CDATA, EMF Software, Knoxville, TN) implemented on an IBM personal computer. K_I values were calculated by the method of Cheng and Prusoff.[18]

Acknowledgment. This research was supported by Grant AG-07418 from the National Institute on Aging.

(18) Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

Registry No. 1, 107010-27-5.

Supplementary Material Available: Tables of structure amplitudes, fractional coordinates, anisotropic thermal parameters, and bond lengths and bond angles (6 pages). Ordering information is given on any current masthead page.

Thienotriazolodiazepines as Platelet-Activating Factor Antagonists. Steric Limitations for the Substituent in Position 2

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The preparations of thienotriazolodiazepines bearing a substituted ethynyl group at the 2-position, and the corresponding *cis*-olefins and fully saturated analogues are described. The compounds were evaluated as potential antagonists of platelet-activating factor (PAF) in in vitro and in vitro test models. The new thienotriazolodiazepines are compared with known related compounds such as WEB 2086 (compound **6**) and the phenylethyl derivatives **27** and **28**.

In a previous publication[1] we reported the preparation of a series of triazolobenzodiazepines and thienotriazolodiazepines carrying a functionalized propynyl group at the 8- and 2-position, respectively. Some of these compounds were among the most potent, orally active platelet-activating factor (PAF) antagonists yet described. When the site of attachment of the propargylic side chain was shifted from the 8-position to the 9-position of the triazolobenzodiazepine system, the activity was essentially lost. We ascribed this result to lack of binding to the PAF receptor brought about by the bulky substituent protruding linearly from the 9-position. We now wish to report on the observation of similar steric limitations for the 2-position substituent of some 2-ethynyl-substituted thienotriazolodiazepines.

Chemistry

The preparation of the unsaturated analogues of WEB 2086[2] (compound **6**) is illustrated in Scheme I. Brotizolam, (**1a**)[3] was coupled with propargyl alcohol by palladium catalysis to give **2**. Oxidation of this propargylic alcohol with activated manganese dioxide in the presence of morpholine led directly in moderate yield to the amide **3**. Hydrogenation of the triple bond to the *cis*-olefin **4** was achieved by using 5% palladium on carbon as catalyst and thiophene as a poison. The known saturated compound **6** (WEB 2086) was obtained by standard hydrogenation of **3** over palladium on carbon. The *trans*-olefin **5** resulted from the reduction of **3** with sodium borohydride in methanol. As suggested by this hydride reduction, the triple bond in compound **3** is quite reactive toward nucleophiles and reacted smoothly with hydrazine at room temperature to form the hydrazone **7**, which was thermally converted to the pyrazolone **9**. Addition of sodium azide to the triple bond led to the vicinal triazole **8** (Scheme II).

The ethynyl derivatives **10–21** were accessible by the coupling of the iodo compound **1b**[1,4] with various acetylenes as described in our previous paper[1] (Method A). The monosubstituted acetylene **10** was prepared by coupling of **1b** with (trimethylsilyl)acetylene to give **11** and subsequent hydrolysis of the trimethylsilyl group. Compound **10** could then be functionalized by coupling with aryl iodides as shown by the reaction of **10** with 1-iodonaphthalene to yield **13**, and by coupling with 1-(4-iodophenyl)imidazole (**45a**) to yield the acetylenic precursor of **30** (Method A'). It was generally preferable to prepare the substituted acetylenes prior to the coupling with the triazolothienodiazepine **1b**. The required acetylenes **41–43**, **47b–d**, and **50** were formed by reaction of the appropriate aryl halide with (trimethylsilyl)acetylene and subsequent hydrolysis (Method E). The aryl iodides **36** and **45a**, as well as the known compounds **45b**[5] and **45c**[6] were prepared by Sandmeyer reaction of the corresponding anilines (Method D). 1-(4-Aminophenyl)imidazole (**44a**) was accessible by reduction of the nitro compound as described in the literature.[7] The iodides **37** and **38** were obtained by iodination (Method F) of the dihydrobenzofurans **39** and **40**,[8] respectively (Scheme III). The known 4-iodoisobutylbenzene[9] (**45d**) was accessible by direct iodination of commercially available **46** with iodine monochloride.

While the hydrogenation of the triple bond to the single bond (Method C) presented no problems, the partial hydrogenation (Method B) to the *cis*-olefins was more difficult and compounds **22–26** generally had to be isolated chromatographically from the mixture containing some starting material and some over-hydrogenated saturated product. The saturated analogue **6**, **27**, and **28** had been previously prepared by different syntheses as disclosed in

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‡ Department of Pharmacology.

(1) Walser, A.; Flynn, T.; Mason, C.; Crowley, H.; Yaremko, B.; Maresca, C.; O'Donnell, M. *J. Med. Chem.* **1990**, submitted.
(2) (a) Weber, K.-H.; Heuer, H. O. *Med. Res. Rev.* **1989**, *9*, 181. (b) Casals-Stenzel, J.; Muacevic, G.; Weber, K.-H. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 974.
(3) Weber, K.-H.; Bauer, A.; Danneberg, P.; Kuhn, J. US patent 4,094,984; June, 1978.
(4) This compound was first prepared by M. Gerecke at Hoffmann-La Roche & Co, AG., Basle, Switzerland.
(5) Boedtker *Bull. Soc. Chim.* *45*, 648, *Beilstein*, 5, II, 318.
(6) Mayes; Turner *J. Chem. Soc.* **1929**, 504. *Beilstein*, 5, II, 396.
(7) Netherland patent Application 6,413,474; May 1965; Merck & Co., Inc. CA 1965, 62, 14867h.
(8) Glaser, R.; Gabbay, E. J. *J. Org. Chem.* **1970**, *35*, 2904.
(9) Klages; Storp *J. Prakt. Chem.* *65*, [2] 570. *Beilstein*, 5, 415.

