[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A.]

4-Nitrocinnamic and β-(5-Nitro-2-thienyl)-acrylic Derivatives

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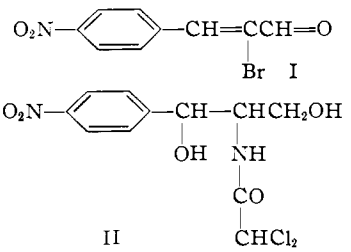
A series of derivatives of *p*-nitrocinnamaldehyde and *p*-nitrocinnamic acid and their thiophene analogs have been synthesized. All products are highly bactericidal and fungicidal *in vitro* and possess typical absorption spectra in the ultraviolet.

It has been known for several years that aromatic acroleins are of marked biological interest.[1] In a recent paper Affonso and Khorana[2] have reported that halogenated derivatives of cinnamic acid and *p*-nitrocinnamic acid possess a very high antibacterial activity. It was shown particularly that α-bromo-*p*-nitrocinnamaldehyde (I) at a concentration of 2 μg./ml. is able to inhibit the growth of *Staphylococcus aureus* completely.

The relative structural resemblance between I and chloramphenicol (II) has prompted us to synthesize a number of related compounds in the



I

II

p-nitrocinnamic series and their analogs in the thiophene series. Previous work carried out in this Laboratory[3] demonstrated the bactericidal activity of the thiophene analog of II and in general of 5-nitro-2-thienyl derivatives.

We were mainly interested in comparing the activities of aldehydes, alcohols, acids and amides in the two aromatic systems. The compounds prepared are listed in Tables I, II and III. The synthesis of these compounds was accomplished by al-

TABLE I

BENZENE SERIES O_2N—C$_6$H$_4$—R

R	Microbiological activity on[a] *E. coli*	*M. aureus*
—CH=CHCHO	50	10
—CH=CHCH(OCOCH$_3$)$_2$	>50	>50
—CH=CBrCHO	0.6	0.6
—CH=CBrCH(OC$_2$H$_5$)$_2$	>100	50
—CH=CBrCH(OCOCH$_3$)$_2$	20	6
—CH=CBrCH(OH)OSO$_2$Na	10	5
—CH=CBrCH=NNHCONH$_2$	>3	>3
—CH=CHCH$_2$OH	>100	>100
—CH=CBrCH$_2$OH	>100	>100
—CH=CBrCH$_2$OCO—C$_6$H$_4$—NO$_2$-*p*	>50	>50
—CH=CHCOOH	>100	>100
—CH=CBrCOOH	>100	>100
—CH=CHCONH$_2$	>50	>50
—CH=CBrCONH$_2$	>30	>30

[a] Minimal inhibitory concentration in μg./ml.

TABLE II

THIOPHENE SERIES O_2N—C$_4$H$_2$S—R

R	Microbiological activity on[a] *E. coli*	*M. aureus*
—CH=CHCHO	10	5
—CH=CHCH=NNHCONH$_2$	>20	10
—CH=CHCH=NNHCSNH$_2$	>25	25
—CH=CHCH(OCOCH$_3$)$_2$	50	20
—CH=CBrCHO	2	5
—CH=CBrCH=NNHCONH$_2$	>10	>10
—CH=CBrCH=NNHCSNH$_2$	>10	>10
—CH=CBrCH(OCOCH$_3$)$_2$	20	10
—CH=CHCH$_2$OH	10	50
—CH=CHCH$_2$OCO—C$_6$H$_4$—NO$_2$-*p*	>10	>10
—CH=CBrCH$_2$OH	40	40
—CH=CBrCH$_2$OCO—C$_6$H$_4$—NO$_2$-*p*	>10	>10
—CH=CHCOOH	25	25
—CH=CHCOOC$_2$H$_5$	>100	50
—CH=CBrCOOH	>100	100
—CH=CBrCOOC$_2$H$_5$	>10	2
—CH=CHCONH$_2$	>20	>20
—CH=CBrCONH$_2$	30	10
—CH=CBrCH$_2$Cl	6	3

[a] Minimal inhibitory concentration in μg./ml.

TABLE III

α-BROMO-β-(5-NITRO-2-THIENYL)-ACROLEIN DERIVATIVES

O_2N—C$_4$H$_2$S—CH=CBr—R

	Microbiological activity on[a] *E. coli*	*M. aureus*
—CH=N—NC$_4$H$_8$O[b]	>10	>10
—CH=N—NC$_5$H$_{10}$[c]	>20	20
—CH=NNHCO—C$_4$H$_3$O[d]	Not soluble	
—CH=NN—CO—NH—CO—CH$_2$	Not soluble	
—CH=NN—CS—NH—CO—CH$_2$	Not soluble	
—CH=NNHCO—C$_5$H$_{10}$N[e]	20	5
—CH=NNH$_2$	20	20
—CH=N—C$_6$H$_5$	>20	>20
—CH=N—C$_6$H$_4$—COOH-*p*	5	5
—CH=NOH	10	10
—CH(NHCOOC$_2$H$_5$)$_2$	>20	>20
—CH—S—CH(CH$_2$OH)—CH$_2$—S	20	10

[a] Minimal inhibitory concentration in μg./ml. [b] NC$_4$H$_8$O = morpholino. [c] NC$_5$H$_{10}$ = piperidino. [d] CO—C$_4$H$_3$O = furoyl. [e] CO—C$_5$H$_{10}$N = isonicotinyl.

