Cyclization. The chalcones were refluxed in aqueous alcoholic hydrochloric acid (3%) solution or suspension. The amounts of alcohol and hydrochloric acid used varied with the solubility of the chalcone and are given in Table II.

Different methods were adopted for isolating the flavanone depending on the nature of the chalcone.

Groups I *and* II. The reaction mixture was cooled well and the chalcone that had separated was filtered. The filtrate was concentrated under reduced pressure till turbidity appeared. It was then cooled and diluted. The solid obtained was fractionally crystallized from benzene to get the flavanone. In the case of Chalcone Ia, the reaction mixture was diluted and the mixture of chalcone and flavanone separated by virtue of the higher solubility of the chalcone in alcohol. The mixture was triturated with cold alcohol and filtered. The white residue was crystallized from alcohol when the pure flavanone separated.

Group III. The reaction mixture was cooled to about 45° and the yellow chalcone that had separated was filtered. The filtrate was cooled in ice when the crude flavanone separated which was crystallized from benzene.

Group IV. The reaction mixture was cooled and the solid that separated was recrystallized from a mixture of alcohol and ethylacetate to get the pure flavanone.

All the flavanones were white or very pale yellow in color. They did not give the magnesium–hydrochloric acid test and many of them gave colors other than yellow with concentrated sulfuric acid (see Table II). Groups I and III flavanones gave pale brown colors with alcoholic ferric chloride, while the isomeric chalcones gave deep brownish red colors. Both the chalcones and flavanones of group IV gave red colors with alcoholic ferric chloride.

Tests for stability of flavanones. (a) The flavanone (0.1 g.) was warmed with sodium hydroxide solution (10 cc.; 5%) for 10 min. and acidified. All the flavanones gave back the chalcone when thus treated. (b) The flavanone (0.1 g.) was refluxed in alcohol (10 cc.) with concentrated hydrochloric acid (10 cc.). Flavanone Ia was completely converted into the chalcone in 15 min. Only part of flavanone IIIa had reverted to the chalcone even after refluxing for an hour. Flavanone IVa was unaffected.

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BOMBAY, INDIA

[CONTRIBUTION FROM THE RESEARCH LABORATORY, LEPETIT S.P.A., MILAN]

Cinnamic and 2-Thienylacrylic Derivatives

ALBERTO VECCHI AND GAETANO MELONE

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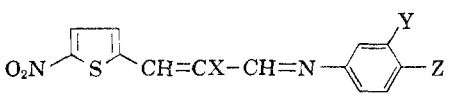
As a further development of previous studies on two exceptionally active antibacterial substances, β-(5-nitro-2-thienyl)-acrolein and its α-bromo derivative, the effects of introducing a 5-cyano group instead of the 5-nitro group and of a nitro instead of the aldehyde group were studied. Similar substitutions were tried in the benzene analogs. Furthermore, 4-cyanocinnamylidene acetaldehyde and 4-methylsulfonyl derivatives of the benzene series have been prepared. Outstanding antifungal activity was displayed by α-bromo-β-(5-cyano-2-thienyl)acrolein, α-bromo-4-cyanocinnamaldehyde, and their Schiff's bases with *p*-aminobenzoic acid, as well as by 1-(5-nitro-2-thienyl)-2-nitroethylene and 1-(5-nitro-2-thienyl)-2-bromo-2-nitroethylene. Other members of the described classes were also highly active.

In continuation of our previous work on cinnamic and 2-thienylacrylic derivatives,[1–3] which was suggested by a consideration of the marked biological interest of aromatic acroleins[4] and confirmed by a paper of Affonso and Khorana[5] on halogenated derivatives of cinnamic and *p*-nitrocinnamic acid, we have now synthesized a series of new compounds having structural resemblance to the acroleins already described.

