

**Strontium 3-(Carboxymethoxymethoxy)-2-methoxy-3-methylbutyrate (XXV).**—A solution containing 1.24 g. (6 mM.) of methyl novioside (XXI) and 2.57 g. (12 mM.) of sodium metaperiodate in 150 ml. of water was allowed to react in the dark at room temperature for 1 hr. and 10 minutes. A hot solution of 1.595 g. of strontium hydroxide octahydrate in 25–30 ml. water was added portionwise along with 24 ml. of 0.5 *N* hydrochloric acid. The pH was maintained between 5 and 6. After 30 minutes the precipitated salts were removed by filtration through a Celite pad. The filtrate and water wash were combined, 0.4 g. of strontium carbonate was added and the suspension concentrated *in vacuo* to about one-third volume. The salts were removed by filtration and the filtrate was taken to dryness. The residue was extracted with absolute ethanol and the filtered extract made up to 50 ml. with absolute ethanol. Forty ml. of this solution was evaporated to dryness to yield 694 mg. of the dialdehyde XXIV as a pale yellow oil. The oil was dissolved in 75 ml. of water; 8 g. of strontium carbonate and 1 ml. of bromine were added. The mixture was swirled and shaken every few minutes for 0.5 hr., then allowed to react in the dark for 23 hr. The excess bromine was removed by aeration, the strontium carbonate by filtration and the bromide by precipitation with silver carbonate (8 g.). The filtrate was freed of silver ions with hydrogen sulfide and the excess hydrogen sulfide removed by aeration. The colorless solution was concentrated at the water-pump to a volume of 3–4 ml. Ethanol (5 ml.) was added and the product separated as needles. A total of 807.23 mg. (77%) of the crystalline salt was obtained. For analysis a sample was recrystallized from 50% ethanol,  $[\alpha]^{25}_D +10^\circ$  (*c* 0.734 in water).

*Anal.* Calcd. for  $C_9H_{14}O_7Sr \cdot 1.5H_2O$ : C, 31.00; H, 4.91; OCH<sub>3</sub>, 17.39; Sr, 25.12. Found: C, 31.18; H, 5.07; OCH<sub>3</sub>, 19.65; Sr, 25.68.

**Hydrolysis of Methyl 3-O-Carbamyl-4-O-methyl-5,5-dimethyl-L-lyxoside (XIV) to 3-O-Carbamyl-4-O-methyl-5,5-dimethyl-L-lyxose (XXIII).**—A solution of 303.5 mg. (0.928 mM.) of XIV in 30 ml. of 0.5 *N* sulfuric acid was heated at ca. 80°. At 15–30 minute intervals the solution was cooled quickly to room temperature and the specific rotation was determined. After about an hour of heating there appeared to be no further change in rotation (Fig. 4). The solution was neutralized with excess barium carbonate, filtered and concentrated to dryness *in vacuo*. The residue was taken up in ethanol, the solution was filtered and the clear, colorless filtrate evaporated to yield 257 mg. of colorless glass. The product gave a positive Benedict reaction

and consumed one mole of periodate with the formation of one mole of formic acid (Table I). After thorough drying the material gave satisfactory elemental analyses but failed to crystallize.

*Anal.* Calcd. for  $C_9H_{17}NO_6$ : C, 45.95; H, 7.29; N, 5.96. Found: C, 45.95; H, 7.66; N, 5.92.

To check the homogeneity of amorphous XXIII, the hydrolysis was repeated on larger scale using 2.50 g. of XIV in 250 ml. of 0.5 *N* sulfuric acid. The rotation *vs.* time plot for this experiment (Fig. 4) gave an indication that a secondary reaction was starting toward the end of the one-hour reaction time. The reaction mixture was worked up as before and the amorphous product was subjected to countercurrent distribution analysis using 1-butanol and water as the solvent system (Fig. 5). After 175 transfers in the 200-tube machine, analysis by solids measurement revealed the presence of three components: a well-resolved, fast-moving minor component ( $K = 1.692$ ), the major component ( $K = 0.452$ ) and a minor component ( $K = 0.215$ ) incompletely resolved. The fast-moving component was removed from the machine yielding 200 mg. of colorless crystals identified as methyl 3-O-carbamylnovioside (XIV). The empty tubes were refilled with fresh solvent and the distribution continued to a total of 340 transfers. At this point the remaining two components were resolved. Contents of appropriate tubes were pooled and worked up to yield 1.5595 g. (ca. 76% over-all yield from XIV) of 3-O-carbamylnoviose and 336 mg. of material, presumably the monohydrate of XXVI. After prolonged drying *in vacuo*, 3-O-carbamylnoviose became birefringent and melted at 124–126°. The compound gave a positive Benedict reaction and consumed one mole of periodate,  $[\alpha]^{25}_D +45.3^\circ$  (*c*, 0.971 in 95% ethanol).

*Anal.* Calcd. for  $C_9H_{17}NO_6$ : C, 45.95; H, 7.29; N, 5.96. Found: C, 46.15; H, 7.75; N, 5.63.