(1) E. Keeser and J. Houben's "Fortschritte der Heilstoffchemie," 2 Abt., Berlin-Leipzig, 1932, p. 254.

(2) A. Affonso and M. L. Khorana, *Indian J. Pharm.*, **14**, 3 (1952).

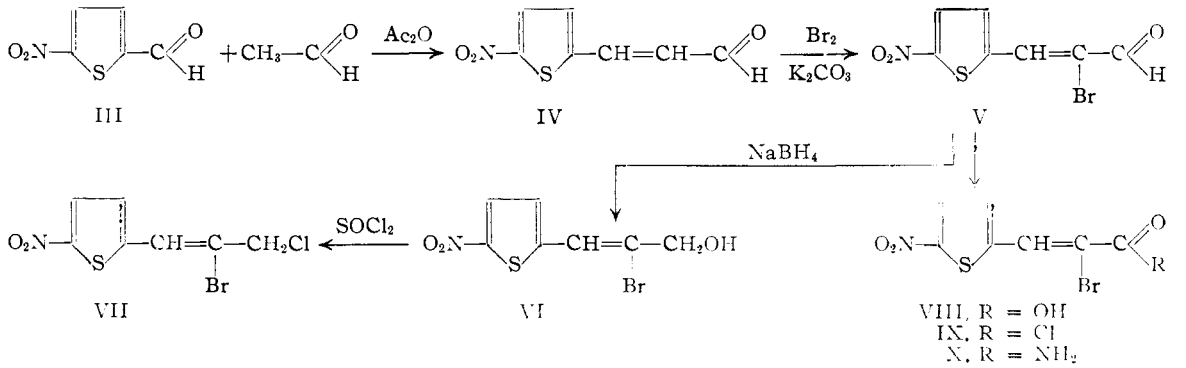
(3) (a) G. Carrara, F. M. Chiancone, V. D'Amato, E. Ginoulhiac, *Il Farmaco*, **6**, 3 (1951); (b) M. Bellenghi, G. Carrara, F. Fava, E. Ginoulhiac, C. Martinuzzi, A. Vecchi and G. A. Weitnauer, *Gazz. chim. ital.*, **82**, 773 (1952); (c) G. Carrara and G. A. Weitnauer, *ibid.*, **81**, 142 (1951).

kali-catalyzed condensation of *p*-nitrocinnamaldehyde and 5-nitro-2-thiophene aldehyde (III) with aldehydes and esters.

The dehydration was carried out as usual with acetic anhydride. The condensation of III with freshly distilled acetaldehyde in the presence of potassium hydroxide under carefully controlled conditions yielded β-(5-nitro-2-thienyl)-acrolein (IV) which, like the corresponding *p*-nitrocinnamaldehyde, reacted instantly with bromine. Isolation of the dibromo derivative was not possible owing to its instability, since hydrogen bromide was rapidly lost on standing. This is particularly true for the thiophene derivative. In practice, addition of one mole of potassium carbonate was sufficient to effect smooth elimination of hydrogen bromide and yielded β-(5-nitro-2-thienyl)-α-bromoacrolein (V).

yields of β-(5-nitro-2-thienyl)-acrylic acid. Addition of bromine to these unsaturated acids followed by dehydrobromination[8] gave poor yields of α-haloacrylic acids. It was found more convenient to carry out low temperature oxidation of the aldehydes with chromic acid in acetic acid.[9] Excellent yields of β-(5-nitro-thienyl)-α-bromoacrylic acid (VIII) were obtained using one mole of perphthalic acid as the oxidizing agent. The amides X were prepared by treating the corresponding acid chlorides IX with ammonia. Table III lists the derivatives of V which were prepared.