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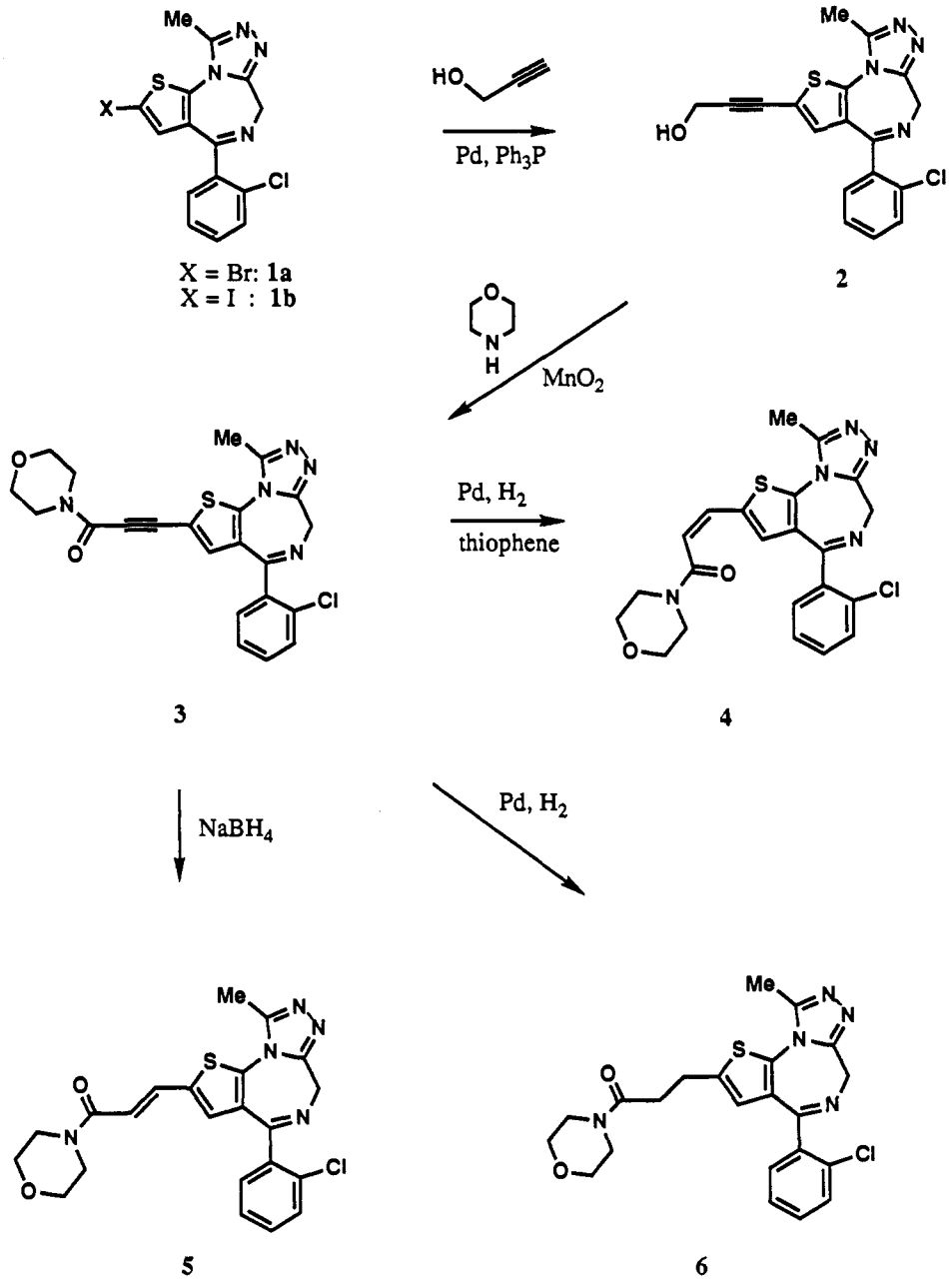
Scheme I



patents by Weber et al.[2] and by Tahara et al.[10] We obtained these compounds by hydrogenation of the corresponding ethynyl derivatives **3**, **15**, and **16**, respectively.

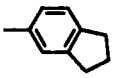
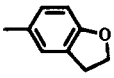
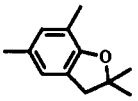
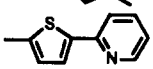
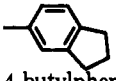
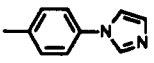
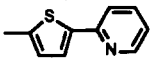
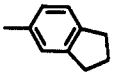
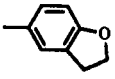
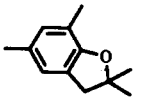
Results and Discussions

Compounds were evaluated for PAF-antagonist activity in vitro in a binding assay employing washed, whole dog platelets and in vivo for their ability to inhibit PAF-induced bronchoconstriction in the guinea pig. These bioassays have been previously described.[11] The data listed in Table I indicates that the compounds with the triple bond are generally less active than the analogue with the double or single bond. This observation is contrary to the results reported earlier[1] with the propargyl series. Hydrogenation of the triple bond in these propargyl compounds to the corresponding *cis*-propenyl analogues or the fully saturated propyl compounds[12] did not improve the PAF-inhibitory activity (data not shown). The propargylic alcohol **2** is equivalent to compound **6** (WEB 2086) in both the in vitro and in vivo assays. The ethynyl derivative **3** is inferior to the saturated compound **6** (WEB 2086), especially in the in vivo bronchoconstriction test. The corresponding *cis*-olefin **4** is almost equipotent to **6**, while the *trans*-olefin **5** is clearly less active. The hydrazone **7** is weakly active, but the triazole **8** and the pyrazolone **9** exhibited virtually no activity at the initial testing dose. The lack of activity for **8** and **9** may be due to the polar, acidic nature of the substituent rather than to its bulkyness.

The ethynyl derivatives **10**, **13**, **14**, and **21** demonstrate good intravenous activity comparable to compound **6**

(10) Tahara, T.; Moriwaki, M.; Abe, M.; Yuasa, S. EP 0 268 242 Al; May 1988.
(11) Tilley, J. W.; Clader, J. W.; Zawoiski, S.; Wirkus, M.; LeMahieu, R. A.; O'Donnell, M.; Crowley, H.; Welton, A. F. *J. Med. Chem.* **1989**, *32*, 1814.
(12) Walser, A.; Flynn, T.; Mason, C. Unpublished data.
(13) Takatsu, H.; Sasaki, M.; Tanaka, Y.; Sato, H. US patent 4,726, 910, Feb. 1988. (No preparation given).
(14) Galantay, E. E.; Kathawala, F. G. US patent 4,011,339; March 1977. (No preparation given).