The third component obtained as an amorphous, hygroscopic glass, was not fully characterized. Its infrared absorption with a strong band at 1695  $cm^{-1}$  assured the presence of a carbonyl, probably in a cyclic system. The absence of absorption in the 1600  $cm^{-1}$  region indicated that the simple carbamate structure had been altered. Elemental analyses showed that the nitrogen was retained and that the gummy product was solvated,  $[\alpha]^{25}_D +63^\circ$  (*c*, 0.96 in 95% ethanol).

*Anal.* Calcd. for  $C_9H_{15}NO_5 \cdot H_2O \cdot \frac{1}{2}C_2H_5OH$ : C, 46.50; H, 7.81; N, 5.42. Found: C, 46.95; H, 7.45; N, 5.61.

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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

## 6-Phenylthieno [2,3-b]pyridine from 2-Nitro-3-thenaldehyde

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3-Methylthiophene was converted to 3-thenyl acetate which on nitration gave a mixture of 2- and 5-nitro-3-thenyl acetates. The readily isolated 2-isomer was hydrolyzed to the alcohol, nitric acid oxidation of which gave 2-nitro-3-thenaldehyde. The aldehyde condensed readily with malonic acid and with acetophenone. The product from the latter reaction was reduced and cyclized to 6-phenylthieno[2,3-b]pyridine.

Recently, an interest developed in the synthesis of compounds containing fused thiophene rings of the  $C_4N-C_4S$  or  $C_5S-C_5N$  systems in which the sulfur and nitrogen atoms are in the peri position. Of particular interest as an intermediate was 2-nitro-3-thenaldehyde (I) which by analogy to *o*-nitrobenzaldehyde would be a satisfactory starting material for the preparation of a number of the desired type compounds. Using commercially available 3-methylthiophene (VI), 2-nitro-3-thenaldehyde (I) was prepared in an over-all yield of 5%. The al-

dehyde was converted *via* the condensation product with acetophenone to 6-phenylthieno[2,3-b]pyridine (XII), the thiophene analog of 2-phenylquinoline.

3-Methylthiophene (VI) was treated with *N*-bromosuccinimide as described by Campaigne and Tuller<sup>2</sup> to give 3-thenyl bromide which without isolation was converted immediately to 3-thenyl acetate (IV) in 58% over-all yield. The small amount of 2-bromo-3-methylthiophene formed in the bromination step was removed readily from the ester by distillation. The physical properties of the ace-

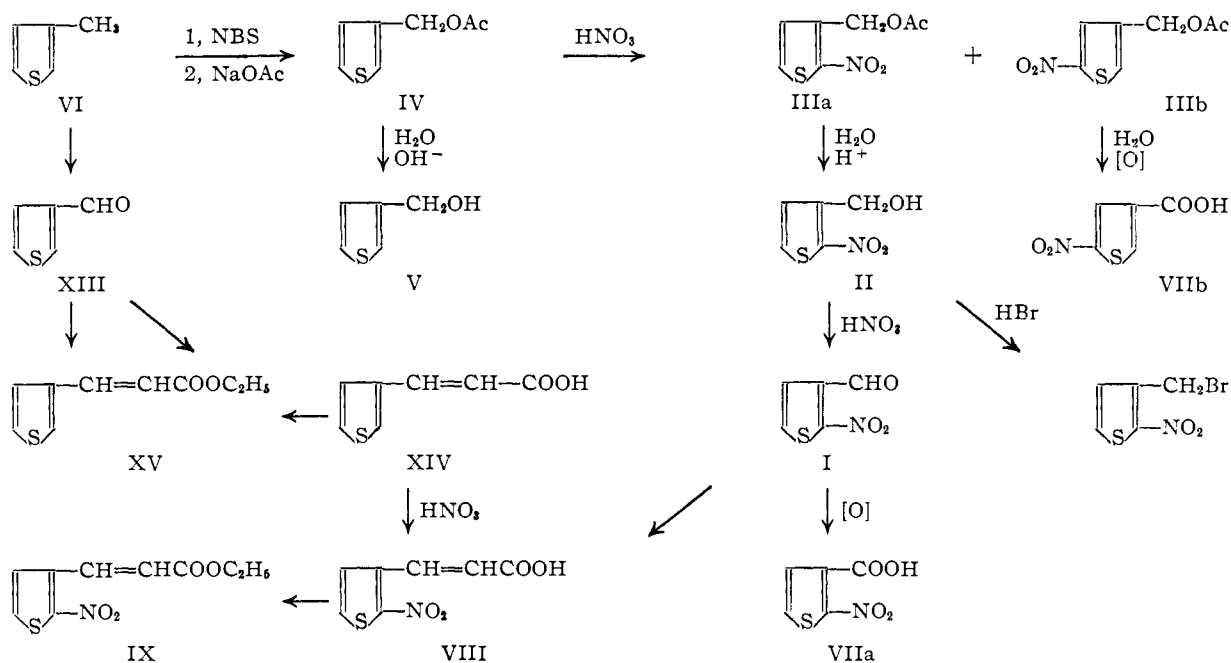
(1) Parke, Davis Fellow, 1952–1955. The Dow Chemical Company, Midland, Michigan.

