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Studies on Furan Derivatives. X.[1] Preparation of 2-Substituted 3-(5-Nitro-2-furyl)quinoxaline 1,4-Dioxides and Determination of Their Antibacterial Activity

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2-Substituted 3-(5-nitro-2-furyl)quinoxaline 1,4-dioxides (Va—g) were prepared by the reaction of benzofurazan 1-oxide with α-aryl- or α-(2-furyl)-β-(5-nitro-2-furyl)-vinylamines and aryl or 2-furyl 5-nitro-2-furfuryl ketones. It was found that primary enamines, as well as tertiary enamines, are useful in this reaction. One-pot synthesis of 2-(2-furyl)-3-(5-nitro-2-furyl)quinoxaline 1,4-dioxide (Va) from 2-[β-(5-nitro-2-furyl)ethynyl]furan was examined, and afforded Va in 11% yield. Compounds Va—g were subjected to antibacterial activity tests and some of them showed activity at 6.25—25 μg/ml (minimal inhibitory concentration).

Keywords——nitrofuran derivatives; quinoxaline 1,4-dioxide derivatives; 2-substituted 3-(5-nitro-2-furyl)quinoxaline 1,4-dioxides; 5-nitro-2-furylvinylamines; benzofurazan 1-oxide; antibacterial activity

Various quinoxaline 1,4-dioxides are known to be potent antibacterial agents,[2] and nitrofuran derivatives have also been widely recognized as having antibacterial activity. There are many reports on the synthesis and biological activity of 5-nitro-2-furyl-heterocyclic compounds.[3] Few examples of 5-nitro-2-furylquinoxalines[4] and no reports on their N-oxides were found in a literature search. We felt that synthesis of 5-nitro-2-furylquinoxaline 1,4-dioxides, possessing both 5-nitro-2-furan and quinoxaline 1,4-dioxide moieties, might provide the compounds with increased antibacterial activity.

Quinoxaline 1,4-dioxide and its analogy are usually prepared by peracid oxidation of the parent quinoxalines.[5] On the other hand, Haddadin and Issidorides[6] reported a simple quinoxaline 1,4-dioxide synthesis by the condensation of benzofurazan 1-oxide (BFO)[7] with tertiary enamines. Later, several groups[8] extended the scope of this type of reaction by employing a variety of carbonyl compounds having the $-COCH_2-$ grouping. We now report the synthesis of 2-substituted 3-(5-nitro-2-furyl)quinoxaline 1,4-dioxides by the reaction of BFO with α-aryl- or α-(2-furyl)-β-(5-nitro-2-furyl)vinylamines (IIIa—h),[9] aryl or 2-furyl 5-nitro-2-furfuryl ketones (IIa—h),[10] and 2-[β-(5-nitro-2-furyl)ethynyl]furan (IV).[9a,10,11]

Synthesis

At first we invesitigated the reaction of BFO with 2-furyl 5-nitro-2-furfuryl ketone pyrrolidino enamine (I)[12] in refluxing methanol, but the expected quinoxaline 1,4-doxide could not be obtained. Thus, 2-furyl 5-nitro-2-furfuryl ketone (IIa)[9a] was allowed to react with BFO in the presence of methylamine to yield the desired 2-(2-furyl)-3-(5-nitro-2-furyl)quinoxaline 1,4-dioxide (Va), mp 222—224°, in 39% yield (method A). The structure of Va was fully supported by microanalytical results and spectral data: mass spectrum *m/e* 339 (M^+), 323 ($M^+ -16$), and 307 ($M^+ -32$); NMR (ppm in DMSO-d_6) 6.79 (1H, q, furan H-4), 7.52 (1H, d, nitrofuran H-3), 7.70—8.20 (5H, m, furan H-3 and 5, nitrofiran H-4, and quinoxaline H-6 and 7), and 8.30—8.70 (2H, m, quinoxaline H-5 and 8).