The considerable interest aroused by the prior work is shown by several publications of Japanese scientists concerning furan analogs of the series.[6–12] Strict furan analogs of the thiophene compounds described in our previous papers have been recorded, such as β-(5-nitro-2-furyl)acrolein[6] and many functional derivatives thereof.

In view of the slight water solubility of the β-(5-nitro-2-thienyl)acroleins,[1] which prevented their use by the parenteral route and their absorption by the gastro-enteric tract, we have prepared functional derivatives of the following formula:



I	X = H,	Y = H,	Z = COOH
II	X = H,	Y = OH,	Z = COOH
III	X = H,	Y = H,	Z = SO_3H
IV	X = H,	Y = H,	Z = SO_2NH_2
V	X = Br,	Y = H,	Z = COOH[1]
VI	X = Br,	Y = H,	Z = SO_2NH_2
VII	X = Br,	Y = H,	Z = $SO_2NHCOCH_3$

(1) G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa and A. Vecchi, *J. Am. Chem. Soc.*, **76**, 4391 (1954).

(2) G. Rolland and M. T. Timbal, *Atti VI Congresso Int. Microbiologia Roma*, 1953, vol. I, sect. 2, p. 629.

(3) G. Carrara, E. Ginoulhiac, G. Rolland, and M. T. Timbal, *Il Farmaco, Sci. ed.*, **9**, 39 (1954).

(4) E. Keeser and J. Houben, *Fortschritte der Heilstoffchemie*, 2 Abt., Berlin, Leipzig, 1932, p. 254.

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

(6) T. Toda and I. Mifuchi, *Tuberculosis*, **28**, 19 (1953).

(7) T. Sasaki, *Pharm. Bull. (Japan)*, **2**, 123 (1954).

(8) M. Ikeda, *J. Pharm. Soc. Japan*, **75**, 628 (1955).

(9) M. Ikeda, *J. Pharm. Soc. Japan*, **75**, 631 (1955).

(10) A. Ohyama, *Bull. Inst. Chem. Research Kyoto Univ.*, **34**, 25 (1956).

(11) M. Ikeda, *Ann. Rept. Fac. Pharm. Kanazawa Univ.*, **3**, 25 (1953).

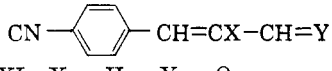
(12) S. Yasuda, *Ann. Rept. Fac. Pharm. Kanazawa Univ.*, **3**, 30 (1953).

Unfortunately, no substantial improvement in solubility was achieved, so we tried to overcome this difficulty by forming salts with hydrophilic bases, such as hydroxyethylamine, piperazine, and morpholine. These salts, however, when dissolved in water quickly hydrolyzed (in some instances after a few minutes) with precipitation of the acidic moiety.

The antibacterial activity on a molar basis of the compounds of this class was generally slightly lower than that of the corresponding aldehydes. Table I is representative of these and all results obtained *in vitro* with the compounds of the present paper.

Another untoward feature of the free nitroaldehydes is the brown coloration they impart to the tissue proteins, which impaired also their topical use in ointments and alcohol solutions. Since this property could be attributed to the simultaneous presence of bromine, nitrothiophene, and aldehyde groups in the molecule, an attempt was made to prepare analogs bearing a cyano instead of a nitro group. The cyano group being electronegative, the polarity of the molecule should not be markedly different, and the antibacterial activity should be maintained. The same substitution was tried also for the benzene analogs for the purpose of comparison; the following series of compounds were thus prepared:

VIII X = H, Y = O
IX X = Br, Y = O
X X = Br, Y = NC_6H_4COOH-*p*

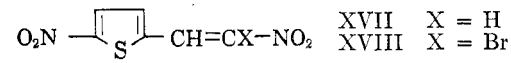


XI X = H, Y = O
XII X = Br, Y = O
XIII X = H, Y = CH—CHO
XIV X = H, Y = $NNHCSNH_2$
XV X = Br, Y = $NNHCSNH_2$
XVI X = Br, Y = NC_6H_4COOH-*p*