(2) E. Campaigne and B. F. Tuller, *Org. Syntheses*, **33**, 96 (1953).

tate IV were nearly identical with those of 2-thenyl acetate as reported by Emerson and Patrick.<sup>3</sup>

Hydrolysis of 3-thenyl acetate (IV) with dilute alkali gave a fair yield of 3-thenyl alcohol (V).<sup>4</sup> 3-Thenyl *N*- $\alpha$ -naphthylcarbamate synthesized from the alcohol gave the same melting point as reported by Campaigne and Bourgeois.<sup>4</sup> The *N*-phenylcarbamate was also prepared.

The work of Grimaux<sup>5</sup> and of Beilstein and Kuhlberg<sup>6</sup> as well as some unpublished work in this Laboratory on the nitration of benzyl acetate indicated the acetoxyethyl group to be *ortho-para* directing, while Rinkes<sup>7</sup> showed that the methyl group in 3-methylthiophene directs to the 2-position predominantly in nitration. With nitric acid in acetic anhydride at  $-10^\circ$  3-thenyl acetate (IV) gave a 30% yield of 2-nitro-3-thenyl acetate (IIIa) plus a 53% yield of a low-melting mixture of 2-nitro- and 5-nitro-3-thenyl acetates (IIIa and IIIb).



Attempts to obtain the 5-nitro isomer pure by fractional crystallization failed. Chromatography of the isomer mixture on alumina gave a small amount of pure 5-nitro-3-thenyl acetate (IIIb) due mainly to decomposition of the 2-isomer in the process. By projecting the results of the chromatographic experiment it was estimated that nitration of 3-thenyl acetate (IV) in the 2-position is favored 4:3 over nitration in the 5-position. No evidence of the existence of the third possible isomer, 4-nitro-3-thenyl acetate, was found although small amounts may have been present. The addition of

3-thenyl acetate (IV) to a solution of acetyl nitrate gave lower yields of more difficultly purified product.

The hydrolysis of 2-nitro-3-thenyl acetate (IIIa) to the alcohol II proceeded satisfactorily only in acid solution because of the sensitivity of both compounds to decomposition in base. Although 2-nitro-3-thenyl alcohol (II) recrystallized easily, sublimation proved to be the best means of purification for analysis. The alcohol II was converted to 2-nitro-3-thenyl bromide when treated with hydrobromic acid as described by Norris, Watt and Thomas<sup>8</sup> for the preparation of *o*-nitrobenzyl bromide.

Helferich, Streeck and Gunther<sup>9</sup> have described the uncontrolled oxidation of *o*-nitrobenzyl alcohol with nitric acid to give *o*-nitrobenzaldehyde in 85% yield. In applying their procedure to the oxidation of 2-nitro-3-thenyl alcohol (II) maximum yields were obtained when the reaction was carried out at  $35^\circ$ . At this temperature the yield of 2-

nitro-3-thenaldehyde (I) remained nearly constant at 54% over a 15 to 30 minute reaction time. With shorter reaction periods larger amounts of 2-nitro-3-thenyl alcohol (II) were recovered while reactions of longer duration yielded increasing amounts of 2-nitro-3-thenoic acid (VIIa). The aldehyde I was isolated from the crude reaction mixture by steam distillation and further purified by sublimation in the dark. The phenylhydrazone and thiosemicarbazone of 2-nitro-3-thenaldehyde (I) were prepared most conveniently by appropriate treatment of the filtrate from the steam distillate.

The structure of 2-nitro-3-thenoic acid (VIIa) had been established earlier by Rinkes.<sup>7</sup> The iso-

(3) W. S. Emerson and T. M. Patrick, *J. Org. Chem.*, **14**, 790 (1949).

(4) E. Campaigne and R. C. Bourgeois, *THIS JOURNAL*, **76**, 2445 (1954), obtained this alcohol from the lithium aluminum hydride reduction of some halo-3-thenoic acids and refer to its previous preparation by W. C. McCarthy at the University of Indiana.

(5) E. Grimaux, *Compt. rend.*, **65**, 211 (1867).

(6) F. Beilstein and A. Kuhlberg, *Ann.*, **147**, 339 (1868).

(7) I. J. Rinkes, *Rec. trav. chim.*, **53**, 643 (1934).

(8) J. F. Norris, M. Watt and R. Thomas, *THIS JOURNAL*, **38**, 1070 (1916).