In order to study the behavior of BFO with a primary enamine, the reaction of IIIa[9a] with BFO was carried out, and afforded Va in 84% yield (method B). The quinoxaline 1,4-dioxide thus obtained was identical with the compound prepared by method A. This is the

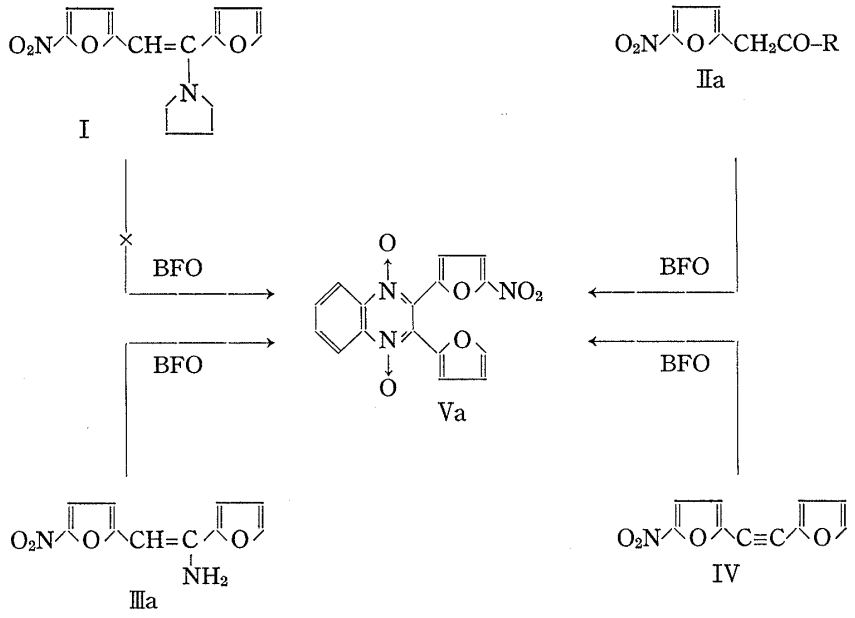
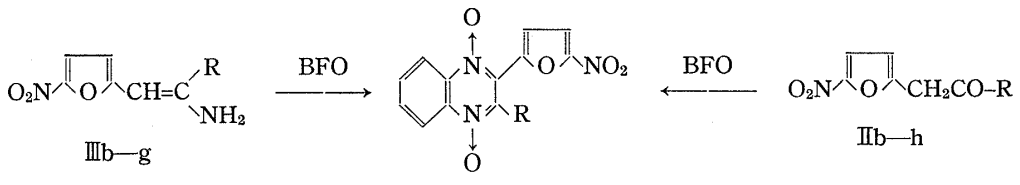


Chart 1

first example of a quinoxaline 1,4-dioxide prepared by the reaction of a primary enamine with BFO. Since it was found that the primary enamine (IIIa) is more useful than the tertiary enamine (I) in the reaction with BFO, other primary enamines (IIIb—g)[9b] were similarly examined. These results are listed in Table I. Moreover, this reaction was applied to other representative primary enamines. Methyl β-aminocrotonate was allowed to react with BFO to give 2-methoxycarbonyl-3-methylquinoxaline 1,4-dioxide (VI), mp 177—179°, in 40% yield. The quinoxaline 1,4-dioxide (VI) was identical with a sample prepared by the method of Kasubick and Robertson.[13] Similarly, 2,3-bis(4-nitrophenyl)quinoxaline 1,4-dioxide (VII) was obtained from 4,4'-dinitrostibylamine,[14] mp 265—267°, in 60% yield. The structure of VII was supported by the elemental analysis and spectral data. Thus, it was established that a wide variety of the primary enamines, as well as tertiary enamines, can be used in this type of reaction.



b; R=phenyl, c; R=4-chlorophenyl, d; R=4-bromophenyl, e; R=4-iodophenyl, f; R=4-methoxyphenyl, g; R=4-nitrophenyl, h; R=1-naphthyl

Chart 2

The carbon-carbon triple bond of 2-[β-(5-nitro-2-furyl)ethynyl]furan (IV)[9a,10,11] is active towards nucleophilic agents such as amines because of the electron-withdrawing nature of the 5-nitro-2-furyl group.[12,15] Therefore, one-pot synthesis of Va *via* enamine was examined. When a mixture of BFO, IV, methylamine, and tetrahydrofuran was stirred for 7 days, Va was obtained in 11% yield with partial recovery of IV (50%).