Condensation of V with substituted hydrazines was usually carried out by refluxing equimolecular amounts of the two products in acid-catalyzed solutions. Schiff bases were formed in a similar manner. Boiling V with acetic anhydride with



Reduction of the carbonyl of *p*-nitrocinnamaldehyde was carried out by Meerwein and co-workers[4] with aluminum isopropoxide. Although Hochstein and Brown[5] report that under normal reduction procedures cinnamaldehyde yields hydrocinnamyl alcohol, selective reduction of the aldehyde can be carried out smoothly in alcoholic solution with sodium borohydride leaving the double bond untouched.[6] Furthermore, both the nitro group and the α-halogen atom are unaffected by this reagent. The aryl-allyl alcohols are stable crystalline products. They were characterized by their *p*-nitrobenzoate esters. Replacement of the hydroxyl with chlorine was carried out in the case of α-bromo-β-(5-nitro-2-thienyl)-allyl alcohol (VI) by treatment with thionyl chloride. The chlorobromo derivative VII was very light-sensitive. All attempts to replace the chlorine atom with hydrogen using lithium aluminum hydride, sodium borohydride and zinc–acetic acid failed. VII, which contains both an allylic and vinylic halogen, did not react with silver nitrate at room temperature and yielded only gummy products with alkaline reagents. *p*-Nitrocinnamic acid was at first synthesized by a malonic ester condensation[7] using *p*-nitrobenzaldehyde in the presence of alcoholic ammonia or aniline. Due to the poor yields obtained with this method, we synthesized the acid by a Perkin condensation, using acetic anhydride and fused sodium acetate. The same reaction applied to III gave excellent

traces of concentrated sulfuric acid yielded the diacetate derivative, while reaction with urethan in alkaline solution gave the corresponding diurethan derivative. V was also condensed with 2,3-dithiopropanol.

Ultraviolet Absorption.—All compounds listed in Tables I, II and III have strong characteristic absorption bands in the ultraviolet. Hartough[10] reports that the introduction of a double bond extending conjugation at C_2 of the thiophene nucleus effects a bathochromic shift of about 40 mμ. Our data confirm his findings: thus Δλ β-(5-nitro-2-thienyl)-acrolein (IV)/5-nitro-2-thiophenealdehyde (III) amounts exactly to 41 mμ. Replacement of the α-hydrogen of the carbonyl with bromine effects a further small bathochromic shift of 7–9 mμ which is in agreement with the results of Nussbaum, *et al.*,[11] for α-bromo-α,β-unsaturated carbonyls in the benzene series.

The ultraviolet absorption characteristics of the allyl alcohols confirm that the reduction with sodium borohydride does not affect the double bond in the side chain. The absorption maxima for compounds VI and VII are at 263 mμ, since both possess a similar chromophoric system. This value agrees with the one that would be expected by simply adding the individual contributions of the different chromophoric groups present in the molecule. The

(4) H. Meerwein and co-workers, *J. prakt. Chem.*, **147**, 211 (1937).

(5) F. A. Hochstein and W. G. Brown, THIS JOURNAL, **70**, 3484 (1948).

(6) S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949).

(7) E. Knoevenagel, *Ber.*, **31**, 2612 (1898).

(8) V. B. Drewsen, *Ann.*, **212**, 153 (1882); A. Müller, *ibid.*, **212**, 124 (1882).

(9) A. Naar, *Ber.*, **24**, 250 (1891).

(10) H. D. Hartough, "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 101.

(11) A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3263 (1951).

difference between the alcohols of the benzene and thiophene series is again 58 mμ.

Microbiological Activity.[12]—Previous investigations in these laboratories[3b] had shown that of the possible mononitro derivatives of thiophene the 5-nitro compounds containing a carbonyl group at C_2 adjacent to the nucleus were the most active *in vitro*. The present work shows that insertion of a double bond between the carbonyl and aromatic ring causes a marked increase of the bactericidal activity. The activities against *Micrococcus aureus* and *Escherichia coli* are reported in Tables I, II and III. These compounds, especially the most active ones IV and V and their corresponding benzene analogs, have a broad spectrum of activity as can be seen from Table IV. It is interesting to note in particular the great activity on actinomycetes, yeasts and fungi. Their mode of action is essentially bactericidal even in conditions of resting bacteria. In the same way these products have demonstrated fungicidal activity. From previous experiments we consider this mode of action to be typical of the 5-nitrothiophene ring system.

TABLE IV

MINIMAL INHIBITORY CONCENTRATION (μg./ml.)

	β-(5-Nitro-2-thienyl)-α-bromo-acrolein	β-(5-Nitro-2-thienyl)-acrolein	α-Bromo-*p*-nitro-cinnamaldehyde	*p*-Nitro-cinnamaldehyde	Chloramphenicol
Micrococcus aureus	5	5	5	50	5
Micrococcus flavus	1	2	2	10	2
Sarcina lutea	5	5	5	10	1
Streptococcus hemol.	2	10	10	>50	2
Streptococcus faec.	20	10	10	20	5
Diplococcus pneumoniae	1	10	10	50	1
Escherichia coli	2	10	10	50	5
Klebsiella pneumoniae PCi 602 (non-capsulated)	2	5	5	50	2
Klebsiella pneumoniae ISM (capsulated)	5	10	20	50	5
Shigella sonnei	5	5	10	50	5
Salmonella typhi	2	5	5	50	5
Proteus vulgaris	2	5	5	20	1
Pseudomonas aeruginosa	10	50	50	>50	>100
Brucella abortus	2	10	5	>50	5
Bacillus subtilis	1	2	2	10	5
Bacillus cereus	1	2	5	10	5
Bacillus anthracis	2	5	2	50	5
Clostridium welchii	10	10	20	20	5
Mycobacterium phlei	5	10	5	20	>100
Mycobacterium ranae	10	20	10	20	>100
Mycobact. tuberc. H37Rv	1	1	1	5	12.5
Actinomyces bovis	1	5	1	5	>100
Aspergillus niger	2	10	5	>50	>100
Trichophyton mentagrophytes	1	5	1	20	>100
Candida albicans	5	10	5	>50	>100
Saccharomyces cerevisiae	5	20	5	>50	>100