The expected equivalence of cyano and nitro analogs was substantially confirmed for the simplest members of the benzene series, since the antibacterial activity of compounds XI and XII paralleled that of 4-nitrocinnamaldehyde and α-bromo-4-nitrocinnamaldehyde. In the thiophene series, however, the cyano compounds were somewhat less active, although this disadvantage was balanced by the fact that skin coloration was almost totally eliminated. More extensive details on this subject will be published elsewhere.[13]

Compound XIII does not properly belong to the present class, and was only prepared for the purpose of ascertaining whether a lengthening of chain with the insertion of a second double bond would improve antibacterial activity. However XIII was practically devoid of activity. The thiosemicarbazones, as expected, were only active on *Mycobacterium tuberculosis var. hominis H37Rv*.

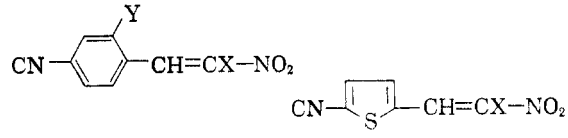
As a further development of the present study, in view of the interesting antibacterial and antifungal properties of β-nitrostyrenes, β-nitrovinylfurans, and β-nitrovinylthiophenes as described in several works,[14-22] 1-(5-nitro-2-thienyl)-2-nitroethylene (XVII) and 1-(5-nitro-2-thienyl)-2-bromo-2-nitroethylene (XVIII) were prepared and compared with the corresponding known benzene analogs (XIX and XX).[23]



XVII X = H
XVIII X = Br

Whereas in any case the halogenated compounds were generally more active, it can be observed that benzene derivatives were superior for their antibacterial activity (except for H37Rv), while thiophene compounds reached higher values of antifungal effectiveness, XVII being of the utmost interest in this respect.

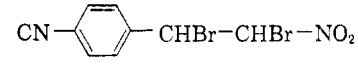
Moreover, analogs of these last compounds in which the ring nitro group was substituted by a cyano group were prepared, giving compounds XXI–XXIV



XXI X = H Y = H XXIII X = H
XXII X = Br Y = H XXIV X = Br
XXV X = Br Y = NO_2

whereby a slightly higher antibacterial and antifungal activity of the benzenes was ascertained.

The introduction of a ring nitro group in XXII (compound XXV) gave a fairly active compound; also compound XXVI,



XXVI

(13) M. T. Timbal, unpublished results.

(14) J. C. McGowan, P. W. Brian, and H. G. Hemming, *Ann. Applied Biol.*, **35**, 25 (1948).

(15) P. W. Brian, J. F. Grove and J. C. McGowan, *Nature*, **158**, 876, 1946.

(16) O. Dann and E. F. Moeller, *Ber.*, **82**, 76 (1949).

(17) O. Schales and H. A. Graefe, *J. Am. Chem. Soc.*, **74**, 4486 (1952).

(18) F. C. Bocobo, A. C. Curtis, W. D. Block, and E. R. Harrell, *Proc. Soc. Exptl. Biol. Med.*, **85**, 220 (1954).

(19) A. C. Curtis, F. C. Bocobo, E. R. Harrel and W. D. Block, *Arch. Dermatol. and Syphilol.*, **70**, 786 (1954).

(20) A. C. Huitric, R. Pratt, Y. Okano, and W. D. Kumbler, *Antibiotics & Chemotherapy*, **6**, 299 (1956).

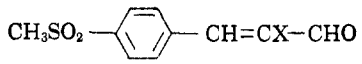
(21) F. C. Bocobo, A. C. Curtis, W. D. Block, E. R. Harrel, E. E. Evans, and R. F. Haines, *Antibiotics & Chemotherapy*, **6**, 385 (1956).

(22) E. E. Evans, R. F. Haines, A. C. Curtis, F. C. Bocobo, W. D. Block, and E. R. Harrell, *J. Invest. Dermatol.*, **28**, 43 (1957).