(9) B. Helferich, R. Streeck and E. Gunther, *J. prakt. Chem.*, **151**, 251 (1938).

lation of this acid from the oxidation reaction substantiated the structures of the 2-nitro aldehyde I, alcohol II and acetate IIIa. The acid VIIa was converted to the previously unreported 2-nitro-3-thenamamide without isolation of the intermediate acid chloride. The structure of 5-nitro-3-thienyl acetate (IIIb) was proved by hydrolysis and oxidation to the known 5-nitro-3-thenoic acid<sup>4,7</sup> (VIIb). Although the yield in the oxidation step was poor, only one acid was isolated. As a further check the acid VIIb was converted to 5-nitro-3-thenamamide identical in melting point with that reported by Campaigne and Bourgeois.<sup>4</sup>

Besides forming the usual derivatives of the carbonyl group 2-nitro-3-thenaldehyde (I) underwent typical condensations with active methyl or methylene groups. With malonic acid in pyridine it reacted to form  $\beta$ -(2-nitro-3-thienyl)-acrylic acid (VIII). On heating the acrylic acid decomposed with the evolution of carbon dioxide; a reproducible melting point was obtained only when approached rapidly. Although no attempt was made to isolate the product, it is presumed that 2-nitro-3-vinylthiophene was formed as in the decarboxylation of similar acids to form substituted styrenes and vinylfurans.<sup>10</sup> Several attempts to reduce the nitro group and ring close the amino acid to 6-hydroxythieno[2,3-b]pyridine produced only polymeric material. Treatment of the acid VIII with ethanol-sulfuric acid gave the ester, ethyl  $\beta$ -(2-nitro-3-thienyl)-acrylate (IX).

A trace of sodium hydroxide catalyzed the reaction of 2-nitro-3-thenaldehyde (I) with acetophenone as described by Tanasescu and Bacic<sup>11</sup> for the preparation of *o*-nitrochalcone. The crude product was a mixture of the desired 2-nitro-3-thienylideneacetophenone (X) and a lower melting compound which was not obtained pure. Since the latter compound was converted by Lucas reagent to the  $\alpha,\beta$ -unsaturated ketone X, it is presumed to be the intermediate aldol, 1-(2-nitro-3-thienyl)-3-phenylpropan-1-ol-3-one (XI). The reduction of the nitro group in 2-nitro-3-thienylideneacetophenone (X) with stannous chloride in hydrochloric acid took place readily at 40°. Isolation of the intermediate stannic chloride complex was possible but not necessary. Cyclization of the amino compound to 6-phenylthieno[2,3-b]pyridine (XII) in 66% yield occurred spontaneously when the crude reduction mixture was added to an excess of cold potassium hydroxide solution. It was found that both the impure aldol XI and the crude acetophenone condensation product gave only slightly lower yields of the fused ring compound under the same conditions.

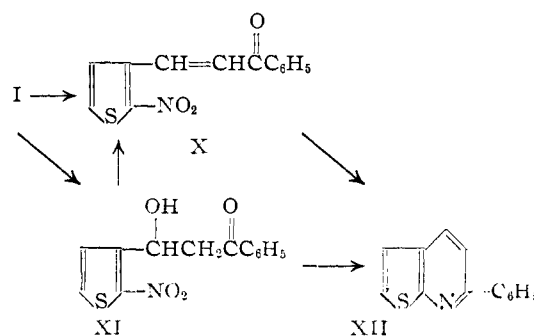
Only four other thieno[2,3-b]pyridines have been reported in the literature. Two of these, the parent compound<sup>12</sup> and the 4,6-dimethyl derivative,<sup>13</sup> were prepared from 2-aminothiophene while the other two were synthesized from pyridine derivatives.

(10) R. H. Wiley and N. R. Smith, *THIS JOURNAL*, **72**, 5198 (1950).

(11) I. Tanasescu and A. Bacic, *Bull. soc. chim. France* [5], **4**, 1742 (1937).

(12) W. Steinkopf and G. Lutzkendorf, *Ann.*, **403**, 45 (1914).

(13) W. S. Emerson, F. W. Holly and L. H. Klemm, *THIS JOURNAL*, **63**, 2569 (1941).



6-Phenylthieno[2,3-b]pyridine (XII) is a solid quite similar in odor and appearance to 2-phenylquinoline. Of the compounds prepared in this work only the thienopyridine (XII) and  $\beta$ -(2-nitro-3-thienyl)-acrylic acid (VIII) exhibit melting points below those of the analogous benzene compounds. The similarity in physical properties between corresponding thiophene and benzene compounds is quite evident with the simple derivatives but may not exist among more complex analogs as Herz<sup>14</sup> reports both 7-phenylthieno[2,3-c]pyridine and 4-phenylthieno[3,2-c]pyridine, isomers of solid 1-phenylisoquinoline, as liquids.

Another route to  $\beta$ -(2-nitro-3-thienyl)-acrylic acid (VIII) was investigated in the hope that larger amounts of the compound might be made available for further studies on the reduction and ring closure. 3-Thenaldehyde (XIII)<sup>15</sup> was condensed with malonic acid to give  $\beta$ -3-thienylacrylic acid (XIV) in 78% yield. This modification of the Knoevenagel reaction was used by Barger and Easson<sup>16</sup> and by King and Nord<sup>17</sup> to prepare  $\beta$ -2-thienylacrylic acid from 2-thenaldehyde. When the half ester was substituted for malonic acid in the above condensation, an 86% yield of ethyl  $\beta$ -3-thienylacrylate (XV) was obtained identical in properties with a sample of the ester prepared by direct esterification of the acrylic acid (XIV). Recently Schuetz and Houff<sup>18</sup> prepared ethyl  $\beta$ -3-thienylacrylate from 3-thenaldehyde and ethyl bromoacetate in a Reformatsky reaction. Their product exhibited a lower index of refraction than was observed in this investigation. A similar difference (*cf.* Table I) may be found in ethyl  $\beta$ -2-thienylacrylate prepared by the Claisen and the Reformatsky methods.