Table I. Thienotriazolodiazepines (For Structures, See Schemes I and II)

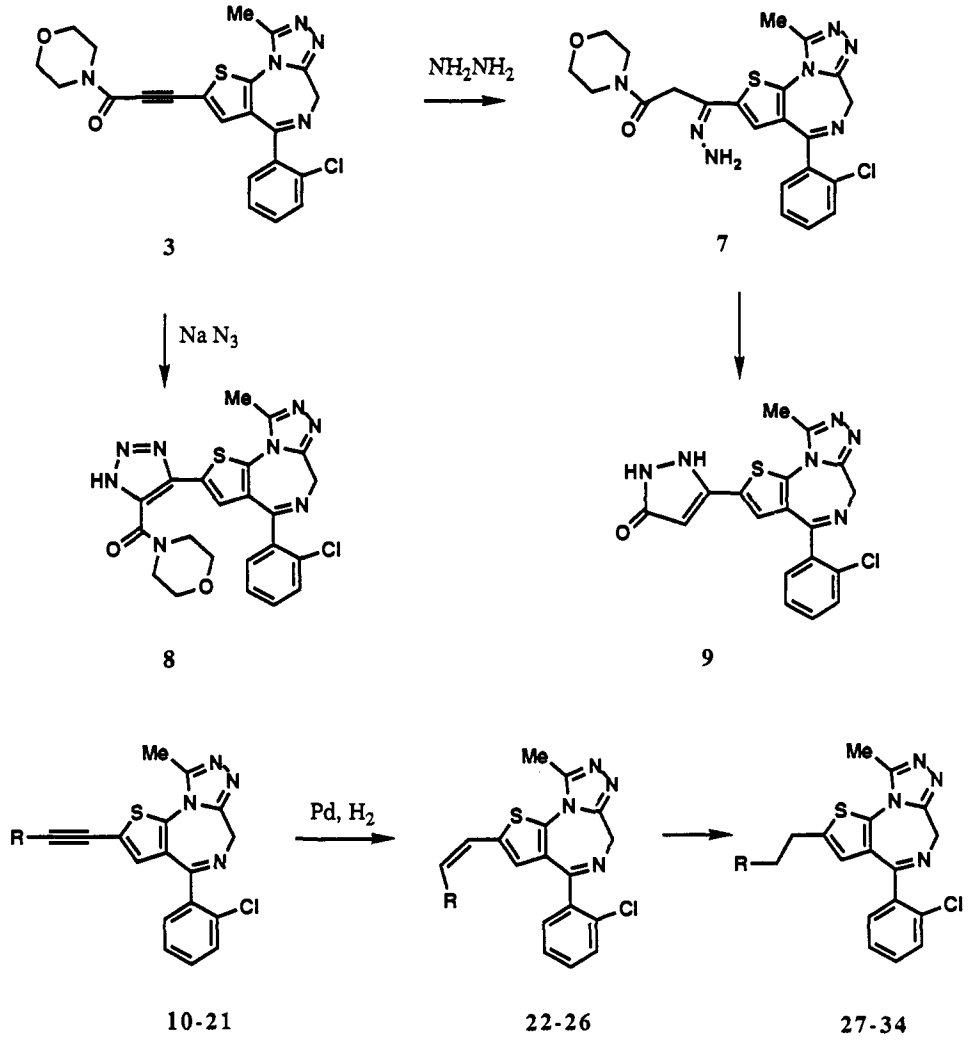
compd	R	PAF binding IC_{50}, nM[a]	guinea pig bronchoconstriction assay: ID_{50}, mg/kg, iv[a,b]	% inhib, 1 mg/kg, po[b]	ID_{50}, mg/kg, po[a,b]
1a		300	0.5	11 ± 5	
1b		370	0.2	4 ± 3	
2		180	0.02	20 ± 8	
3		260	0.5	16 ± 6	
4		180	0.06	20 ± 11	
5		450	0.4	27 ± 7	
6		200	0.03	42 ± 11	1.2
7		420	0.5	12 ± 7	
8		1000	inact		
9		1000	inact		
10	H	10	0.02	9 ± 4	
11	trimethylsilyl	20	0.3	28 ± 8	
12	Ph	100	0.3	6 ± 3	
13	1-naphthyl	150	0.03	14 ± 3	
14	2-pyridyl	250	0.06	5 ± 1	
15	4-butylphenyl	650	0.2	6 ± 4	
16	4-isobutylphenyl	100	0.3	2 ± 2	
17	4-cyclohexylphenyl	300	0.3	22 ± 8	
18		380	0.2	20 ± 8	
19		420	0.2	7 ± 6	
20		400	inact		
21		60	0.003	93 ± 4	0.08
22	2-pyridyl	400	0.05	20 ± 11	
23	4-butylphenyl	10	0.0004	93 ± 7	0.35
24	4-isobutylphenyl	80	0.004	99 ± 7	0.03
25	4-cyclohexylphenyl	120	0.03	85 ± 8	0.4
26		110	0.03	58 ± 3	0.7
27	4-butylphenyl	10	0.003	98 ± 1	0.2
28	4-isobutylphenyl	30	0.002	99 ± 0	0.03
29	4-cyclohexylphenyl	35	0.005	68 ± 1	0.4
30		100	0.003	95 ± 3	0.4
31		8	0.003	89 ± 7	0.4
32		20	0.04	99 ± 0	0.03
33		20	0.003	44 ± 9	
34		400	0.01	96 ± 0	0.3

[a] IC_{50} and ID_{50} values were determined by linear regression analysis; the correlation coefficient for each regression line was >0.95. [b] 1-min pretreatment time. [c] 2-h pretreatment time. [d] Inact = no significant inhibition at 1 mg/kg iv.

(WEB 2086). However, the phenylethynyl compounds **12**, **15**, **16**, and **17** and the fused-ring relatives **18**, **19**, and **20** are at least 10-fold less potent than the unsubstituted acetylene **10** in both the in vitro and the in vivo assays and 20-fold less potent intravenously than compound **6**. Incorporation of a pyridylthienyl group in the 2-position resulted in the most potent compound **21** of this limited ethynyl series. Compound **21** is 10-fold more potent intravenously and 15-fold more active orally than the corresponding saturated compound **31**. With exception of compound **21**, none of the ethynyl derivatives is of interest on the basis of their weak inhibitory activity when tested at a trial dose of 1 mg/kg po.

The intravenous and oral potencies increased dramatically when the triple bond was converted to the cis double bond. This is true in particular for compounds **23** and **24**. Compound **23** is the most potent of this series exhibiting a 500-fold increase in potency upon intraveneous administration over the acetylene **15**. Surprisingly, the isobutyl analogue **24** demonstrates the best oral potency of this series (IC_{50} = 0.03 mg/kg). The 10-fold difference in oral potency between the *n*-butyl analogue **23** and the isobutyl compound **24** is noteworthy and is also observed with the corresponding saturated analogues **27** and **28**, patented by

Scheme II



Tahara et al.[10] Good oral activity was also found with the indane derivative **32**. The oxygen isostere **33** of this compound, on the other hand, demonstrated low oral potency, suggesting again that minor structural changes have a big effect on oral activity. It is unlikely, that the physical parameters between *n*-butyl and isobutyl are different enough to account for the observed effects. It seems more probable, that higher metabolic stability of the isobutyl versus the *n*-butyl side chain may be responsible for the difference in oral activity. The same argument may be valid for the difference between the indane **32** and the benzofuran **33**.