(23) T. Posner, *Ber.*, **31**, 657 (1898); R. Fürscheim, *J. prakt. Chem.* [2] **66**, 16 (1902).

obtained as an intermediate of the preparation of XXII, retained a good order of activity.

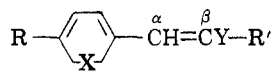
Our work has been concluded with the synthesis of compounds XXVII and XXVIII, structurally related to the derivatives, made by Affonso and Khorana,[5] but bearing a methylsulfonyl group at position 4. This substitution has been suggested by the considerable activity of the *p*-methylsulfonyl analog of chloramphenicol.[23,24]



XXVII X = H
XXVIII X = Br

While XXVII was practically devoid of any *in vitro* activity, the introduction of the bromine atom brought a marked degree of antibacterial and antifungal activity.

From an inspection of a generic formula embracing most of the componds prepared in this and in the other papers it can be concluded with respect to the antibacterial and antifungal activity:



1. The carbon atom at position β from the ring must be totally substituted, since where Y is hydrogen a considerable decrease of activity results. The presence of a bromine atom at β is of great importance; however, a methyl group[17] or chlorine may be substituted for it thus obtaining fairly active compounds.

2. Compounds in which R′ is a nitro group are generally slightly more active than in the case of R′ being an aldehyde carbonyl. Also in this case the β carbon atom must be totally substituted, as stated in item 2.

3. No substantial difference in activity is found when R is a cyano instead of a nitro group.

4. In any case, thiophene compounds, except in some isolated instances, have somewhat superior activity when compared with the benzene analogs.

EXPERIMENTAL

N-[γ-(5-Nitro-2-thienyl)acrylidene]-p-aminobenzoic acid (I). A mixture of 2 g. β-(5-nitro-2-thienyl)acrolein[1] and 100 ml. anhydrous ethanol was refluxed on a steam bath in a 250-ml. round bottom flask to complete solution, then 1.5 g. *p*-aminobenzoic acid were quickly added in one portion and refluxing was continued. After a few minutes complete solution occurred followed by precipitation of brick red crystals. After 10 min. the mixture was filtered hot by suction, and the solid on the filter was washed with hot anhydrous ethanol and dried. The yield was 2.65 g. (67%) m.p. 221–23°.

Anal. Calcd. for $C_{14}H_{10}N_2O_4S$: N, 9.26; S, 10.60. Found: N, 9.22; S, 10.61.

By strictly analogous procedures the following compounds were prepared.

N-[γ-(5-Nitro-2)thienyl)acrylidene]-4-aminosalicylic acid (II). Yield, 75%; m.p. 187–188° (dec.).

Anal. Calcd. for $C_{14}H_{10}N_2O_5S$: N, 8.80; S, 10.07. Found: N, 8.32; S, 9.65.

N-[γ-(5-Nitro-2-thienyl)acrylidene]sulfanilic acid (III). Yield, 64%; m.p. above 300°.

Anal. Calcd. for $C_{13}H_{10}N_2O_5S_2$: N, 8.28; S, 18.95. Found: N, 7.99; S, 18.20.

N⁴-[γ-(5-Nitro-2-thienyl)acrylidene]sulfanilamide (IV). Yield, 52%; m.p. 198–199°.

Anal. Calcd. for $C_{13}H_{11}N_3O_4S_2$: N, 12.45; S, 19.00. Found: N, 12.10; S, 19.50.

N⁴-[β-Bromo-γ-(5-nitro-2-thienyl)acrylidene]sulfanilamide (VI). From α-bromo-β-(5-nitro-2-thienyl)acrolein[1] and sulfanilamide. Yield, 47%; m.p. 163–164°.

Anal. Calcd. for $C_{13}H_{10}BrN_3O_4S_2$: N, 10.09; S, 15.40. Found: N, 9.82; S, 15.25.