Lastly, ketones (IIb—h)[10] were allowed to react with BFO by method A to give the corresponding quinoxaline 1,4-dioxides (Vb—g) in 20—30% yields as shown in Table II. These low yields may be due to the fact that the nitrofuran ring is usually unstable under basic

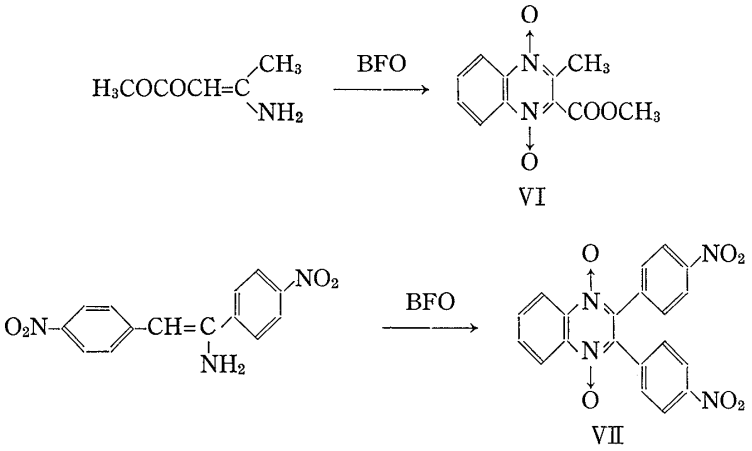


Chart 3

Table I. Yields of Va—g from IIIa—g

Compd. No.	Va	Vb	Vc	Vd	Ve	Vf	Vg
Yield (%)	84	79	66	29 (50) [a]	0 (60) [a]	59	0 (80) [a]

a) Recovery (percent) of enamines.

Table II. Physical Data for Va—g

Compd. No.	Yield (%) from II	mp (°C)	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N
Va	39	222—224 (dec.)	Orange needles	$C_{16}H_9N_3O_6$	56.64 (56.38	2.67 2.73	12.39 12.21)
Vb	29	269—270 (dec.)	Yellow needles	$C_{18}H_{11}N_3O_5$	61.89 (61.58	3.17 3.38	12.03 12.20)
Vc	24	255—257	Yellow leaves	$C_{18}H_{10}ClN_3O_5$	56.34 (56.32	2.63 2.78	10.95 10.08)
Vd	28	240—241.5	Yellow leaves	$C_{18}H_{10}BrN_3O_5$	50.49 (50.56	2.35 2.30	9.81 10.13)
Ve	34	254—255	Yellow leaves	$C_{18}H_{10}IN_3O_5$	45.50 (45.66	2.12 2.03	8.84 9.08)
Vf	21	240—242 (dec.)	Yellow prisms	$C_{19}H_{13}N_3O_6$	60.16 (59.87	3.45 3.56	11.08 10.93)
Vg	32	258—259 (dec.)	Yellow leaves	$C_{18}H_{10}N_4O_7$	54.83 (54.63	2.56 2.65	14.21 13.89)

conditions. Although the reason for the failure of IIh to react is unclear, we assume it to be due to repulsive interactions between the 1-oxide or 3-(5-nitro-2-furyl) and 2-(1-naphthyl) moieties on the developing quinoxaline system. The structures of IIb—g were fully assigned on the bases of their elemental analyses and spectral data.

Biological Results

Compounds Va—g were tested *in vitro* against both gram-negative and gram-positive bacteria. The minimum inhibitory concentration (MIC) was determined by the twofold agar-dilution method.[16] One loopful of an overnight culture in Trypto-Soy Broth (Eiken) was inoculated onto 10 ml drug-containing agar in a Petri dish. Bacterial growth was observed after incubation for 20 hr at 37°. The MIC was defined as the lowest drug concentration

Table III. Antibacterial Activity (incubation time: 20 hr, MIC: μg/ml)

Compd. No.	*Str. hem.* Group A089	*Sta. aur.* 209 P-JC	*Sta. aur.* 72 r	*Sal. ent.* 1891	*E. coli.* NIHJ-JC	*E. coli.* K-60	*Kle. pneu.* ST-101	*Pro. vulg.* HX 19
Va	12.5	12.5	12.5	25	25	>25	25	>25
Vb	>12.5	12.5	12.5	>12.5	>12.5	>12.5	>12.5	>12.5
Vc	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25
Vd	12.5	12.5	12.5	>12.5	>12.5	>12.5	>12.5	>12.5
Ve	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25
Vf	25	12.5	25	>25	>25	>25	>25	>25
Vg	6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25	>6.25
AF-2	<0.39	0.78	1.56	0.78	1.56	3.13	0.78	6.25