As indicated above, we attribute the generally inferior potency of the substituted ethynyl compounds to steric factors. The rigid, linear 3-bond unit of the ethynyl group places portions of the large 2-position substituent into an area which may interfere with the binding to the PAF binding site. By converting the triple bond to a cis double bond, the large substituent can assume a conformation which does not interfere with binding. The steric effects appear to be most critical for the para substituted phenyl compounds, the *n*-butyl derivative in particular. The pyridylthienyl analogue **21**, which could be expected to have sterical demands similar to those of compounds **14–19**, may owe its higher affinity to the two heteroatoms which could interact with the binding site and contribute additional binding energy.

In conclusion, we suggest that rigidity and excessive bulk of the 2-position substituent is reponsible for the lower affinity and potency of the ethynyl compounds as compared to the corresponding *Z*-ethenyl and ethyl derivatives. Oral potency appears to be greatly influenced by minor structural changes through mechanisms which are not yet understood.

Experimental Section

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-200 spectrometer. Microanalyses were obtained for C, H, and N and were within 0.4% of the calculated values except as indicated for noncrystalline materials. Silica gel Merck 70–230 mesh was used for preparative column chromatography. Short-path distillations were carried out in the Buechi Kugelrohr oven. Anhydrous sodium sulfate was used for drying purposes. Dry ice and acetone were employed for low-temperature reactions.

Data for compounds not described in this section are found in Table II.

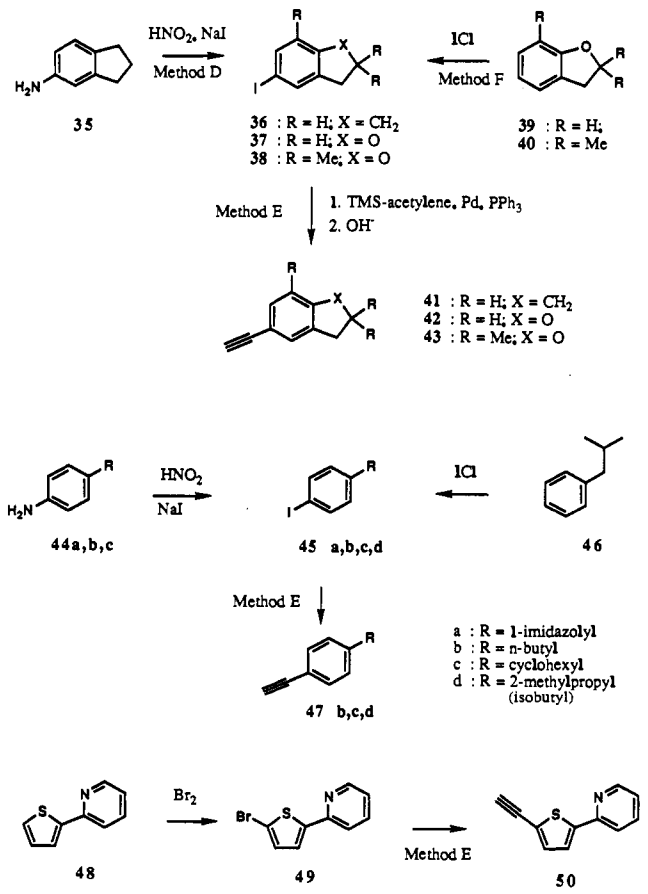
4-(2-Chlorophenyl)-2-(3-hydroxypropyn-1-yl)-9-methyl-6*H*-thieno[3,2-*f*][2,4]triazolo[4,3-*a*][1,4]diazepine (2). A mixture of 3.55 g (10 mmol) of 2-bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine,[3] 0.3 g of triphenylphosphine, 40 mg of cuprous iodide, 2.5 mL of propargyl alcohol, 10 mL of triethylamine, and 75 mL of DMF was degassed with argon for 10 min. Palladium acetate (0.15 g) was then added, and the mixture was heated under argon to 65–70 °C for 15 min. It was evaporated under reduced pressure, and the residue was partitioned between CH_2Cl_2 and saturated sodium bicarbonate solution. The organic phase was dried and evaporated, and the residue was chromatographed over 120 g of silica gel with 10% of ethanol in CH_2Cl_2 used for elution. The combined clean fractions were crystallized from methanol/ethyl acetate to yield 2.3 g (62%) of off-white crystals with mp 234–235 °C dec: ^1H

Table II. Data for Compounds Not Described in Experimental Section[a]

compd	mp, °C	solvents of cryst	method	yield %	formula	anal.
12	215–7	EA	A	51	$C_{23}H_{15}ClN_4S$	CHN, ^{1}H NMR
14	153–5	THF/M	A	62	$C_{22}H_{14}ClN_5S$	CHN, ^{1}H NMR
16	153–5	Et_2O/H	A	60	$C_{27}H_{23}ClN_4S$	CHN, ^{1}H NMR
17	180–3	E/EA	A	87	$C_{29}H_{25}ClN_4S\cdot 2HCl\cdot 0.5H_2O$	CHN, ^{1}H NMR
18	227–9	E/EA	A	67	$C_{26}H_{19}ClN_4S$	CHN, ^{1}H NMR
19	172–5	EA/Et_2O	A	39	$C_{25}H_{17}ClN_4OS$	CHN, ^{1}H NMR
20	185–7	E/EA	A	84	$C_{28}H_{23}ClN_4OS\cdot 2HCl\cdot 0.5H_2O$	CHN, ^{1}H NMR
21	145–50	EA/H	A	54	$C_{26}H_{16}ClN_5S_2$	CHN, ^{1}H NMR
22	198–200	EA/H	B	37	$C_{22}H_{16}ClN_5S$	CHN, ^{1}H NMR
24	135–8	Et_2O/H	B	29	$C_{27}H_{25}ClN_4S$	CHN, ^{1}H NMR
25	145–7	Et_2O/H	B	22	$C_{29}H_{27}ClN_4S$	CHN, ^{1}H NMR
26	160–2	EA/H	B	52	$C_{26}H_{21}ClN_4S$	CHN, ^{1}H NMR
28[b]	158–61[c]	Et_2O	C	50	$C_{27}H_{27}ClN_4S$	CHN, ^{1}H NMR
29	183–6	E/EA	C	65	$C_{29}H_{29}ClN_4S\cdot 2HCl\cdot H_2O$	CHN, ^{1}H NMR
30	118–20	E/EA/H	A',C	50	$C_{26}H_{21}ClN_6S(E)$	CHN, ^{1}H NMR
31	180–5	EA	C	80	$C_{26}H_{20}ClN_5S_2$	CHN, ^{1}H NMR
32	117–20	EA/Et_2O	C	43	$C_{26}H_{23}ClN_4S\cdot 0.5H_2O$	CHN, ^{1}H NMR
33	143–5	EA	C	44	$C_{25}H_{21}ClN_4OS$	CHN, ^{1}H NMR
34	172–5	E/EA	C	47	$C_{28}H_{27}ClN_4OS\cdot 2HCl\cdot H_2O$	CHN, ^{1}H NMR
38	oil		F	74	$C_{11}H_{13}IO$	CHN, ^{1}H NMR
42	62–4	solidified	E	52	$C_{10}H_8O$	CHN, ^{1}H NMR
43	oil		E	50	$C_{13}H_{14}O$	CHN, ^{1}H NMR
45a	146–7	EA/H	D	33	$C_9H_7IN_2$	CHN, ^{1}H NMR
47b[d]	oil		E	53	$C_{12}H_{14}$	^{1}H NMR
47c[e]	oil		E	91	$C_{14}H_{16}$	^{1}H NMR
47d	oil		E	65	$C_{12}H_{14}$	CHN, ^{1}H NMR
50	114–5	M	E	27	$C_{11}H_7NS$	CHN, ^{1}H NMR