TABLE I  
REFRACTIVE INDICES OF ETHYL THIENYLACRYLATES

Ethyl ester	Method of preparation	( <i>n</i> <sub>D</sub> , °C.)
$\beta$ -(3-Thienyl)-acrylate	Reformatsky <sup>a</sup>	1.5562 (25)
	Knoevenagel <sup>b</sup>	1.5796 (25)
$\beta$ -(2-Thienyl)-acrylate	Reformatsky <sup>c</sup>	1.5573 (30)
	Claisen <sup>d</sup>	1.5868 (20)

<sup>a</sup> Ref. 18. <sup>b</sup> Present work. <sup>c</sup> R. E. Miller and F. F. Nord, *J. Org. Chem.*, **15**, 89 (1950). <sup>d</sup> Ref. 17.

Since the nitration of cinnamic acid has been re-

(14) W. Herz, *ibid.*, **73**, 351 (1951).

(15) E. Campaigne, R. C. Bourgeois and W. C. McCarthy, *Org. Syntheses*, **33**, 93 (1953).

(16) G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938).

(17) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).

(18) R. D. Schuetz and W. H. Houff, *THIS JOURNAL*, **77**, 1836 (1955).

ported<sup>19</sup> to yield predominantly *o*- and *p*-nitrocinnamic acids, it was hoped that the nitration of  $\beta$ -3-thienylacrylic acid (XIV) would yield useful quantities of the desired 2-nitro isomer VIII. In practice the separation of the isomers formed proved formidable. However, a small amount of the desired isomer was obtained by repeated crystallizations. The work was hampered by the low solubility of the acids and the difficulty in reproducing the melting or decomposition points. The 5-nitro derivative presumably present could not be obtained pure enough for characterization.

### Experimental<sup>20</sup>

**3-Thenyl Acetate (IV).**—3-Methylthiophene (VI) (109 g. 1.1 moles) was brominated with *N*-bromosuccinimide (178 g., 1.0 mole) as described by Campaigne and Tuller.<sup>2</sup> The benzene solution of crude 3-thenyl bromide remaining after removal of succinimide was added to a flask containing 90 g. (1.1 moles) of freshly fused sodium acetate. While stirring to prevent bumping the benzene was removed by distillation and replaced simultaneously with acetic anhydride until the temperature of the mixture reached 120°. Heating and stirring at this temperature continued for 8 hours. The salt removed from the mixture by filtration was dissolved in water and extracted twice with chloroform. The combined extracts and organic filtrate were washed with water and dried before removal of the solvent under reduced pressure. The dark residue was distilled through a six-inch Vigreux column to give a small forerun containing 2-bromo-3-methylthiophene and 90.1 g. (58%) of colorless 3-thenyl acetate (IV), b.p. 98–107° (17 mm.),  $n_D^{20}$  1.5169. Two fractionations through a Podbielniak column<sup>21</sup> gave analytical material, b.p. 105.5° (16 mm.),  $n_D^{20}$  1.5138,  $d_4^{20}$  1.174.

*Anal.* Calcd. for  $C_7H_8O_2S$ : C, 53.83; H, 5.17. Found: C, 53.93; H, 5.39.

**3-Thenyl Alcohol (V).**—One-tenth mole of 3-thenyl acetate (IV) was heated under reflux for 3 hours with 200 ml. of 2 *N* sodium hydroxide containing a trace of synthetic detergent. After cooling the organic layer was separated with the aid of benzene, washed and dried. Following removal of the benzene, the material was distilled through a six-inch Vigreux column to give 6.6 g. (58%) of impure 3-thenyl alcohol (V), b.p. 106–115° (20 mm.),  $n_D^{20}$  1.5609 (Campaigne and Bourgeois<sup>4</sup> reported b.p. 88–90° (10 mm.))

With phenyl isocyanate the alcohol V formed 3-thenyl *N*-phenylcarbamate, m.p. 73.5–74.0° (c), after recrystallization from cyclohexane.

*Anal.* Calcd. for  $C_{12}H_{11}NO_2S$ : C, 61.78; H, 4.75; N, 6.01. Found: C, 61.68; H, 4.88; N, 6.02.

3-Thenyl *N*- $\alpha$ -naphthylcarbamate was found to melt at 132–133° as reported by Campaigne and Bourgeois.<sup>4</sup>

**2-Nitro-3-thenyl Acetate (IIIa).**—Fuming nitric acid (10 ml., 0.24 mole, sp. gr. 1.51) was added *cautiously* drop by drop to a stirred solution of 31.2 g. (0.2 mole) of 3-thenyl acetate (IV) in 60 ml. of acetic anhydride cooled to below –10° with a Dry Ice-acetone bath. Stirring was continued for 3 hours while the temperature was allowed to rise slowly to 10°. The mixture was poured into about 1 liter of ice-water and stirred until crystallization of the oil was complete. The solid was washed twice with cold water by decantation, then was collected on a Büchner funnel with the aid of 100 ml. of cold 50% methanol. Three rapid recrystallizations from minimum amounts of boiling 95% ethanol gave 12.0 g. (30%) of 2-nitro-3-thenyl acetate (IIIa) as yellow platelets, m.p. 88–91°.