N¹-Acetyl-N⁴-[β-bromo-γ-(5-nitro-2-thienyl)acrylidene]-sulfanilamide (VII). Acetic acid was used as a solvent in this case. Yield, 36%; m.p. 217° (dec.).

Anal. Calcd. for $C_{15}H_{12}BrN_3O_5S_2$: N, 9.16; Br, 17.43; S, 13.99. Found: N, 8.95; Br, 17.62; S, 14.02.

In addition, the hydroxyethylamine (V), piperazine (Va), and morpholine (Vb) salts of *N*-[β-bromo-γ-(5-nitro-2-thienyl)acrylidene]-*p*-aminobenzoic acid, a compound already described in our previous work,[1] were prepared. Va and Vb could not be subjected to microbiological experimentation in view of their insolubility.

2-Methyl-5-cyanothiophene (XXIX). A mixture of 255 ml. anhydrous pyridine, 26.2 g. cuprous cyanide, and 34.9 g. 2-methyl-5-iodothiophene[25] were refluxed in a round bottom flask on an oil bath under vigorous stirring for 8 hr. Pyridine was then removed by distillation *in vacuo*, and the residual dark mixture of oil and crystals was extracted with four 150-ml. portions of hot ethyl acetate. The combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the dark oily residue was distilled from a Claisen flask to yield a light orange liquid, b.p. 87–90°/10 mm. n_D^{20} 1.5512. Yield, 14 g. (73%).

Anal. Calcd. for C_6H_5NS: N, 11.38; S, 26.03. Found: N, 10.96; S, 25.78.

5-Cyano-2-thiophenecarboxaldehyde diacetate. Into a well stirred mixture of 14.0 g. of 2-methyl-5-cyanothiophene, 175 ml. acetic anhydride, and 175 ml. glacial acetic acid, previously cooled to below 20°, 25 ml. concd. sulfuric acid were added dropwise taking care that the temperature did not exceed 25°. The mixture was then cooled to below 5° and 31.2 g. chromium trioxide were added in small portions with stirring for 2 hr. without exceeding 8°. Stirring was continued for an additional 30 min. between 10 and 12°, and the mixture was poured into 400 ml. of ice water. The precipitated crystals were collected by suction, washed with cold water, and dried *in vacuo* at 40° to yield, 15.3 g. (56%) of material, m.p. 74–75°.

Anal. Calcd. for $C_{10}H_9NO_4S$: N, 5.85. Found: N, 5.90.

5-Cyano-2-thiophenecarboxaldehyde (XXX). The above product (15.3 g.) was suspended in a mixture of 60 ml. water, 60 ml. 95% ethanol, and 4.5 ml. concd. sulfuric acid and refluxed for 20 min. The solution was treated with charcoal and filtered when hot. On cooling, long white needles separated, which were collected by suction, washed with water, and dried *in vacuo* at 40°. An additional crop was obtained on concentration of the mother liquor; yield, 8.45 g. (51.5% calculated on 2-methyl-5-cyanothiophene); m.p. 96–97°.

Anal. Calcd. for C_6H_3NOS: N, 10.21; S, 23.38. Found: N, 10.25; S, 23.15.

The antibacterial activity of the intermediate compounds XXIX and XXX are also tabulated in Table I.

β-(5-Cyano-2-thienyl)acrolein (VIII). This product was

(24) R. A. Cutler, R. J. Stenger, and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952).

(25) E. Grischkewitsch-Trochimowski, *J. Russ. Phys. Chem. Soc.*, **43**, 804 (1911).

TABLE I

MINIMAL INHIBITORY CONCENTRATION, γ/ML.