[a] E = ethanol; EA = ethyl acetate; H = hexane; M = methanol. [b] Reference 10. [c] Literature mp 118–121 °C. [d] Reference 13. [e] Reference 14.

Scheme III



NMR ($CDCl_3$) 2.14 (t, 1, J = 6 Hz, OH), 2.72 (s, 3, CH_3), 4.5 (d, 2, J = 6 Hz, CH_2), 4.98 (s, 2, C_6-H), 6.82 (s, 1, C_3-H), 7.3–7.6 (m, 4, aromatic H). Anal. ($C_{18}H_{13}ClN_4OS$) C, H, N.

4-[3-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-1-oxo-2-propynyl]-morpholine (3). A mixture of 1.35 g (3.66 mmol) of **2**, 250 mL of CH_2Cl_2, 3 mL of morpholine, and 10 g of activated manganese dioxide was stirred at room temperature for 30 min. The MnO_2 was filtered off and washed with CH_2Cl_2 containing 5% of ethanol. The filtrate was evaporated, at the end azeotropically with xylene. Crystallization of the residue from ethyl acetate gave 0.6 g (36%) of product which was further purified by passing over 3 g of silica gel by using 5% of ethanol in CH_2Cl_2. Crystallization from ethyl acetate/hexane gave yellowish crystals with mp 209–210 °C: ^{1}H NMR ($CDCl_3$) 2.7 (s, 3, CH_3), 3.65 (s, 4) and 3.7 (s, 4) (morpholine), 4.93 (s, 2, C_6-H), 6.94 (s, 1, C_3-H), 7.2–7.5 (m, 4, aromatic H). Anal. ($C_{22}H_{18}ClN_5O_2S$) C, H, N.

(*Z*)-4-[3-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-1-oxo-2-propenyl]-morpholine (4). A mixture of 0.2 g of **3**, 0.1 g of palladium on carbon (5%), 10 mL of THF, 5 mL of ethanol, and 5 drops of thiophene was hydrogenated at atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was evaporated. The residue was crystallized from ethyl acetate to leave 0.15 g (75%) of crystals which were recrystallized twice from methanol/ethyl acetate to leave colorless crystals with mp 245–247 °C (the same melting point as the *E* isomer): ^{1}H NMR ($CDCl_3$) 2.78 (s, 3, CH_3), 3.5–3.8 (m, 8, morpholine), 4.94 (s, 2, C_6-H), 6.1 (d, 1, J = 12 Hz, olefinic H), 6.76 (d, 1, J = 12 Hz, olefinic H), 6.78 (s, 1, C_3-H), 7.3–7.6 (m, 4, aromatic H). Anal. ($C_{22}H_{20}ClN_5O_2S$) C, H, N.

(*E*)-4-[3-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-1-oxo-2-propenyl]-morpholine (5). A mixture of 0.3 g of **3**, 20 mL of methanol, and 0.15 g of sodium borohydride was stirred at room temperature for 15 min. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated, and the residue was crystallized from ethyl acetate. The crystals were purified by passing over a plug of 0.5 g of silica gel by using 10% of ethanol in CH_2Cl_2. Crystallization of the evaporated filtrate from ethyl acetate gave 0.14 g (47%) of colorless crytals with mp 245–247 °C: ^{1}H NMR ($CDCl_3$) 2.75 (s, 3, CH_3), 3.73 (m, 8, morpholine), 5.0 (s, 2, C_6-H), 6.67 (d, 1, J = 15 Hz, olefinic H), 6.82 (s, 1, C_3-H), 7.3–7.6 (m, 4, aromatic H), 7.68 (d, 1, J = 15 Hz, olefinic H). Anal. ($C_{22}H_{20}ClN_5O_2S$) C, H, N.

4-[3-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]-[1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-3-hydrazono-1-oxopropyl]morpholine (7). A suspension of 0.15 g of **3** in 5 mL of 2-propanol was treated with 5 drops of hydrazine. The mixture was stirred at room temperature for 1 h. The starting material