*Anal.* Calcd. for  $C_7H_7NO_4S$ : C, 41.78; H, 3.51; N, 6.96. Found: C, 41.95; H, 3.56; N, 6.86.

The combined ethanolic filtrates from the above recrystallizations were cooled and diluted slowly with water until crystallization was complete. After drying in a vacuum

desiccator over phosphorus pentoxide, the collected solid mixture of 2- and 5-nitro-3-thenyl acetates weighed 21.4 g. (53%) and melted below 55°.

**5-Nitro-3-thenyl Acetate (IIIb).**—Three grams of the low melting isomer mixture obtained above was dissolved in ether and placed on a chromatographic column prepared from 300 g. of alumina (Merck). Development and elution were carried out with ether. A light yellow band moved rapidly down the column and was collected to give 2.2 g., m.p. 59–61°. After recrystallization from ethyl acetate-petroleum solvent (b.p. 89–98°) and from isopropyl ether the material melted at 65.0–65.5° (c). This was shown below to be 5-nitro-3-thenyl acetate (IIIb).

*Anal.* Calcd. for  $C_7H_7NO_4S$ : C, 41.78; H, 3.51; N, 6.96. Found: C, 41.59; H, 3.39; N, 6.94.

A dark red band had formed and moved slowly down the column in a diffuse manner. When fractions containing this material were evaporated, only a brown oil was obtained. An ether solution of 2-nitro-3-thenyl acetate (IIIa) placed on a similar column could not be eluted as such but produced a similar dark oil.

A 2.0-g. sample of 2-nitro-3-thenyl acetate (IIIb) was heated with 35 ml. of 10% sulfuric acid for 1.5 hours, then filtered with an acetic acid wash to remove some carbonaceous material present. A saturated solution of 3 g. (1.5 oxidation equivalents) of sodium dichromate dihydrate in water was added slowly over an hour at 30–35°. After an additional hour at 50°, the mixture was thoroughly cooled and the dark green solid, wt. 0.3 g., collected. Extraction of the filtrate with ether gave an additional 0.2 g. of less colored material. Recrystallization of the first solid from water and from benzene (charcoal) gave colorless prisms of 5-nitro-3-thenoic acid (VIIb), m.p. 147° (reported<sup>4,7</sup> as 147° and 145–146°). The acid VIIb was converted to 5-nitro-3-thenamidine, m.p. 162–163° as reported by Campaigne and Bourgeois.<sup>4</sup>

**2-Nitro-3-thenyl Alcohol (II).**—A mixture of 10 g. of 2-nitro-3-thenyl acetate (IIIa) and 150 ml. of 10% sulfuric acid was heated under reflux until solution was complete (about 2 hours), filtered with charcoal while hot, and cooled to give 6.8 g. (86%) of pale yellow needles of 2-nitro-3-thenyl alcohol (II), m.p. 88–91°. An additional 0.6 g., m.p. 65–72°, was extracted from the filtrate with ether. The colorless alcohol II melted at 90–91.5° after recrystallization from water and sublimation at 55° (300  $\mu$ ).

*Anal.* Calcd. for  $C_7H_9NO_3S$ : C, 37.73; H, 3.17; N, 8.80. Found: C, 37.88; H, 3.16; N, 8.85.

When treated with concd. hydrobromic acid at 75° for 1.5 hours,<sup>8</sup> the alcohol was converted to 2-nitro-3-thenyl bromide, m.p. 58–61°, in 71% yield. After recrystallizations from ethanol-water and from benzene-petroleum ether (b.p. 30–60°) the pale yellow crystals melted at 62°. The compound was a lachrymator and skin irritant.

*Anal.* Calcd. for  $C_7H_8NO_2SBr$ : C, 27.04; H, 1.81; N, 6.31; Br, 35.99. Found: C, 27.32; H, 1.78; N, 6.19; Br, 35.96.<sup>22</sup>

**2-Nitro-3-thenaldehyde (I).**—A stirred solution of 4 g. of 2-nitro-3-thenyl alcohol (II) in 8 ml. of concd. nitric acid was warmed to 30° until an exothermic reaction and the evolution of nitrogen oxides began. Cooling was applied as necessary to keep the temperature at 35° until no further heat effects were noted (about 20 min.). The green mixture was poured onto 20 g. of ice and the yellow solid which formed collected by filtration. The material was distilled with steam, and from 500 ml. of cold distillate there was obtained 1.5 g. (37%) of yellow needles of 2-nitro-3-thenaldehyde (I), m.p. 52–54°. For analysis the aldehyde I was recrystallized from ether-petroleum ether (b.p. 30–60°) and then sublimed at 30–35° (150  $\mu$ ); m.p. 54–55°.