Experimental

p-Nitrocinnamaldehyde.—This product was prepared according to the method described by Fecht[13] and found to melt at 142–144°. *p*-Nitrocinnamaldehyde diacetate was prepared in an analogous way to α-bromo-β-(5-nitro-2-thienyl)-acrolein diacetate and found to melt at 116–117°.

Anal. Calcd. for $C_{13}H_{13}NO_6$: CH_3CO, 30.8. Found: CH_3CO, 30.3.

α-Bromo-*p*-nitrocinnamaldehyde.—This product was prepared according to the method described by Einhorn and Gehrenbeck[14] and found to melt at 136–137°. The semicarbazone was found to melt at 210–211°. α-Bromo-*p*-nitrocinnamaldehyde diethyl acetal was prepared in the following manner: to a solution of 10 g. of α-bromo-*p*-nitrocinnamaldehyde and 0.3 g. of ammonium chloride in 32 ml. of absolute ethanol was added 20 ml. of ethyl orthoformate. The mixture was refluxed for six hours and then allowed to remain for 48 hours at room temperature. Most of the ethanol was removed *in vacuo*, and the oily residue was first dissolved in ether and extracted with water, then with a saturated sodium carbonate solution and finally with water. The ether solution was dried with anhydrous sodium sulfate and evaporated; the residue was distilled *in vacuo* and the fraction boiling at 190–192° (1 mm.) collected. This product was again dissolved in ether, shaken with a saturated bicarbonate solution and dried over anhydrous sodium sulfate. Ether was removed *in vacuo;* the yellow oil obtained on treatment with petroleum ether gave 3.5 g. of light yellowish crystals, m.p. 124–126°.

Anal. Calcd. for $C_{13}H_{16}BrNO_4$: Br, 24.20. Found: Br, 23.8.

The preparation of α-bromo-*p*-nitrocinnamaldehyde was similar to that of α-bromo-β-(5-nitrothienyl)-acrolein diacetate. The product was found to melt at 115–116°.

Anal. Calcd. for $C_{13}H_{12}BrNO_6$: Br, 22.39. Found: Br, 22.4.

The sodium bisulfite addition product of α-bromo-*p*-nitrocinnamaldehyde was prepared as follows: a solution of 1.5 g. of α-bromo-*p*-nitrocinnamaldehyde in 4 ml. of aqueous saturated sodium bisulfite solution, was shaken mechanically for 3 hours. One gram of α-bromo-*p*-nitrocinnamaldehyde was then added to the resultant solution and the mixture was shaken for an additional two hours. The mixture became brown and the precipitate obtained was filtered, washed with absolute ethanol, then with ethyl ether and rapidly dried *in vacuo;* yield 1.30 g.

Anal. Calcd. for $C_9H_7BrNNaO_5S$: Br, 22.3. Found: Br, 22.2.

β-(5-Nitro-2-thienyl)-acrolein.—Ten grams of dried 5-nitro-2-thenaldehyde was placed in a 250-ml. flask fitted with a stirrer, a dropping funnel, a reflux condenser and a thermometer. After cooling with an ice–salt-bath, 30 ml. of freshly distilled acetaldehyde was added drop by drop with stirring. The temperature was allowed to rise to +5° and 1–1.5 ml. of a methanol solution of 25% potassium hydroxide was added to the stirred mixture. A sudden rise of temperature to 30° was observed, and the product entirely dissolved. After rapid cooling, 20 ml. of acetic anhydride was added in one portion; the solution was boiled for 20 minutes and then cooled to 10°. After the addition of 60 ml. of water and 7 ml. of hydrochloric acid, the mixture was refluxed for 30 minutes, cooled, and the precipitate collected and recrystallized from 150 ml. of 66% acetic acid; yield 4.9 g. Dilution of the mother liquor with water gave an additional crop of 1.3 g.; m.p. 129–130°; $\lambda_{max.}$ 356 mμ, log $\epsilon_{max.}$ 4.33 (determined in methanol solution).

Anal. Calcd. for $C_7H_5NO_3S$: S, 17.52. Found: S, 17.88.

The semicarbazone was found to melt at 215–217°. *Anal.* Calcd. for $C_8H_8N_4O_3S$: S, 13.35. Found: S, 13.58.