Compd. No.	*Ps. aerg.* 347	*Ps. aerg.* K-99	*Sta. aur.* Smith	*Sta. epi.* 12228	*Ser. mar.* IID620	*E. coli.* K-74	*Pro molg.* IFO3168	*Sal. pull.* Thuyu
Va	>25	>25	6.25	6.25	>25	>25	>25	>25
Vb	>12.5	>12.5	12.5	12.5	>12.5	>12.5	>12.5	>12.5
Vc	>6.25	>6.25	>6.25	6.25	>6.25	>6.25	>6.25	>6.25
Vd	>12.5	>12.5	12.5	6.25	>12.5	>12.5	>12.5	>12.5
Ve	>6.25	>6.25	>6.25	6.25	>6.25	>6.25	>6.25	>6.25
Vf	>25	>25	12.5	12.5	>25	>25	>25	>25
Vg	>6.25	>6.25	>6.25	6.25	>6.25	>6.25	>6.25	>6.25
AF-2	12.5	>50	<0.39	<0.39	25	6.25	12.5	1.56

which prevented visible bacterial growth. The data for Va—g are presented in Table III, and AF-2[17] is included for comparison. Although these compounds could not be tested at hgh concentrations owing to poor solubility, some of them showed activity at 6.25—25 μg/ml (MIC).

Experimental

All melting points were determined with a Yanaco MP-1 apparatus and are uncorrected. Infrared spectra were recorded with a Jasco IRI-1 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on JEOL JNM-60 HL and PS-100 spectrophotometers with tetramethylsilane as an internal standard. Mass spectra were obtained (direct solid inlet) on a Shimadzu LKB-9000 instrument. Benzofurazan 1-oxide was prepared from 2-nitrophenylazide[18] and methyl β-aminocrotonate was purchased from Aldrich Chemical Co.

Reaction of I with BFO——A mixture of I (0.5 g, 0.00182 mol), BFO (0.25 g, 0.00182 mol), and MeOH (20 ml) was refluxed for 50 hr, and evaporated down. The residue was chromatographed on silica gel, eluting with benzene, to give I (0.4 g) and BFO (0.23 g).

Reaction of IIa—h with BFO——$MeNH_2$ (0.5 ml) was added to a mixture of one of IIa—h (0.5 g), BFO (1 molar equivalent), and MeOH (15 ml), and stirred for 24 hr at room temperature. The precipitate was filtered off and recrystallized from AcOEt to give the corresponding compounds, Va—g.

Reaction of IIIa—h with BFO——A mixture of one of IIIa—h (0.5 g), BFO (1 molar equivalent), and MeOH (20 ml) was refluxed for 50 hr. After cooling the precipitate was filtered and recrystallized from AcOEt to give the corresponding compound, Va—d, f.

Reaction of IV with BFO——$MeNH_2$ (0.5 ml) was added to a mixture of IV (0.5 g, 0.00246 mol), BFO (0.33 g, 0.00246 mol), and MeOH (20 ml), and the mixture was stirred for 7 days at room temperature. The precipitate was filtered and recrystallized from AcOEt to give Va (0.09 g, 11%). The filtrate was cromatographed on silica gel, eluting with benzene, to give IV (0.25 g) and 2-furyl 5-nitro-2-furfuryl ketone (0.14 g) which showed melting point and spectral absorption properties identical with those previously reported in the literature.[10]

2-Methoxycarbonyl-3-methylquinoxaline 1,4-Dioxide (VI)——A mixture of methyl β-aminocrotonate (1 g, 0.0087 mol), BFO (1.18 g, 0.0087 mol), and MeOH (30 ml) was refluxed for 50 hr, and poured into ice-water, then extracted with benzene. The benzene extract was dried over anhydrous Na_2SO_4 and evaporated down. The residue was treated with MeOH to give 1.0 g of crude crystals, which were recrystallized from MeOH to give 0.8 g of yellow needles, mp 177—179°. MS (*m/e*): 234 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O), 1330, 1355 (N→O); NMR (δ in $CDCl_3$): 7.70—8.10 (2H, m, quinoxaline H-6 and 7), 8.50—8.90 (2H, m, quinox-