*Anal.* Calcd. for  $C_6H_5NO_3S$ : C, 38.21; H, 1.92; N, 8.92. Found: C, 38.28; H, 1.83; N, 8.77.

By treatment of the filtrate from the steam distillate with phenylhydrazine-acetic acid solution, 2-nitro-3-thenaldehyde phenylhydrazone was obtained in amount corresponding to an additional 0.6 g. (17%) of the aldehyde. The phenylhydrazone crystallized from absolute ethanol as dark red platelets, m.p. 213–215° dec.

(22) Analysis for bromine by the Parr bomb method was performed by Dr. K. C. Kennard.

(19) W. Davey and J. R. Gwilt, *J. Chem. Soc.*, 204 (1950).

(20) Melting points are uncorrected unless marked (c).

(21) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, pp. 234–242.

*Anal.* Calcd. for  $C_{11}H_9N_3O_2S$ : N, 16.99. Found: N, 17.08.

Similar treatment of the filtrate with an aqueous solution of thiosemicarbazide gave 2-nitro-3-thenaldehyde thiosemicarbazone, m.p. 243–244° dec., which could not be crystallized without decomposition.

*Anal.* Calcd. for  $C_8H_6N_4O_2S_2$ : N, 24.33. Found: N, 24.26.

Evaporation of the ether extract of the filtrate from the diluted reaction mixture gave 1.1 g. of yellow solid which after two recrystallizations from benzene proved to be 2-nitro-3-thenoic acid (VIIa), m.p. 156–157° (Rinkes<sup>7</sup> reported 155–156°). The acid was converted through the acid chloride to 2-nitro-3-thenamamide, m.p. 184–185°, as yellow needles from hot water.

*Anal.* Calcd. for  $C_8H_8N_2O_3S$ : N, 16.28. Found: N, 16.28.

**$\beta$ -(2-Nitro-3-thienyl)-acrylic Acid (VIII) and Ethyl Ester (IX).**—A mixture of 1.5 g. of 2-nitro-3-thenaldehyde (I), 2.0 g. of malonic acid and 5 ml. of dry pyridine containing two drops of piperidine was heated under reflux for 1 hour. The cooled, red mixture was diluted with two volumes of ice-water and acidified with hydrochloric acid. The dark solid was collected by filtration, washed with water, and dried in air to give 1.5 g. (79%), m.p. 217–219° dec. with rapid heating, of  $\beta$ -(2-nitro-3-thienyl)-acrylic acid (VIII). Recrystallization from hot water (charcoal) was accompanied by considerable loss but gave nearly colorless needles of the acid, m.p. 220–222° dec.

*Anal.* Calcd. for  $C_7H_7NO_4S$ : C, 42.21; H, 2.53; N, 7.03. Found: C, 42.21; H, 2.54; N, 6.92.

Decomposition of the  $\beta$ -(2-nitro-3-thienyl)-acrylic acid began as low as 175° as noted when the melting point was approached slowly. The evolution of carbon dioxide was shown by allowing the decomposition gas to bubble through a faintly pink, dilute phenolphthalein solution.

Ethyl  $\beta$ -(2-nitro-3-thienyl)-acrylate (IX) was prepared by treating the above acid VIII with absolute ethanol containing a trace of sulfuric acid. After recrystallization from ether–petroleum ether (b.p. 30–60°) and from ethanol–water, the ester IX melted at 73–74°.

*Anal.* Calcd. for  $C_9H_9NO_4S$ : C, 47.57; H, 3.99; N, 6.16. Found: C, 47.46; H, 3.93; N, 6.19.

**Condensation of 2-Nitro-3-thenaldehyde (I) with Acetophenone.**—Four ml. of a 1% solution of sodium hydroxide in 95% ethanol was added to a cold solution of 1.40 g. of 2-nitro-3-thenaldehyde (I) and 1.08 g. of acetophenone in 9 ml. of ether. The reaction mixture immediately darkened and became warm enough to boil away most of the ether. After 30 minutes the mixture was cooled, acidified with acetic acid and diluted with 20 ml. of water. Filtration gave 1.45 g. of brown solid, m.p. 116–130°. Extraction of this material with 50 ml. of boiling 95% ethanol left 0.85 g., (36%) m.p. 165–181°, which, after two recrystallizations from absolute ethanol, was obtained as long, light yellow needles, m.p. 181–182°, of 2-nitro-3-thenyldeneacetophenone (X).

*Anal.* Calcd. for  $C_{13}H_9NO_3S$ : C, 60.22; H, 3.50; N, 5.40. Found: C, 60.24; H, 3.69; N, 5.47.

From the original filtrate and the ethanol extract of the reaction product, 0.54 g. of material melting below 130° was obtained by evaporation and dilution with water. Fractional crystallization of the material, from ethanol by the addition of water, gave material melting 131–134°. No further improvement of the melting point could be obtained. Concentrated hydrochloric acid–zinc chloride solution (Lucas reagent) converted the material to 2-nitro-3-thenyldeneacetophenone (X). The material was presumed to be the aldol, 1-(2-nitro-3-thienyl)-3-phenylpropan-1-ol-3-one (XI).

