give directly a high yield (83.6%) of the more potent 5-chloro analog, 2-[(5-chloro-2-thenyl)(2-dimethylaminoethyl)amino]pyridine (Chlorothen).[6,7] The quality of the product generated by this process was demonstrated by conversion in 90% yield to its citrate salt, which has excellent quality according to N. F. standards for Chlorothen citrate.[8]

Careful fractionation of the forecut obtained from relatively large scale operations revealed the nature of the major by-products formed in this process. Apparently chlorination of the methylene group of the thenyl radical in both Methapyrilene and Chlorthen occurs to the extent of 5 to 7% which leads to the formation of 2-thiophenecarboxaldehyde, 5-chloro-2-thiophenecarboxaldehyde, and 2-[(2-dimethylaminoethyl)amino]pyridine. It is interesting that the presence of unchanged Methapyrilene could not be detected. This provides an explanation why the chlorinated product can be obtained in high purity by a simple take-over distillation.

By contrast, when a patented method employing chlorine[9] was applied to Methapyrilene, Chlorothen was obtained in low yield (48%) and in a very impure state. This product formed a gummy citrate salt in only 60% isolable yield.

In order to define better this sulfuryl chloride chlorination procedure, four additional *N*-substituted 2-thenylamines were synthesized and their hydrochlorides chlorinated in the manner described. *N*-Butyl-, *N*-cyclohexyl-, and *N*,*N*-diethyl-2-thenylamine[10] were prepared from 2-(chloromethyl)thiophene and an excess of the appropriate amine. 2-(2-Thenylamino)pyridine was prepared according to the literature.[5b]

On chlorination, these *N*-substituted 2-thenylamines gave their corresponding 5-chloro analogs in yields of approximately 45 to 85% with the tertiary amines giving the higher yields. For analytical purposes, the starting 2-thenylamines and their corresponding 5-chloro derivatives were converted to the hydrochloride salts.

EXPERIMENTAL

The procedure given below is illustrative of the sulfuryl chloride chlorination process.

Chlorination of methapyrilene to form chlorothen. A solution of Methapyrilene[5] (183.0 g., 0.7 mole) in 400 ml. of chloroform was stirred and cooled to 5° while 80.2 g. (2.2 moles) of dry hydrogen chloride gas was introduced.[11] The solution of Methapyrilene trihydrochloride was stirred and maintained at 5° with cooling while 97.3 g. (0.72 mole) of sulfuryl chloride was added over a period of 1 hr. Upon completion of the addition, the reaction mixture was stirred for an additional 1.5 hr. at 5°. The solution was then degassed at a reduced pressure of 100 to 150 mm. for 1 hr. at 5°.

The degassed solution was stirred and made distinctly basic (*p*H above 10) by adding 240 g. of a 50% sodium hydroxide solution while maintaining the temperature at 25°. Water (240 ml.) was then added with stirring to dissolve the

(2) H. L. Coonradt, H. D. Hartough, and G. C. Johnson,[1] *J. Am. Chem. Soc.*, **70**, 2564 (1948).

(3) E. Campaigne and W. M. LeSuer, *J. Am. Chem. Soc.*, **70**, 415 (1948).

(4) For additional information and references on chlorothiophene derivatives, see H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, 1952, pp. 173–189.

(5) (a) L. P. Kyrides, U. S. Patent **2,581,868** (1952). (b) F. Leonard and U. V. Solmssen, *J. Am. Chem. Soc.*, **70**, 2064 (1948).

(6) L. P. Kyrides, U. S. Patent **2,581,869** (1952).

(7) For pharmacological references to the antihistaminic agents derived from thiophene, see A. Burger, "Medicinal Chemistry," Vol. I, 1st ed., Interscience Publishers, Inc., New York, 1951, p. 449.

(8) "National Formulary," Eleventh Revision, Mack Printing Co., Easton, Pa., 1960, p. 82.

(9) N. Sperber, D. Papa, and E. Schwenk, U. S. Patent **2,604,473** (1953).

(10) D. R. Smith and C. J. Cavallito, *J. Am. Chem. Soc.*, **75**, 3033 (1953) previously prepared this compound by the Leuckart reaction.