The thiosemicarbazone melted at 238–239°. *Anal.* Calcd. for $C_8H_8N_4O_2S_2$: S, 20.02. Found: S, 20.05.

β-(5-Nitro-2-thienyl)-acrolein diacetate prepared in an analogous way to α-bromo-β-(5-nitro-2-thienyl)-acrolein diacetate was found to melt at 92–93°. *Anal.* Calcd. for $C_{11}H_{11}NO_6$: S, 11.24. Found: S, 11.6.

β-(5-Nitro-2-thienyl)-α-bromoacrolein.—Five grams of β-(5-nitro-2-thienyl)-acrolein and 100 ml. of glacial acetic acid were heated to 50–60° and slowly treated with a solution of 4.4 g. of bromine in 20 ml. of glacial acetic acid. The mixture was again heated to 50–60° for half an hour and

(12) G. Rolland and M. T. Timbal, Communication presented at the International Congress of Microbiology in Rome, September 6–12, 1953, to be published shortly.

(13) H. Fecht, *Ber.*, **40**, 3898 (1907).

(14) A. Einhorn and A. Gehrenbeck, *Ann.*, **253**, 351 (1886).

then treated with 3.8 g. of potassium carbonate; long yellow needles separated immediately. The temperature was raised to 80–90°, 100 ml. of water was added and the mixture was heated for half an hour. After cooling, the precipitate was collected, washed with water, dried on a steam-bath and recrystallized from absolute ethanol; yield 6.35 g. of yellow needles, m.p. 186–188°; $\lambda_{max.}$ 365 mμ, log $\epsilon_{max.}$ 4.27 (determined in methanol solution).

Anal. Calcd. for $C_7H_4BrNO_3S$: S, 12.24. Found: S, 12.35.

The semicarbazone was prepared and found to have a melting point of 246–248°. *Anal.* Calcd. for $C_8H_7BrN_4O_3S$: S, 10.05. Found: S, 10.45.

The thiosemicarbazone melted at 227–228°. *Anal.* Calcd. for $C_8H_7BrN_4O_2S_2$: S, 19.11. Found: S, 19.39.

The α-Bromo-β-(5-nitro-2-thienyl)-acrolein Diacetate.—Twenty milliliters of acetic anhydride and a few drops of concentrated sulfuric acid were added to 2.62 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein with constant stirring and cooling to 0–5° with an ice-bath. When solution was complete, the ice-bath was removed and the reaction mixture maintained at room temperature for 2 hr. before pouring on ice; yield 1.4 g., m.p. 170–171° (from 95% ethanol).

Anal. Calcd. for $C_{11}H_{10}BrNO_6S$: CH_3CO, 23.62. Found: CH_3CO, 23.0.

3-(5-Nitro-2-thienyl)-2-propen-1-ol.—Three grams of β-(5-nitro-2-thienyl)-acrolein was dissolved in 250 ml. of hot 95% ethanol. To the solution at 50° was added 0.22 g. of sodium borohydride in 10 ml. of ethanol. After cooling with water, the mixture was allowed to remain at room temperature for three hours. The scarce precipitate was filtered, the solution acidified with hydrochloric acid until the red-violet color of the solution turned to light brown, and then refiltered. The solution was treated with charcoal and evaporated *in vacuo* on a steam-bath at a moderate temperature. The residue was dissolved in chloroform, washed with water and dried over anhydrous sodium sulfate. The solution was filtered, treated with charcoal, refiltered and evaporated to a small volume. On cooling, long yellow needles precipitated which were collected by suction and washed with ether; yield 1.22 g., m.p. 78–80°.

Anal. Calcd. for $C_7H_7NO_3S$: S, 17.35. Found: S, 16.95.

The *p*-nitrobenzoate was prepared and found to melt at 147–148°. *Anal.* Calcd. for $C_{14}H_{10}N_2O_6S$: N, 8.37. Found: N, 7.95.

***p*-Nitrocinnamyl Alcohol.**—This product was prepared in an analogous way to 3-(5-nitro-2-thienyl)-2-propen-1-ol and found to melt at 127–128°.[4]

Anal. Calcd. for $C_9H_9NO_3$: N, 9.75. Found: N, 9.55.

α-Bromo-*p*-nitrocinnamyl Alcohol.—The product was prepared in a similar manner to 3-(5-nitro-2-thienyl)-2-propen-1-ol and found to melt at 114–115°; $\lambda_{max.}$ 305 mμ, log $\epsilon_{max.}$ 4.12 (determined in methanol solution).

Anal. Calcd. for $C_9H_8BrNO_3$: Br, 31.0. Found: Br, 30.9.

The *p*-nitrobenzoate melted at 145–147°. *Anal.* Calcd. for $C_{16}H_{11}BrN_2O_6$: N, 6.88. Found: N, 6.87.