**6-Phenylthieno[2,3-b]pyridine (XII).**—2-Nitro-3-thienyl-

deneacetophenone (X) (0.26 g., 0.001 mole) was suspended in a solution of 1.80 g. (0.008 mole) of stannous chloride dihydrate in 5 ml. of concd. hydrochloric acid and 5 ml. of 95% ethanol. Cooling was applied as necessary to keep the reaction temperature at 40°. After no further evidence of reaction was noted, the resulting solution was allowed to stand at 35° for two hours. The entire reaction mixture was added dropwise with stirring to 25 ml. of aqueous 50% potassium hydroxide cooled below 10°. Evaporation of the ether extract of the alkaline mixture and crystallization of the residue from ethanol–water gave 0.14 g. (66%) of 6-phenylthieno[2,3-b]pyridine (XII) as orange platelets, m.p. 74–76°. Additional crystallizations from ethanol–water gave colorless material, m.p. 77–78° (c).

*Anal.* Calcd. for  $C_{13}H_9NS$ : C, 73.90; H, 4.29; N, 6.63. Found: C, 74.01; H, 4.34; N, 6.70.

Nearly identical yields of 6-phenylthieno[2,3-b]pyridine (XII) were obtained when the low melting by-product or the crude reaction product from the acetophenone condensation were reduced and cyclized under the above conditions.

Fusion of 6-phenylthieno[2,3-b]pyridine (XII) with an equal weight of picric acid gave the picrate, m.p. 149–150° after recrystallization from 95% ethanol.

*Anal.* Calcd. for  $C_{13}H_9NS \cdot C_6H_3N_3O_7$ : N, 12.72. Found: N, 12.78.

**$\beta$ -(3-Thienyl)-acrylic Acid (XIV) and Ethyl Ester (XV).**—3-Thenaldehyde<sup>16</sup> (XIII) (11.2 g., 0.1 mole) was condensed with 20.4 g. (0.2 of mole) of malonic acid as described by King and Nord<sup>17</sup> for the preparation of  $\beta$ -(2-thienyl)-acrylic acid. The crude solid, wt. 16.0 g., m.p. 141–149°, was obtained pure in 78% yield after a single recrystallization from 30% ethanol, m.p. 153–153.5° (c). Recrystallization from petroleum solvent (b.p. 89–98°) for analysis gave  $\beta$ -(3-thienyl)-acrylic acid (XIV) with no change in m.p.

*Anal.* Calcd. for  $C_7H_6O_2S$ : C, 54.53; H, 3.93. Found: 54.53; H, 3.72.

By substituting ethyl hydrogen malonate for malonic acid in the above procedure and isolating the liquid ester by ether extraction, an 86% yield of ethyl  $\beta$ -(3-thienyl)-acrylate (XV) was obtained after distillation through a six-inch Vigreux column; b.p. 147–152° (14 mm.),  $n_D^{20}$  1.5755. For analysis the ester was fractionated in a Podbielniak column,<sup>21</sup> b.p. 154–155° (17 mm.),  $n_D^{20}$  1.5819,  $n_D^{20}$  1.5796,  $d_4^{20}$  1.163 (Schuetz and Houff<sup>18</sup> reported  $n_D^{20}$  1.5562).

*Anal.* Calcd. for  $C_9H_{10}O_2S$ : C, 59.32; H, 5.53. Found: C, 59.33; H, 5.71.

Ethyl  $\beta$ -(3-thienyl)-acrylate (XV), b.p. 148° (14 mm.),  $n_D^{20}$  1.5790, was obtained from the esterification of  $\beta$ -(3-thienyl)-acrylic acid (XIV) with absolute ethanol containing a trace of sulfuric acid.

**Nitration of  $\beta$ -(3-Thienyl)-acrylic Acid (XIV).**—Fuming nitric acid (2.1 ml., 0.05 mole, sp. gr. 1.51) was added slowly to a stirred mixture of 4.6 g. (0.03 mole) of  $\beta$ -(3-thienyl)-acrylic acid (XIV), 10 ml. of acetic acid and 15 ml. of acetic anhydride cooled below 5°. Stirring at 0° was continued for 1 hour after completion of the addition, then the temperature was allowed to rise slowly to 15°. The “mushy” yellow mixture was filtered, and the solid washed and dried; wt. 4.7 g., m.p. 187–197°. An additional 0.5 g., m.p. 177–195°, was obtained from the diluted filtrate. By repeated fractional crystallization from absolute ethanol in which the material was moderately soluble, 0.1 g. of  $\beta$ -(2-nitro-3-thienyl)-acrylic acid (VIII), m.p. 219–222° dec., was obtained. The mixed m.p. with a sample of the acid prepared from the condensation of 2-nitro-3-thenaldehyde (I) with malonic acid was not depressed. No other acid of constant melting point was obtained. The decomposition and dependence of the melting point on rate of heating added to the difficulty of separating any isomers present.

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