(11) In the chlorination of all of the *N*-substituted 2-thenylamines, a 5 to 10% excess of one equivalent of hydrogen chloride gas per nitrogen atom was introduced to assure salt formation of all of the amino groups prior to the addition of the sulfuryl chloride.

precipitated sodium chloride formed during the neutralization.[12] The chloroform layer was separated from the aqueous phase and the latter extracted twice with 50 ml. of chloroform. After removal of the chloroform by distillation, the crude product was fractionated. A forecut (12.4 g.) which boiled at 60–190° (5 mm.) was removed, and the product collected at 190–194° (5 mm.); yield, 173.1 g. (83.6%); $n^{25}D$ 1.5863; d_{25}^{25}, 1.1751.

Determination of by-products formed in the chlorination of methapyrilene. Samples of the forecut from pilot plant operations where the yield of Chlorothen was 77.7% were carefully fractionated through a 3 ft. × 1 in. heated column packed with glass helices. The components were identified by comparison of boiling points, refractive indices, and infrared spectra with authentic samples of the materials in question. The by-products, % of formation based on Methapyrilene, their prominent infrared spectral bands and other physical properties are as follows:

2-Thiophenecarboxaldehyde: 2.0%; 5.96 μ (CO), 8.30 μ, 9.60 μ; b.p. 60.5° (4.5 mm.); $n^{25}D$, 1.5897.

5-Chloro-2-thiophenecarboxaldehyde: 1.4%; 5.98 μ (CO), 9.97 μ, 12.60 μ; b.p. 77.5° (5.2 mm.); $n^{25}D$ 1.6036.

2-[(2-Dimethylaminoethyl)amino]pyridine: 5.6%; 2.95 μ (NH), 6.25 μ, 6.39 μ, 6.75 μ; b.p. 97.5° (1.8 mm.); $n^{25}D$ 1.5450.

Infrared analyses indicate that at least two other by-products, which come over in the aldehyde fractions, are formed in small amounts. They appear to be chloro compounds and are not 2-(chloromethyl)thiophene, 5-chloro-2-(chloromethyl)thiophene, or 5-chloro-2-thiophenecarboxylic acid.

Decomposition of the forecut occurred during fractionation as evidenced by the tar which remained (27.5% of the starting forecut). Nothing could be isolated or identified from this residue.

Chlorothen citrate. The free base (44.4 g., 0.15 mole) and citric acid (31.5 g., 0.15 mole) were refluxed in 237 g. of 95% acetone for 15 min. The resulting solution was then cooled slowly to 0°, and the product filtered and dried; yield, 65.9 g. (90%); m.p. 115.4–116.1°.

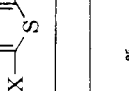
General procedure for the preparation of the N-substituted 2-thenylamines. 2-(Chloromethyl)thiophene[13] (106.0 g., 0.8 mole) was added dropwise to 4.0 moles of the appropriate amine with stirring and cooling to maintain the temperature below 50°.[14] After all of the 2-(chloromethyl)thiophene had been added, the reaction mixture was stirred for 16 hr. at 25°. A 20% sodium hydroxide solution (200 g.) was slowly added. The reaction mixture was then heated at 50° for 1 hr., cooled to 25°, salted, and extracted twice with 150 ml. of chloroform. The chloroform was removed by distillation and the crude product fractionated.

Hydrochloride salts of the N-substituted 2-thenylamines and their 5-chloro analogs. These derivatives were prepared in the usual manner by passing dry hydrogen chloride gas into a solution of the amine in hexane or isopropyl alcohol, filtering the product and recrystallizing from an appropriate solvent.