2-Bromo-3-(5-nitro-2-thienyl)-2-propen-1-ol.—This compound was prepared in an analogous way to 3-(5-nitro-2-thienyl)-2-propen-1-ol and was found to melt at 143–145°; $\lambda_{max.}$ 363 mμ, log $\epsilon_{max.}$ 4.22 (determined in methanol solution).

Anal. Calcd. for $C_7H_6BrNO_3S$: S, 12.15. Found: S, 12.23.

The *p*-nitrobenzoate melted at 186–187°. *Anal.* Calcd. for $C_{14}H_9BrN_2O_6S$: N, 6.55. Found: N, 6.78.

***p*-Nitrocinnamic Acid.**—This product was prepared by condensing *p*-nitrobenzaldehyde with acetic anhydride in the presence of fused sodium acetate according to the Perkin condensation; m.p. 290–291°.

α-Bromo-*p*-nitrocinnamic Acid According to Naar.[9]—This product was prepared by oxidizing α-bromo-*p*-nitrocinnamaldehyde with chromium trioxide in acetic acid at a low temperature; m.p. 213–215°.

β-(5-Nitro-2-thienyl)-acrylic Acid.—In a 100-ml. flask with a reflux condenser bearing a calcium chloride tube, 12 g. of dried 3-(5-nitro-2-thienyl)-acrolein, 16 g. of carefully ground fused sodium acetate and 40 ml. of acetic anhydride were placed. The well blended mixture was slowly heated on an oil-bath to raise the temperature to 140–145°. After two hours at 140–145° the temperature was raised to 175° in half an hour. The mixture was then cooled to 0°, alkalized with a saturated sodium carbonate solution, diluted with 1 liter of water and filtered. The filtrate was extracted with three 100-ml. portions of ether, the ethereal extract discarded and the aqueous solution acidified to congo red with hydrochloric acid. The yellow precipitate was collected, washed with water and recrystallized from ethanol; yield 11.5 g. (83.4%) of yellow plates, m.p. 251–252° dec.

Anal. Calcd. for $C_7H_5NO_4S$: S, 16.09. Found: S, 16.21.

Ethyl (5-nitro-2-thienyl)-acrylate was prepared by refluxing the corresponding acid with ethanol, and simultaneously bubbling dry hydrogen chloride through the solution; m.p. 96–98°.

Anal. Calcd. for $C_9H_9NO_4S$: N, 6.16. Found: N, 6.07.

α-Bromo-β-(5-nitro-2-thienyl)-acrylic Acid.—In a flask fitted with a mechanical stirrer, reflux condenser and thermometer, 5.24 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein and 150 ml. of glacial acetic acid were placed. After the temperature was raised to 55°, 6 g. of chromium trioxide was added in small portions over a period of 30 minutes with constant stirring and the temperature level maintained between 55 and 60°. On completion of this process the mixture was stirred for a further 30 minutes at 55–60°, and then cooled to room temperature and poured into 600 ml. of water. The precipitate obtained was collected by suction, washed with water and recrystallized without drying from 170 ml. of 95% ethanol. The mother liquor concentrated *in vacuo* gave a second crop of crystals, total yield 1.5 g. (27.2%) of yellow crystals melting at 255–256°.

Anal. Calcd. for $C_7H_4BrNO_4S$: Br, 28.73. Found: Br, 28.74.

This compound was also prepared by adding to a solution of 5.2 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 300 ml. of dioxane and 300 ml. of ether an ethereal solution of 4.30 g. of perphthalic acid. The mixture was kept in the dark at room temperature for 4 days, concentrated to a small volume and the product precipitated by adding water; yield 5.25 g. melting at 245°. The m.p. was not depressed when mixed with an authentic sample of α-bromo-β-(5-nitro-2-thienyl)-acrylic acid.

Ethyl α-bromo-β-(5-nitro-2-thienyl)-acrylate was prepared in an analogous way to ethyl (5-nitro-2-thienyl)-acrylate, and found to melt at 128–129°.

Anal. Calcd. for $C_9H_8BrNO_4S$: N, 4.57; Br, 26.1. Found: N, 4.43; Br, 26.1.

β-(5-Nitro-2-thienyl)-acryl Amide.—In a flask fitted with a reflux condenser and a calcium chloride tube, 1.5 g. of β-(5-nitro-2-thienyl)-acrylic acid and 1.64 g. of powdered phosphorus pentachloride, thoroughly mixed, were placed and heated on a water-bath for 25 minutes. The mixture was then treated with 30 ml. of benzene and evaporated to dryness. This treatment was repeated four times. The material was then dissolved in 70 ml. of benzene and filtered from the scarce residue. Gaseous ammonia was bubbled into the solution and a precipitate was immediately formed. After 5 minutes the stream was stopped, the mixture cooled to 0°, filtered and washed with water. Recrystallization from aqueous methanol yielded 0.75 g. of yellow crystals melting at 234–235°.