	Compound	*Micrococcus aureus*	*Streptococcus faecalis*	*Escherichia coli*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*	H37 Rv (With Serum)	*Trichophyton mentagrophytes*	*Candida albicans*
I		10	20	20	5	>100	10	2	5	10
II		10	20	20	10	>100	10	0.5	10	10
III		10	50	20	10	>100	20	10	10	20
IV		10	20	20	5	>100	20	10	5	10
V		5	10	10	5	50	10	10	5	10
VI		5	10	10	10	20	10	5	2	5
VII		5	10	10	5	10	10	5	1	5
VIII		100	>100	>100	100	>100	100	50	100	50
IX		5	20	20	10	10	20	5	2	5
X		10	100	50	5	20	20	5	0.5	5
	Ethanolamine salt of X.	10	100	50	10	20	20	5	0.5	5
XI		100	100	100	50	>100	100	10	10	50
XII		10	20	10	5	50	10	5	0.5	5
XIII		100	>100	>100	>100	>100	>100	10	20	50
XIV		>100	>100	>100	>100	>100	>100	10	>100	>100
XV		>100	>100	>100	>100	>100	>100	5	50	>100
XVI		10	10	10	5	50	10	10	0.2	10
	Ethanolamine salt of XVI	10	10	20	5	>100	20	20	0.5	50
XVII		20	100	50	20	100	50	1	0.3	0.5
XVIII		10	50	20	20	50	50	2	0.5	1
XIX	p-$NO_2C_6H_4CH{=}CHNO_2$	20	100	20	10	>100	20	20	2	2
XX	p-$NO_2C_6H_4CH{=}CBrNO_2$	5	20	10	5	5	20	20	1	2
XXI		10	50	20	10	100	10	20	2	1
XXII		5	20	10	10	5	20	20	1	2
XXIII		50	50	50	20	>100	20	10	1	5
XXIV		10	20	10	10	10	20	5	1	5
XXV		10	50	20	10	20	20	...	1	2
XXVI		50	50	10	10	5	20	20	2	2
XXVII		100	>100	>100	100	>100	>100	50	100	>100
XXVIII		10	50	20	5	>100	20	50	20	2
XXIX	2-Methyl-5-cyanothiophene	>100	>100	>100	>100	>100	>100	>100	>100	>100
XXX	5-Cyano-2-thiophenecarboxaldehyde	>100	>100	>100	>100	>100	>100	100	100	100
α-Bromo-β-(5-nitro-2-thienyl)-acrolein		5	20	2	2	10	2	1	1	5
α-Bromo-5-nitrocinnamaldehyde		5	10	10	5	50	5	1	1	5
Chloramphenicol		5	5	5	1	>100	5	12, 5	>100	>100
4-Amino-salicylic acid		>100	>100	>100	>100	>100	>100	5	>100	>100

prepared with the same technique as described for β-(5-nitro-2-thienyl)acrolein.[1] Yield, 43%; m.p. 128–130°.

Anal. Calcd. for C_8H_5NOS: N, 8.58; S, 19.64. Found: N, 8.26; S, 19.48.

α-Bromo-β-(5-cyano-2-thienyl)acrolein (IX) was prepared as described for α-bromo-(5-nitro-2-thienyl)acrolein.[1] Yield, 77%; m.p. 152–154°.

Anal. Calcd. for C_8H_4BrNOS: 5.78; Br, 33.00. Found: N, 5.62; Br, 33.10.

4-[β-Bromo-γ-(5-cyano-2-thienyl)acrylideneamino]benzoic acid (X). A suspension of 12.3 g. of IX in 230 ml. anhydrous ethanol was refluxed until complete solution was obtained, then 8 g. 4-aminobenzoic acid were added in one portion under stirring. Heating was continued for some minutes, whereby complete solution occurred followed by gradual precipitation of yellow needles. After cooling in ice bath the crystals were collected by suction and dried on a steam bath. Yield, 7.3 g. (41%); m.p. 298° (dec.).

Anal. Calcd. for $C_{15}H_9BrN_2O_2S$: N, 7.75; Br, 22.12. Found: N, 7.70; Br, 22.06.