Table IV. Spectral Data for Va—g

Compd. No.	MS (M^+)	IR ν_{max}^{Nujol} cm^{-1}: N→O and NO_2	UV ν_{max}^{EtOH} cm[a]	NMR δ (DMSO-d_6)[b]
Va	339	1330, 1345 1355, 1520	235, 320 375(s), 395(s)	6.79 (1H, q, $J_{4,5}=1.8$ Hz, $J_{3,4}=3.8$ Hz, F H-4), 7.52 (1H, d, $J=4$ Hz, NF H-3), 7.70—8.20 (5H, m, F H-3 and 5, NF H-5, and Q H-6 and 7), 8.30—8.70 (2H, m, Q H-5 and 8).
Vb	349	1320, 1330 1360, 1520	236, 307 350, 395(s)	7.30—7.70 (7H, m, NF H-3 and 4, and phenyl H), 7.30—8.25 (2H, m, Q H-6 and 7), 8.50—8.80 (2H, m, Q H-5 and 8).
Vc	383	1325, 1335 1360, 1520	235, 309 351, 395(s)	7.57 (4H, s, phenyl H), 7.60 (1H, d, $J=4$ Hz, NF H-3), 7.73 (1H, d, $J=4$ Hz, NF H-4), 7.90—8.30 (2H, m, Q H-6 and 7), 8.40—8.80 (2H, m, Q H-5 and 8).
Vd	427	1320, 1335 1355, 1520	236, 309 352, 395(s)	7.50 (2H, d, $J=4$ Hz, phenyl H), 7.67 (2H, d, $J=9$ Hz, phenyl H), 7.63 (1H, d, $J=4$ Hz, NF H-3), 7.77 (1H, d, $J=4$ Hz, NF H-4), 7.90—8.20 (2H, m, Q H-6 and 7), 8.30—8.75 (2H, m, Q H-5 and 8).
Ve	475	1330, 1360 1525	239, 310 354, 395(s)	7.28 (2H, d, $J=9$ Hz, phenyl H), 7.90 (2H, d, $J=9$ Hz, phenyl H), 7.55 1H, d, $J=4$ Hz, NF H-3), 7.75 (1H, d, $J=4$ Hz, NF H-4), 7.90—8.25 (2H, m, Q H-6 and 7), 8.40—8.75 (2H, m, Q H-5 and 8).
Vf	379	1330, 1355 1520	236, 318 350(s), 395(s)	7.30 (2H, d, $J=9$ Hz, phenyl H), 7.43 (2H, d, $J=9$ Hz, phenyl H), 7.38 (1H, d, $J=4$ Hz, NF H-3), 7.73 (1H, d, $J=4$ Hz, NF H-4), 7.90—8.20 (2H, m, Q H-6 and 7), 8.40—8.75 (2H, m, Q H-5 and 8), 3.80 (3H, s, CH_3).
Vg	394	1320, 1330 1355, 1520	244, 310(s) 352, 395(s)	8.45 (2H, d, $J=9$ Hz, phenyl H), 7.60—8.27 (6H, m, phenyl H, NF H-3 and 4, and Q H-6 and 7), 8.40—8.75 (2H, m, Q H-5 and 8).

a) s: shoulder;
b) s: singlet, d: doublet, m: multiplet, q: quartet, F: furan ring, NF: nitrofuran ring, Q: quinoxaline ring.

aline H-5 and 8), 2.61 (3H, s, CH_3), 4.13 (3H, s, OCH_3). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.33; H, 4.35; N, 12.00.