Table III. Microanalytical Data

compd	formula	calcd			found		
		C	H	N	C	H	N
2	$C_{18}H_{13}ClN_4OS$	58.62	3.55	15.19	58.69	3.57	15.18
3	$C_{22}H_{18}ClN_5O_2S$	58.47	4.01	15.50	58.50	4.10	15.46
4	$C_{22}H_{20}ClN_5O_2S$	58.21	4.44	15.43	58.33	4.49	15.30
5	$C_{22}H_{20}ClN_5O_2S$	58.21	4.44	15.43	58.19	4.58	15.22
7	$C_{22}H_{22}ClN_7O_2S$	54.59	4.58	20.25	54.14	4.60	19.60[b]
8	$C_{22}H_{19}ClN_6O_2S$	53.39	3.87	22.64	53.28	3.97	22.55
9	$C_{18}H_{13}ClN_6OS$	54.48	3.30	21.18	53.70[b]	3.26	20.64[b]
10	$C_{17}H_{11}ClN_4S$	60.26	3.27	16.54	60.45	3.29	16.65
11	$C_{20}H_{19}ClN_4SSi$	58.45	4.66	13.63	58.37	4.76	13.55
12	$C_{23}H_{15}ClN_4S$	66.58	3.64	13.50	66.17	3.85	13.15
13	$C_{27}H_{17}ClN_4S$	69.75	3.69	12.05	69.97	3.58	12.12
14	$C_{22}H_{14}ClN_5S$	63.53	3.39	16.84	63.80	3.28	16.65
15	$C_{27}H_{23}ClN_4S$	68.85	4.92	11.89	68.93	5.15	12.06
16	$C_{27}H_{23}ClN_4S$	68.85	4.92	11.89	68.86	5.06	11.77
17	$C_{29}H_{25}ClN_4S\cdot 2HCl\cdot 0.5H_2O$	60.15	4.87	9.67	59.87	4.80	9.58
18	$C_{26}H_{19}ClN_4S$	68.64	4.21	12.31	68.28	4.25	12.32
19	$C_{25}H_{17}ClN_4OS\cdot 0.5H_2O$	64.44	3.88	12.02	64.56	3.93	12.06
20	$C_{28}H_{23}ClN_4OS\cdot 2HCl\cdot 0.5H_2O$	57.88	4.51	9.64	57.72	4.50	9.30
21	$C_{26}H_{16}ClN_5S_2$	62.71	3.24	14.01	62.85	3.00	14.28
22	$C_{22}H_{16}ClN_5S$	63.23	3.86	16.76	63.33	4.13	16.69
23	$C_{27}H_{25}ClN_4S$	68.56	5.33	11.84	68.28	5.27	11.74
24	$C_{27}H_{25}ClN_4S$	68.56	5.33	11.84	68.46	5.38	11.97
25	$C_{29}H_{27}ClN_4S$	69.79	5.45	11.23	69.90	5.70	11.14
26	$C_{26}H_{21}ClN_4S$	68.33	4.63	12.26	68.20	4.79	12.07
27[a]	$C_{27}H_{27}ClN_4S$	68.27	5.73	11.79	68.51	5.92	12.03
28[a]	$C_{27}H_{27}ClN_4S$	68.27	5.73	11.79	68.30	5.99	11.67
29	$C_{29}H_{29}ClN_4S\cdot 2HCl\cdot 0.66H_2O$	57.98	5.70	9.39	57.94	5.32	9.29
30	$C_{26}H_{21}ClN_6S\cdot C_2H_5OH\cdot 0.33H_2O$	62.62	5.00	15.65	62.74	5.12	15.66
31	$C_{26}H_{20}ClN_5S_2$	62.80	4.02	13.95	61.76	3.90	13.94
32	$C_{26}H_{23}ClN_4S\cdot 0.5H_2O$	66.72	5.17	11.97	66.77	5.23	11.85
33	$C_{25}H_{21}ClN_4OS$	65.14	4.59	12.15	64.92	4.70	11.95
34	$C_{28}H_{27}ClN_4OS\cdot 2HCl\cdot H_2O$	55.76	5.34	9.29	55.70	4.87	9.21
36	C_9H_9I	44.29	3.72		44.37	3.81	
37	C_8H_7IO	39.05	2.87		38.98	2.92	
38	$C_{11}H_{13}IO$	45.85	4.55		45.53	4.20	
41	$C_{11}H_{10}$	92.91	7.09		92.01[b]	7.13	
42	$C_{10}H_8O$	83.31	5.59		83.17	5.56	
43	$C_{13}H_{14}O$	83.83	7.58		83.31	7.37	
45a	$C_9H_7IN_2$	40.03	2.61	10.37	40.03	2.61	10.26
47d	$C_{12}H_{14}$	91.08	8.92		89.94[b]	9.14	
49	C_9H_6BrNS	45.01	2.51	5.83	45.07	2.37	5.92
50	$C_{11}H_7NS$	71.32	3.81	7.56	70.82	3.74	7.48

[a] Reference 10. [b] Microanalyses are outside the usually acceptable limit.

gradually dissolved and the product reprecipitated. It was collected and washed with a little 2-PrOH and ether to leave 0.14 g (87%) of yellowish crystals with mp 190–195 °C dec: ^{1}H NMR ($CDCl_3$) 2.75 (s, 3, CH_3), 3.3–3.8 (m, 10, CH_2, morpholine), 4.98 (s, 2, C_6-H), 6.36 (s, 2, NH_2), 6.5 (s, 1, C_2-H), 7.3–7.6 (m, 4, aromatic H). Anal. ($C_{22}H_{22}ClN_7O_2S$) C, H, N.

5-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-2-yl]-1,2-dihydro-3*H*-pyrazol-3-one (9). A solution of 0.1 g of **7** in 25 mL of xylene was heated to reflux for 45 min. The solvent was evaporated, and the residue was chromatographed over 6 g of silica gel by using CH_2Cl_2 containing 10% of ethanol. The combined clean fractions were evaporated, and the residue was crystallized from methanol/ethyl acetate to yield 40 mg (48%) of colorless crystals with mp 247–250 °C: ^{1}H NMR ($CDCl_3$ + 5 drops of DMSO) 2.56 (s, 3, CH_3), 4.78 (s, 2, C_6-H), 5.45 (s, 1, pyrazole H), 6.63 (s, 1, C_3-H), 7.1–7.5 (m, 4, aromatic H), ca. 11 (very broad s, 2, NH). Anal. ($C_{18}H_{13}ClN_6OS$) C, H, N.

4-[[5-[4-(2-Chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-2-yl]-2*H*-1,2,3-triazol-4-yl]carbonyl]morpholine (8). A mixture of 0.15 g of **3**, 5 mL of DMF, and 40 mg of sodium azide was stirred at room temperature for 2 h and then partitioned between 10% aqueous sodium carbonate solution and CH_2Cl_2. The aqueous phase was acidified with acetic acid and extracted several times with CH_2Cl_2. The extracts were dried and evaporated, at the end azeotropically with xylene, and the residue was crystallized and recrystallized from methanol/ethyl acetate to leave 120 mg (73%) of colorless crystals with mp 295–298 °C: ^{1}H NMR ($CDCl_3$ + 5 drops of DMSO) 2.66 (s, 3, CH_3), 3.5 (m, 8, morpholine), 4.83 (s, 2, C_6-H), 7.06 (s, 1, C_3-H), 7.2–7.5 (m, 4, aromatic H). Anal. ($C_{22}H_{19}ClN_8O_2S$) C, H, N.