The hydroxyethylamine salt had m.p. 173–175° (dec.).

4-Cyanocinnamaldehyde (XI). This product was prepared starting from 4-cyanobenzaldehyde as described for 4-nitrocinnamaldehyde.[26] Yield, 41%; m.p. 136–138°.

Anal. Calcd. for $C_{10}H_7NO$: N, 8.91. Found: N, 9.10.

Thiosemicarbazone (XIV), m.p. 218° (dec.).

α-Bromo-4-cyanocinnamaldehyde XII was prepared starting from XI as described for α-bromo-4-nitrocinnamaldehyde.[27] Yield, 82%; m.p. 158–159°.

Anal. Calcd. for $C_{10}H_6BrNO$: N, 5.93; Br, 33.85. Found: N, 5.93; Br, 33.81.

Thiosemicarbazone (XV), m.p. 207–208° (dec.).

4-(β-Bromo-4-cyanocinnamylideneamino)benzoic acid (XVI) was prepared as described above for X. M.p. 217° (dec.).

Anal. Calcd. for $C_{17}H_{11}BrN_2O_2$: N, 7.88; Br, 22.49. Found: N, 7.68; Br, 22.27.

Hydroxyethylamine salt, m.p. 152–155°.

4-Cyanocinnamylideneacetaldehyde (XIII). A mixture of 3.8 g. XI and 15 ml. acetaldehyde was cooled to about 6–8°, then 0.6 ml. 25% potassium hydroxide solution in methano was added, whereby the temperature rose to about 30°. After cooling 10 ml. acetic anhydride was added and the mixture was refluxed for 1 hr. After cooling, addition of 30 ml. water and 3.5 ml. concd. hydrochloric acid, refluxing for 0.5 hr. and cooling, the precipitated product was collected by suction and recrystallized from 50% ethyl alcohol. Yield (after 2 recrystallizations), 1.2 g. (27.2%)· m.p. 153–155°.

Anal. Calcd. for $C_{12}H_9NO$: N, 7.64. Found: N, 7.41. Bromometric assay: 98.3%.

1-(5-Nitro-2-thienyl)-2-nitroethylene (XVII). To a well-stirred and cooled mixture of 5.82 g. 5-nitro-2-thiophenecarboxaldehyde and 3.7 ml. nitromethane, 1.2 ml. 25% potassium hydroxide solution in methanol were added, whereby the temperature reached 30°. It was cooled to 15°, 21 ml. acetic anhydride was added, and the mixture was refluxed for 30 min. After cooling a solution of 7.5 ml. concd. hydrochloric acid in 60 ml. water was added, the mixture was refluxed for 10 min., cooled, and filtered by suction. The solid was recrystallized from water. Yield, 1.1 g. M.p. 102–104°.

Anal. Calcd. for $C_6H_4N_2O_4S$: N, 13.99; S, 16.01. Found: N, 13.27; S, 15.84.

1-(5-Nitro-2-thienyl)-2-bromo-2-nitroethylene (XVIII). This compound was prepared as described for α-bromo-β-(5-nitro-2-thienyl)acrolein,[1] starting from XVII. M.p. 172–174°.

Anal. Calcd. for $C_6H_3BrN_2O_4S$: N, 10.03; Br, 28.63; S, 11.48. Found: N, 9.83; Br, 28.42; S, 11.30.

4-Cyano-β-nitrostyrene (XXI). This compound was prepared as described for XVII, except that refluxing with diluted hydrochloric acid was avoided. Yield, 47%; m.p. 186–188°.

Anal. Calcd. for $C_9H_6N_2O_2$: C, 62.06; H, 3.47; N, 16.08. Found: C, 61.92; H, 3.80; N, 15.96.