Anal. Calcd. for $C_7H_6N_2O_3S$: N, 14.12. Found: N, 14.05.

***p*-Nitrocinnamyl Amide.**—This product was prepared in an analogous way to the one above and found to melt at 216–217°.

Anal. Calcd. for $C_9H_8N_2O_3$: N, 14.57. Found: N, 14.55.

α-Bromo-*p*-nitrocinnamyl Amide.—The product was prepared in a similar manner to β-(5-nitro-2-thienyl)-acrylamide and found to melt at 191–192°.

Anal. Calcd. for $C_9H_7BrN_2O_3$: Br, 29.48. Found: Br, 29.48.

α-Bromo-β-(5-nitro-2-thienyl)-acryl Amide.—This compound was prepared in an analogous way to β-(5-nitro-2-thienyl)-acrylamide and found to melt at 217–218°.

Anal. Calcd. for $C_7H_5BrN_2O_3S$: N, 10.01. Found: N, 9.98.

2-Bromo-1-chloro-3-(5-nitro-2-thienyl)-2-propene.—Five grams of 2-bromo-3-(5-nitro-2-thienyl)-2-propen-1-ol and 25

ml. of freshly distilled thionyl chloride were heated on a steam-bath for 30 minutes and then concentrated *in vacuo* in order to remove the excess thionyl chloride. The residue was dissolved in chloroform and the solvent distilled. Upon addition of methanol the crystals immediately separated. The mixture was treated with 25 ml. of petroleum ether to complete crystallization; the raw product, melting at 101°, was collected and recrystallized from 50 ml. of methanol. In order to avoid decomposition of the product it was necessary to work in the dark, yield 4.5 g., m.p. 108–109°; $\lambda_{max.}$ 363 mμ, log $\epsilon_{max.}$ 4.20 (determined in methanol solution).

Anal. Calcd. for $C_7H_5BrClNO_2S$: S, 11.35. Found: S, 11.6.

4-{N-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-amino}-morpholine.—To a warm solution of 1.31 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 100 ml. of ethanol a solution of 0.69 g. of N-aminomorpholine hydrochloride in 50 ml. of ethanol was added. The mixture was heated and evaporated to one-third of its volume. After cooling with an ice–salt-bath, a product was obtained which, upon recrystallization from ethanol, yielded 1 g. of red needles melting at 183–184°.

Anal. Calcd. for $C_{11}H_{12}BrN_3O_3S$: S, 9.26. Found: S, 9.11.

1-{N-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-amino}-piperidine.—To a warm solution of 1.3 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 100 ml. of 95% ethanol, a solution of 0.68 g. of N-aminopiperidine hydrochloride in 50 ml. of 95% ethanol was added and the mixture heated and evaporated to one-fourth of its original volume; yield 0.5 g. of red flakes melting at 140° (from benzene–methanol).

Anal. Calcd. for $C_{12}H_{14}BrN_3O_2S$: S, 9.30. Found: S, 9.42.

1-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-2-α-furoylhydrazine.—To a warm solution of 0.630 g. of 2-furoylhydrazine in 50 ml. of absolute ethanol, a solution of 1.31 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 100 ml. of absolute ethanol was added; the mixture was refluxed for 30 minutes, cooled and filtered. Recrystallization from ethanol produced 1.2 g. of yellow crystals melting at 247° dec.

Anal. Calcd. for $C_{12}H_8BrN_3O_4S$: S, 8.66. Found: S, 8.46.

1-{N-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-amino}-hydantoin.—To 0.755 g. of 1-aminohydantoin hydrochloride dissolved in 100 ml. of 95% ethanol, a solution of 1.31 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 100 ml. 95% ethanol was added and the mixture heated on a steam-bath for 30 minutes and then cooled on ice. Recrystallization from ethanol yielded 0.8 g. of yellow crystals, m.p. 258–259° dec.

Anal. Calcd. for $C_{10}H_7BrN_4O_4S$: S, 8.92. Found: S, 8.72.

1-{N-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-amino}-2-thiohydantoin.—A solution of 1.31 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 100 ml. of 95% ethanol and a few drops of 10% hydrochloric acid were added to a warm solution of 0.655 g. of 1-amino-2-thiohydantoin in 25 ml. of water and the mixture heated for 20 minutes. The separated product was collected and recrystallized from ethanol; yield 1.3 g. of yellow needles which decomposed at 330° without melting.

Anal. Calcd. for $C_{10}H_7BrN_4O_3S_2$: S, 17.1. Found: S, 17.3.

1-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-2-isonicotinylhydrazine.—A solution of 2.62 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein and 1.35 g. of isonicotinyl hydrazide in 20 ml. of dioxane and 20 ml. of ethanol was moderately warmed for 30 minutes. The resultant dark red solution was treated with water and the precipitate collected, redissolved in ethanol and concentrated; yield 2.2 g. of green-yellow crystals, m.p. 216–217°.