This structure was identical with the compound prepared by the method of Kasubick and Robertson.[13]

2,3-Bis(4-nitrophenyl)quinoxaline 1,4-Dioxide (VII)——A mixture of α,β-bis(4-nitrophenyl)vinylamine (0.3 g, 0.0011 mol), BFO (0.14 g, 0.0011 mol), and MeOH (20 ml) was refluxed for 50 hr, then cooled. The resulting precipitate was filtered off and recrystallized from AcOEt to give 0.25 g (60%) of yellow needles, mp 265—267° (dec.). MS (*m/e*): 404 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1335, 1350, 1520 (N→O and NO_2); NMR (δ in DMSO-d_6): 7.73 (4H, d, $J=9$ Hz, nitrophenyl H), 8.20 (4H, d, $J=9$ Hz, nitrophenyl H), 7.90—8.40 (2H, m, quinoxaline H-6 and 7), 8.50—8.90 (2H, m, quinoxaline H-5 and 8). *Anal.* Calcd for $C_{20}H_{12}N_4O_6$: C, 59.41; H, 2.99; N, 13.86. Found: C, 59.22; H, 2.58; N, 13.93.

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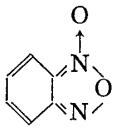
References and Notes

1) Part IX of this series; A. Tanaka, T. Usui, and M. Shimadzu, *Chem. Pharm. Bull.*, **28**, 2846 (1980).
2) M.L. Edwards, R.E. Bambury, and H.W. Ritter, *J. Med. Chem.*, **18**, 637 (1975); *idem, ibid.*, **19**, 330 (1976); J.P. Dirlam and J.E. Presslitz, *ibid.*, **21**, 483 (1978).
3) P.J. Islip and M.R. Johnson, *J. Med. Chem.*, **16**, 1038 (1973); H.A. Burch and L.E. Benjamin, *ibid.*, **17**, 451 (1974); E.B. Akerblom, *ibid.*, **17**, 756 (1974); M.C. Neville and J.P. Verge, *ibid.*, **20**, 946 (1977); A. Tanaka and T. Usui, *Chem. Pharm. Bull.*, **26**, 3576 (1978).
4) H. Saikachi and J. Matsuo, *Yakugaku Zasshi*, **84**, 416 (1964).
5) Y.T. Pratt, "Heterocyclic Compounds," Vol. 6, by R.C. Elderfield, John Wily and Sons, Inc., New York, 1957, p. 473.
6) M.J. Haddadin and C.H. Issidorides, *Tetrahedron Lett.*, **1965**, 3253.

7) 

8) C.H. Issidorides and M.J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966); M.J. Haddadin, G. Agopian, and C.H. Issidorides, *ibid.*, **36**, 514 (1971); J.C. Mason and G. Tennant, *Chem. Commun.*, **1971**, 586; D.P. Claypool, A.R. Sidani, and K.J. Flanagan, *J. Org. Chem.*, **37**, 2372 (1972); E. Abushanab, *ibid.*, **38**, 3105 (1973); M.J. Haddadin, N.C. Chelhot, and M. Pieriou, *ibid.*, **39**, 3278 (1974).
9) *a*) S. Yoshina, A. Tanaka, and T. Usui, *Yakugaku Zasshi*, **97**, 1007 (1977); *b*) *Idem*, *J. Heterocycl. Chem.*, **15**, 555 (1978).
10) S. Yoshina, A. Tanaka, and T. Usui, *Yakugaku Zasshi*, **98**, 286 (1978); A. Tanaka and T. Usui, *Chem. Pharm. Bull.*, **28**, 1604 (1980).
11) A. Tanaka and T. Usui, and S. Yoshina, *J. Heterocycl. Chem.*, **16**, 493 (1979).
12) A. Tanaka and T. Usui, *Chem. Pharm. Bull.*, **27**, 3078 (1979).
13) R.V. Kasubik and R.L. Robertson, Ger. Patent 2215320 (1972) [*Chem. Abstr.*, **78**, 4280*z* (1973)].
14) 4,4′-Dinitrostilbylamine was prepared from N-[α,β-bis(4-nitrophenyl)vinyl]pyridinium bromide; see H. Ahlbrecht and R.F. Kröhnke, *Ann. Chem.*, **701**, 126 (1967).
15) A. Tanaka and T. Usui, *J. Heterocycl. Chem.*, **16**, 1409 (1979).
16) This method was developed by the Japan Society of Chemotherapy; see *Chemotherapy*, **23**, 1 (1975).
17) H. Saikachi and A. Tanaka, *Yakugaku Zasshi*, **83**, 147 (1963).
18) A.O. Fitton and R.K. Smalley, "Practical Heterocyclic Chemistry," Academic Press, Inc., London, 1968, p. 57.