4-(2-Chlorophenyl)-9-methyl-2-[(trimethylsilyl)ethynyl]-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (11). A mixture of 0.88 g (2 mmol) of **1b**,[1,4] 90 mg of triphenylphosphine, 20 mg of cuprous iodide, 1 mL of triethylamine, and 20 mL of DMF was stirred and degassed by argon for 10 minutes. (Trimethylsilyl)acetylene (0.4 mL) was added followed by 30 mg of palladium acetate and stirring at room temperature was continued for 4 h. The mixture was partitioned between CH_2Cl_2 and aqueous sodium bicarbonate. The organic layer was dried and evaporated, at the end azeotropically with xylene. The residue was chromatographed over 40 g of silica gel by using CH_2Cl_2 containing 5% of ethanol. Crystallization of the combined clean fractions from ethyl acetate/ether gave 0.5 g (60%) of crystals. This material was rechromatographed over 20 g of silica gel by using CH_2Cl_2/EtOAc 1:1 for elution. Crystallization from EtOAc/hexane gave off-white crystals with mp. 135–137 °C dec: ^{1}H NMR ($CDCl_3$) 0.18 (s, 9, $SiMe_3$), 2.66 (s, 3, Me), 4.89 (br s, 2, C_6-H), 6.72 (s, 1, C_3-H), 7.2–7.5 (4, aromatic H). Anal. ($C_{20}H_{19}ClN_4SSi$) C, H, N.

4-(2-Chlorophenyl)-2-ethynyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin (10). A mixture of 0.41 g (1 mmol) of **11**, 20 mL of ethanol and 2 mL of 2 N sodium hydroxide solution was stirred at room temperature under argon for 15 min. It was then partitioned between CH_2Cl_2 and saturated sodium bicarbonate solution. The organic layer was separated, dried, and evaporated, and the residue was chromatographed over 6 g of silica gel by using CH_2Cl_2 containing 5% of ethanol for elution. Crystallization of the combined clean fractions from

methanol/ethyl acetate gave 0.28 g (82%) of colorless crystals with mp 232–233 °C dec: ^{1}H NMR ($CDCl_3$) 2.7 (s, 3, Me), 3.39 (s, 1, acetylenic H), 4.93 (s, 2, C_6-H), 6.81 (s, 1, C_3-H), 7.2–7.5 (m, 4, aromatic H). Anal. ($C_{17}H_{11}ClN_4S$) C, H, N.

Method A. 2-[(4-Butylphenyl)ethynyl]-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (15). A mixture of 8.4 g (18.5 mmol) of 4-(2-chlorophenyl)-2-iodo-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine[1], 3.8 g (24 mmol) of (4-butylphenyl)ethyne, 0.78 g (3 mmol) of triphenylphosphine, 190 mg (1 mmol) of cuprous iodide, 20 mL of triethylamine, and 200 mL of DMF was stirred and degassed with a stream of argon for 10 min. Palladium acetate (230 mg, 1 mmol) was then added and stirring under argon was continued for 5 h. The reaction mixture was partitioned between aqueous sodium bicarbonate solution and CH_2Cl_2. The organic layer was dried and evaporated and the residue was chromatographed over silica gel by using 5% (v/v) of ethanol in CH_2Cl_2 for elution. Crystallization of the combined clean fractions from ether gave 6 g (69%) of off-white crystals with mp 140–143 °C: ^{1}H NMR ($CDCl_3$) 0.9 (t, 3, J = 6.5 Hz, CH_3), 1.1–1.7 (m, 4, CH_2CH_2), 2.58 (t, 2, J = 6.5 Hz, CH_2, 2.72 (s, 3, CH_3), 4.94 (s, 2, C_6-H), 6.78 (s, 1, C_3-H), 7–7.5 (m, 8, aromatic H). Anal. ($C_{27}H_{23}ClN_4S$) C, H, N.

Method A. 4-(2-Chlorophenyl)-9-methyl-2-(1-naphthalenylethynyl)-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (13). Compound **10** (0.34 g, 1 mmol) 0.38 g (1.5 mmol) of 1-iodonaphthalene, 45 mg of triphenylphosphine, 10 mg of cuprous iodide, 1 mL of triethylamine, and 10 mL of DMF was combined and degassed with argon for 10 min. Palladium acetate (15 mg) was added, and the mixture was stirred at room temperature for 2 h. It was poured onto ice and an aqueous sodium bicarbonate solution. The precipitate was filtered off, sucked dry, and dissolved in CH_2Cl_2. The solution was dried and evaporated, and the residue was chromatographed over 15 g of silica gel by using THF/hexane 4:1 for elution. The clean fractions were combined and evaporated and the product was crystallized from EtOAc/Et_2O/hexane to yield 0.32 g (68%) of solvated product with mp 133–136 °C. Recrystallization from EtOAc/hexane gave colorless crystals with mp 197–199 °C: ^{1}H NMR ($CDCl_3$) 2.7 (s, 3, Me), 4.95 (s, 2, C_6-H), 6.88 (s, 1, C_3-H), 7.3–8.3 (m, 11, aromatic H). Anal. ($C_{27}H_{17}ClN_4S$) C, H, N.

Method B. (*Z*)-2-[2-(4-Butylphenyl)ethenyl]-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (23). A mixture of 0.47 g (1 mmol) of **15**, 0.3 g of palladium on carbon (5%), 20 mL of ethanol, 10 mL of THF, and 1 mL of thiophene was hydrogenated at atmospheric pressure for 2 h. The catalyst was filtered off and the filtrate was evaporated. Crystallization of the residue from ether gave 0.3 g (63%) of product with mp 114–116 °C. The analytical sample was recrystallized from ether and had the same melting point): ^{1}H NMR ($CDCl_3$) 0.9 (t, 3, J = 6.5 Hz, CH_3), 1.1–1.7 (m, 4, CH_2CH_2), 2.45 (s, 3, CH_3), 2.57 (t, 2, CH_2), 4.85 (s, 2, C_6-H), 6.44 (d, 1) and 6.67 (d, 1)(AB-system, J = 12 Hz, olefinic H), 6.49 (s, 1, C_3-H), 7–7.5 (m, 8, aromatic H). Anal. ($C_{27}H_{25}ClN_4S$) C, H, N.

Method C. 2-[2-(4-Butylphenyl)ethyl]-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (27).[10] A mixture of 2 g of **15**, 1 g of palladium on carbon (5%), 50 mL of ethanol, and 25 mL of THF was hydrogenated at atmospheric pressure for 5 h. The catalyst was separated and the filtrate was evaporated. Crystallization of the residue from ethyl acetate/hexane gave 1.4 g (70%) of colorless crystals with mp 147–150 °C. The analytical sample was recrystallized from the same solvents and had mp 152–155 °C (lit.[10] mp 119–121 °C): ^{1}H NMR ($CDCl_3$) 0.91 (t, 3, J = 6.5 Hz, CH_3), 1.2–1.7 (m, 4, CH_2CH_2), 2.57 (t, 2, CH_2), 2.66 (s, 3, CH_3), 2.9 (t, 2) and 3.05 (t, 2) (J = 6.5 Hz, CH_2CH_2), 4.91 (s, 2, C_6-H), 6.35 (s, 1, C_3-H), 7.07 (m, 4, aromatic H, phenethyl), 7.25–7.5 (m, 4, aromatic H, chlorophenyl). Anal. ($C_{27}H_{27}ClN_4S$): C, H, N.