Acknowledgment. We wish to thank Dr. B. Katlafsky and Messrs. O. E. Kinast, J. L. O'Sullivan, and O. S. Kring for their assistance with the

TABLE I

N-SUBSTITUTED 2-THENYLAMINES AND 5-CHLORO-2-THENYLAMINES



X	R	R′	Formula	Bases: Yield, %	Bases: B.P., °C.	Bases: (mm.)	Bases: $n^{25}D$	Bases: Nitrogen, % Calcd.	Bases: Nitrogen, % Found	Salts: Salt	Salts: M.p., °C.	Salts: Nitrogen, % Calcd.	Salts: Nitrogen, % Found	Salts: Chlorine, % Calcd.	Salts: Chlorine, % Found
H	H	*n*-C_4H_9	$C_9H_{15}NS$	75.5	98–100	(6.0)	1.5027	8.27	8.11	HCl[a]	188–190	6.81	7.16	17.23	16.96
H	H	C_6H_{11}	$C_{11}H_{17}NS$	75.4	96–97	(0.58)	1.5381	7.17	7.19	HCl[a]	207–209	6.04	6.15	15.29	15.46
H	C_2H_5	C_2H_5	$C_9H_{15}NS$[b]	88.6	79–81	(7.0)	1.5027	—	—	HCl[a]	149–150	6.81	6.42	17.23	17.30
Cl	$CH_2CH_2N(CH_3)_2$	C_5H_4N	$C_{14}H_{18}ClN_3S$[c]	83.6	190–194	(5.0)[d]	1.5863	—	—	$C_2H_4(OH)(COOH)_2$	115.4–116.1	8.61	8.53	7.26	7.34
Cl	H	*n*-C_4H_9	$C_9H_{14}ClNS$	46.2	129–132	(8.4)	1.5232	6.84	6.79	HCl[a]	195	5.83	6.00	29.52	29.42
Cl	H	C_6H_{11}	$C_{11}H_{16}ClNS$	62.0	113–117	(0.65)	1.5479	6.10	6.17	HCl[e]	218	5.26	5.33	26.64	26.31
Cl	H	C_5H_4N	$C_{10}H_9ClN_2S$[f]	53.3	163–168	(1.9)	—	12.47	12.41	—	—	—	—	—	—
Cl	C_2H_5	C_2H_5	$C_9H_{14}ClNS$	80.7	105–108	(10.4)	1.5190	6.88	6.54	HCl[g]	122	5.83	5.87	29.52	28.94

[a] Recrystallized from isopropyl alcohol. [b] Ref. 10: $n^{20}D$ 1.5095; b.p., 40°C. (1.5 mm.). [c] d_{25}^{25}, 1.1751. [d] L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey, and L. W. Bannister, *J. Am. Chem. Soc.*, **72**, 745 (1950); b.p. 171–173°C. (1.8 mm.); $n^{25}D$ 1.5863. [e] Recrystallized from ethyl alcohol. [f] M.p. 87–90°C. (out of methyl alcohol); I. A. Kayne and I. C. Kogon, *J. Am. Chem. Soc.*, **73**, 5891 (1951); m.p. 84–86.5°C. [g] Recrystallized from methyl isobutyl ketone.

(12) During the neutralization of the chlorinated reaction mixture of the other *N*-substituted 2-thenylamines, the temperature was allowed to rise to 50°. After the addition of water, the reaction mixture was stirred and heated at 50° for 1 hr. and then cooled to 25°. This method of operation afforded a better separation of the aqueous and chloroform phases.

(13) F. F. Blicke and F. Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).

(14) In the case of the *N,N*-diethyl derivative, the mole ratio of diethylamine to 2-(chloromethyl)thiophene was 3 to 1, respectively, and 200 ml. of butyl alcohol was used as a solvent.

various infrared and elemental analyses. We are also indebted to Drs. F. C. Meyer, M. C. Freerks, and F. B. Zienty for valuable suggestions and advice.

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Preparation of Perfluoronitrosoalkanes. Reaction of Trifluoroacetic Anhydride with Nitrosyl Chloride

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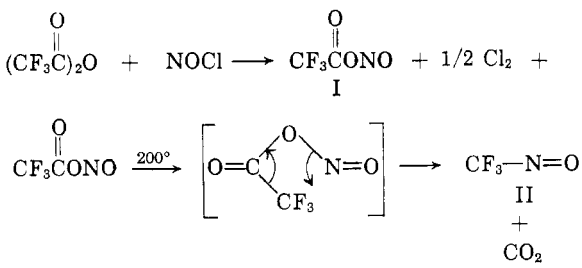
When trifluoroacetic anhydride is treated with nitrosyl chloride at room temperature, distillation of the products at atmospheric pressure leads to low yields of trifluoronitrosomethane. However, under vacuum distillation a yellow liquid is obtained which is quite reactive toward common solvents and various metals. Analysis of this compound shows it to be trifluoroacetyl nitrite (I). Pyrolysis of I at 200° produces trifluoronitrosomethane (II) in greater than 85% yields.