Anal. Calcd. for $C_{13}H_9BrN_4O_3S$: S, 8.26. Found: S, 8.39.

1-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-hydrazine.—A solution of 2.6 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 70 ml. of acetic acid was added to 0.625 g. of an 80% hydrazine solution in 30 ml. of acetic acid. A precipitate formed immediately. The mixture was heated for 10 minutes on a water-bath and then cooled and filtered, yield 1.65 g. of orange crystals, m.p. 232°.

Anal. Calcd. for $C_7H_6BrN_3O_2S$: S, 11.61. Found: S, 11.36.

N-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-aniline.—2.62 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein, 100 ml. of absolute methanol and 50 ml. of dioxane were placed in a 250-ml. flask fitted with a mechanical stirrer, a reflux condenser, a dropping funnel and a thermometer and the mixture was heated and stirred constantly until solution was complete. The mixture was cooled to room temperature and 0.93 g. of freshly distilled aniline in 15 ml. of methanol was added drop by drop and the mixture warmed to 45–50° for 15 minutes. After standing for 24 hr. at room temperature the precipitate was collected. The mother liquor was concentrated *in vacuo* and an additional crop of crystals collected. Recrystallization of the combined precipitates from anhydrous methanol yielded 1.31 g. of orange crystals, m.p. 143–144°.

Anal. Calcd. for $C_{13}H_9BrN_2O_2S$: S, 9.51. Found: S, 9.45.

4-{N-[α-Bromo-β-(5-nitro-2-thienyl)-acrylidene]-amino}-benzoic Acid.—A solution of 1.35 g. of *p*-aminobenzoic acid in 30 ml. of glacial acetic acid was added to 2.62 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein dissolved in 70 ml. of glacial acetic acid and the mixture was heated on a steam-bath for ten minutes. After cooling on ice, the crystalline precipitate was collected, dissolved in dioxane and reprecipitated with water; yield 1.2 g. of golden yellow crystals, m.p. 223°.

Anal. Calcd. for $C_{14}H_9BrN_2O_4S$: Br, 20.8. Found: Br, 20.98.

α-Bromo-β-(5-nitro-2-thienyl)-acrolein Oxime.—A solution of 2 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein in 20 ml. of dioxane was added to a filtered solution of 4 g. of hydroxylamine hydrochloride and 8 g. of fused sodium acetate in 10 ml. of dioxane and 20 ml. of water. The mixture was allowed to stand for 45 minutes at room temperature, and was then diluted with boiling water. The precipitate obtained was collected by suction and recrystallized from ethanol in the presence of activated charcoal; yield 1.4 g. of orange colored needles, m.p. 225–226°.

Anal. Calcd. for $C_7H_5BrN_2O_3S$: Br, 28.25. Found: Br, 28.5.

Diethyl 2-Bromo-3-(5-nitro-2-thienyl)-allylidenedicarbamate.—7.86 g. of α-bromo-β-(5-nitro-2-thienyl)-acrolein was dissolved in 1500 ml. of absolute ethanol, and the solution, cooled to room temperature, was treated with a few ml. of 4% sodium alcoholate solution and 5.34 g. of urethan. The mixture was allowed to stand overnight, concentrated to a small volume, the residue collected and recrystallized from benzene; yield 3.5 g. of slightly yellowish crystals, melting at 200–201°.

Anal. Calcd. for $C_{13}H_{16}BrN_3O_6S$: S, 7.59. Found: S, 7.86.

The 2-[1-Bromo-2-(5-nitro-2-thienyl)-vinyl]-4-hydroxymethyl-1.3-dithiocyclopentane.—2.62 g. of β-(5-nitro-2-thienyl)-acrolein and 110 ml. of dioxane were placed in a flask fitted with a mechanical stirrer, a reflux condenser, a thermometer and an inlet tube for hydrogen chloride. The product dissolved on heating: the solution was cooled to room temperature and 1.24 g. of 2,3-dimercaptopropanol in 10 ml. of dioxane was added. A rapid stream of hydrogen chloride was bubbled into the solution and the temperature raised to 50°. The mixture was cooled in order to maintain the temperature between 35 and 45°. The addition of hydrogen chloride was continued for one hour and a half, the reaction being carried out in the dark. The dioxane was removed *in vacuo*. The viscous oily residue was dissolved in ethyl acetate, decolorized with charcoal, filtered and dried over anhydrous sodium sulfate. The solvent was removed at low temperature and the oily residue kept in high vacuum at room temperature for four hours. The oil could not be distilled as it decomposed at 240°; yield 3.1 g. of an orange oil which darkened on exposure to light.

Anal. Calcd. for $C_{10}H_{10}BrNO_3S$: Br, 21.7; S, 26.05. Found: Br, 21.6; S, 25.9.

MILANO, ITALY