1-(4-Cyanophenyl)-2-nitro-1,2-dibromoethane (XXVI). A mixture of 2 g. XXI and 1.84 g. bromine was sealed in a glass tube and heated in a water bath at 100° for 1.5 hr. After cooling and opening of the tube the thick brown-red liquid was taken up in 10 ml. glacial acetic acid, whereby thin yellowish crystals separated which were collected by suction, washed with acetic acid, then with water, and recrystallized from anhydrous ethanol. Yield, 2.1 g. (55%); m.p. 141–143°.

Anal. Calcd. for $C_9H_6Br_2N_2O_2$: N, 8.38; Br, 47.85. Found: N, 8.38; Br, 48.00.

4-Cyano-β-bromo-β-nitrostyrene (XXII). Two grams XXVI were dissolved in hot glacial acetic acid (6 ml.), then 0.415 g. anhydrous potassium carbonate were added in portions. The mixture was heated on a boiling water bath for 15 min., then cooled, whereby a yellow precipitate formed which was collected by suction, washed well with water, and dried in an oven. Yield, 1.2 g. (79%); m.p. 148–150° (from anhydrous ethanol).

Anal. Calcd. for $C_9H_5BrN_2O_2$: N, 11.07; Br, 31.57. Found: N, 10.80; Br, 30.95.

4-Cyano-2,β-dinitrostyrene. This compound was prepared as described for XVII; m.p. 133–135°.

Anal. Calcd. for $C_9H_5N_3O_4$: N, 19.17. Found: N, 18.86.

4-Cyano-β-bromo-2,β-dinitrostyrene (XXV). The above compound (0.3) was admixed with 0.22 g. bromine in a sealed glass tube and heated for 1 hr. at 100° in a boiling water bath. The resulting brown-reddish residue was dissolved in 3 ml. hot glacial acetic acid and mixed with 0.1 g. anhydrous potassium carbonate. After heating to 100° for an additional 15 min. the mixture was cooled, filtered from some insoluble material, and diluted with an equal volume of water. The flocculent yellow precipitate was dissolved by heating and the solution allowed to cool. The precipitate was collected by suction and recrystallized from 95% ethanol. Yield, 0.22 g. (54%); m.p. 103–104°.

Anal. Calcd. for $C_9H_4BrN_3O_4$: N, 14.09. Found: N, 12.95.

1-(5-Cyano-2-thienyl)-2-nitroethylene (XXIII). This compound was prepared as described for XXI, starting from XXX. Yield, 77%; m.p. 181–182°.

Anal. Calcd. for $C_7H_4N_2O_2S$: N, 15.54; S, 17.79. Found: N, 15.45; S, 17.48.

1-(5-Cyano-2-thienyl)-2-bromo-2-nitroethylene (XXIV). A mixture of 8.2 g. XXIII and 7.7 g. bromine was heated for 20 min. on a boiling water bath in a round-bottom flask fitted with a reflux condenser. After cooling and addition of 45 ml. glacial acetic acid the preparation was carried on as described for XXV using 3.2 g. anhydrous potassium carbonate. Yield, 8.8 g. (75%) of light yellow crystals melting at 151–153° (from 95% ethanol).

Anal. Calcd. for $C_7H_3BrN_2O_2S$: N, 10.81; Br, 30.84. Found: N, 10.82; Br, 30.60.

4-Methylsulfonylcinnamaldehyde (XXVII). This product was prepared as described for 4-nitrocinnamaldehyde,[26] except that refluxing with dilute hydrochloric acid was avoided; the product crystallizing directly from acetic anhydride. M.p. 207–208°.

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.12; H, 4.79. Found: C, 57.37; H, 4.97.

α-Bromo-4-methylsulfonylcinnamaldehyde (XXVIII) was prepared starting from XXVII as described for α-bromo-4-nitrocinnamaldehyde.[27] Yield, 75%; m.p. 102–104°.

Anal. Calcd. for $C_{10}H_9BrO_3S$: Br, 27.63; S, 11.08. Found: Br, 27.68; S, 10.87.

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