Care must be exercised in heating the acyl nitrites for they have a tendency to detonate at high temperatures.

The scope of this reaction may prove to be quite extensive as it has been successfully applied to the pentafluoropropionic and heptafluorobutyric anhydrides.

EXPERIMENTAL

Reaction of trifluoroacetic anhydride with nitrosyl chloride. In an evacuated 7-l. flask equipped with one two-way stopcock and one three-way stopcock, 45 g. of trifluoroacetic anhydride, and 22 g. of nitrosyl chloride were introduced in the vapor state. The gases were condensed by cooling the flask with Dry Ice and then allowed to warm up to room temperature.

A 300-watt incandescent lamp was positioned a few inches from the flask and irradiation was continued for two days with intermittent shaking.

Yield: 10.1 g. of trifluoroacetyl nitrite, n_D^{25} 1.3722, b.p. 46°/80 mm.

Anal. Calcd. for $C_2F_3O_2N$: C, 16.80; N, 9.79; F, 39.72. Found: C, 17.00; N, 9.85; F, 39.72.

Trifluoronitrosomethane was characterized by its infrared spectrum and the physical properties found to be identical with that produced by the method of Haszeldine.[1]

Acknowledgment. The authors gratefully acknowledge support for this work from the Quartermaster Corps, Research and Development Command, U. S. Army, Natick, Mass., and to their Dr. Juan C. Montermoso for his continued encouragement and support.

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(1) R. N. Haszeldine, *J. Chem. Soc.*, 2075 (1953).

A New Preparation of 2-Methylthio-4,6-dichloropyrimidine and Synthesis of 2-Alkylthio-4-chloro(or methoxy)-6-pyrimidinols

NAOTAKA YAMAOKA AND KIYOSHI ASO

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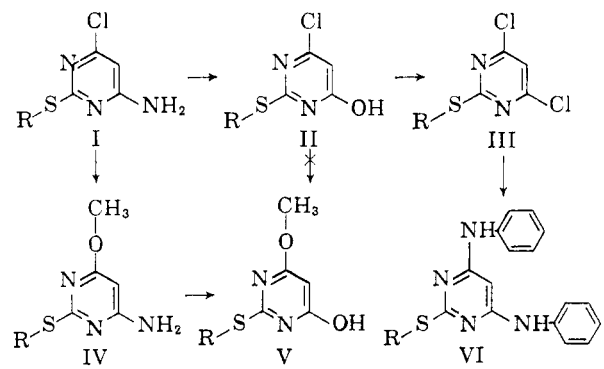
2-Methylthio-4,6-dichloropyrimidine (III, R = CH_3)[1,2] is a very important intermediate for the preparation of a number of pyrimidine derivatives. The present communication describes a convenient synthesis of this compound by chlorination of 2-methylthio-4-chloro-6-pyrimidinol (II. R = CH_3)[1] with phosphoryl chloride in the presence of the dimethylaniline.

Unlike previously described syntheses of 2-methylthio - 4,6 - dichloropyrimidine, this method does not involve the 2-methylthio-4,6-pyrimidinediol as intermediate.[2] The yield of dichloropyrimidine (III. R = CH_3) from 6-pyrimidinol (II. R = CH_3) (96%) compares favorably with those



(1) H. C. Koppel, R. H. Springer, R. K. Roland, and C. C. Cheng, *J. Org. Chem.*, **26**, 794 (1961); H. C. Koppel, R. H. Springer, and C. C. Cheng, *J. Org. Chem.*, **26**, 1884 (1961).

(2) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 342 (1904).