Method D. 2,3-Dihydro-5-iodo-1*H*-indene (36). A solution of 13.3 g (0.1 mol) of 5-aminoindan (**35**) in 100 mL of acetic acid and 10 mL of trifluoroacetic acid was cooled in ice water. Sodium nitrite (8 g, 0.116 mol) was added in portions within 5 min. After addition, the mixture was stirred for 15 min with cooling and for 5 min at room temperature. It was again cooled in ice water and 33 g (0.22 mol) of sodium iodide was added in 3 portions. After stirring on ice for 30 min, the mixture was diluted with water and extracted with hexane. The extracts were washed with aqueous sodium bisulfite solution, dried, and evaporated. The residue was chromatographed over silica gel by using hexane to give 10.6 g of colorless oil. A small sample was distilled in the kugelrohr: ^{1}H NMR ($CDCl_3$) 2.0 (m, 2, C_2-H), 2.83 (m, 4, C_1-H, C_3-H), 6.91 (d, 1, J = 8 Hz, C_7-H), 7.37 (d with fine structure, 1, J = 8 Hz, C_6-H), 7.5 (s with fine structure, 1, C_4-H). Anal. (C_9H_9I) C, H.

Method E. 5-Ethynyl-2,3-dihydro-1*H*-indene (41). A mixture of 9.76 g (0.04 mol) of **36**, 1.58 g (6 mmol) of triphenylphosphine, 0.38 g (2 mmol) of cuprous iodide, 20 mL of triethylamine, and 200 mL of acetonitrile was degassed with argon for 10 min. (Trimethylsilyl)acetylene (8.15 g, 0.08 mol) was added followed by 0.45 g (2 mmol) of palladium acetate. The mixture was stirred under argon for 2 h at room temperature. It was evaporated under reduced pressure, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried and evaporated. The residue was slurried with hexane, filtered, and evaporated. The crude product was dissolved in 200 mL of methanol and stirred with 2 g of potassium carbonate for 2 h at room temperature. The mixture was filtered and evaporated, and the residue was partitioned between hexane and water. The hexane layer was dried and evaporated, and the oil was chromatographed over silica gel by using hexane to give 3.3 g (58%) of colorless oil. A portion was distilled in the kugelrohr for analysis: ^{1}H NMR ($CDCl_3$) 2.05 (m, 2, C_2-H), 2.87 (m, 4, C_1-H, C_3-H), 2.98 (s, 1, acetylenic H), 7.11 (d, 1) and 7, 24 (d, 1) (AB-system, J = 8 Hz, C_6-H and C_7-H), 7.31 (s, 1, C_4-H). Anal. ($C_{11}H_{10}$) C, H.

Method F. 5-Iodo-2,3-dihydrobenzofuran (37). Iodine monochloride (32.5 g, 0.2 mol) was added to a solution of 24 g (0.2 mol) of 2,3-dihydrobenzofuran (**39**) in 100 mL of acetic acid. After stirring for 15 min at room temperature, the mixture was diluted with water and aqueous sodium bisulfite solution. The product was extracted with CH_2Cl_2, and the extracts were washed with sodium bicarbonate solution, dried, and evaporated. Crystallization of the residue from methanol yielded 37.6 g (76%) of product with mp 60–63 °C. The analytical sample was recrystallized from mehanol to leave colorless crystals with mp 64–65 °C: ^{1}H NMR ($CDCl_3$) 3.15 (t, 2, J = 8 Hz, C_3-H), 4.51 (t, 2, J = 8 Hz, C_2-H), 6.51 (d, 1, J = 8 Hz, C7-H), 7.32 (d with fine structure, 1, J = 8 Hz, C_6-H), 7.4 (s with fine structure, 1, C_4-H). Anal. (C_8H_7IO) C, H, N.

2-(5-Bromo-2-thienyl)pyridine (49). Bromine (16 g, 0.1 mol) was added to a solution of 8.05 g (0.05 mol) of 2-(2-thienyl)pyridine (**48**) in 250 mL of CH_2Cl_2. After stirring for 10 min, the reaction mixture was washed with 10% aqueous Na_2CO_3 solution, dried, and evaporated. Crystallization of the residue from ethanol gave 9.5 g of product with mp 85–87 °C. The analytical sample was recrystallized from ethanol and had the same melting point. Anal. (C_9H_6BrNS) C, H, N.

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Registry No. **1a**, 57801-81-7; 1b, 67860-41-7; **2**, 132464-59-6; **3**, 132464-60-9; **4**, 132464-61-0; **5**, 132464-62-1; **6**, 105219-56-5; **7**, 132491-37-3; **8**, 132464-63-2; **9**, 132464-64-3; **10**, 125031-31-4; 11, 125030-59-3; **12**, 125048-51-3; **13**, 125030-60-6; **14**, 125030-79-7; **15**, 132464-65-4; **16**, 132464-66-5; **17**·2HCl, 132464-67-6; **18**, 132464-68-7; **19**, 132464-69-8; **20**·2HCl, 132464-70-1; **21**, 132464-71-2; **22**, 132464-72-3; **23**, 132464-73-4; **24**, 132464-74-5; **25**, 132464-75-6; **26**, 132464-76-7; **27**, 117279-67-1; **28**, 117279-63-7; **29**·2HCl, 132464-77-8; **30**, 132464-78-9; **31**, 132464-79-0; **32**, 132464-80-3; **33**, 132464-81-4; **34**·2HCl, 132464-82-5; **35**, 24425-40-9; **36**, 132464-83-6; **37**, 132464-84-7; **38**, 132464-85-8; **39**, 496-16-2; **40**, 30590-60-4; **41**, 132464-86-9; **42**, 132464-87-0; **43**, 132464-88-1; **44a**, 2221-00-3; **45a**, 132464-89-2; **45b**, 20651-67-6; **47b**, 79887; **48**, 3319-99-1; **49**, 123784-07-6; **50**, 132464-90-5; PhC≡CH, 536-74-3; *i*-Bu-4-C_6H_4C≡CH, 132464-91-6; *c*-C_6H_{11}-4-C_6H_4C≡CH, 63327-42-4; 2-ethynylpyridine, 1945-84-2; 1-ethynylnaphthalene, 15727-65-8; 1-iodonaphthalene, 90-14-2; (trimethylsilyl)acetylene, 1066-54-2.