Oxazepines and Thiazepines, XXVII[1]:

Chemical Transformations of 2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one

Albert Lévai* and Zoltán Bálint[+]

Department of Organic Chemistry, Lajos Kossuth University, H-4010 Debrecen, Hungary

Received February 4, 1992

N-Alkyl (**2** - **11**) and *N*-acyl (**18** - **30**) derivatives of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (**1**) have been synthesized. 4-Alkyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thiones **12** - **15** arose from compounds **2**, **3**, **5**, and **6** with *Lawesson's* reagent. Bis-[2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-onyl]-alkanes **16** and **17** were prepared from **1** and dihaloalkanes.

Oxazepine und Thiazepine, 27. Mitt.: Umsetzungen des 2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-ons

N-Alkyl- (**2** bis **11**) und *N*-Acylderivate (**18** bis **30**) des 2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-ons (**1**) wurden hergestellt. Umsetzung der Verbindungen **2**, **3**, **5** und **6** mit *Lawessons* Reagenz führt zu den 4-Alkyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thionen **12** bis **15**. Die Bis-[2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-onyl]-alkane **16** and **17** entstanden bei der Umsetzung von **1** mit Dihaloalkanen.

Benzodiazepines and benzothiazepines played a prominent role in drug research during the last three decades: now the active ingredient of various well-known and popular medicines is either a benzodiazepine or a benzothiazepine derivative. However, benzoxazepines, their oxygen analogues, have hitherto gained less attention. Therefore, we synthesized new benzoxazepines of potential bioactivities by conversions of an easily accessible intermediate, 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (**1**) prepared from flavanone by several groups[2-6]. Formerly we have studied synthesis, stereochemistry, and some transformations of 2-aryl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones[5,7]. Here the synthesis of new 2,3-dihydro-1,4-benzoxazepines is reported.

N-Alkylations of 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones were performed either in the presence of TlOEt in dioxan[8] or with K_2CO_3 in acetone[9]. Because of the inconvenience of the use of a Tl-compound and since K_2CO_3 proved to be inadequate in our case, strong basic reaction conditions have been used for our *N*-alkylation experiments.

So, **1** reacted with the appropriate alkyl halide in anhydrous dimethylformamide NaH to afford the *N*-alkyl derivatives **2** - **9**. Compound **9** gave methyl and ethyl esters **10** and **11**. - Substances **2**, **3**, **5**, and **6** were converted into 4-alkyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thiones **12** - **15** with *Lawesson's* reagent. Bis-[2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-onyl]-alkanes **16** and **17** have been prepared by the above-mentioned *N*-alkylation method. Compound **1** was *N*-acylated with mesyl chloride and benzenesulfonyl chloride, respectively, under the same conditions to obtain substances **18** and **19**.

4-Acyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-ones have been prepared by various procedures. **1** was reacted with appropriate anhydrides and anhydrous pyridine to yield the *N*-acyl derivatives **20** - **23**. *N*-Chloroacyl compounds **24** and **25** have been obtained by acylation of **1** with chloroacetyl chloride and 3-chloropropionyl chloride, respectively.

Compounds **24** and **25** were allowed to react with thiophenols in anhydrous toluene/1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to yield the thioethers **26** - **30**. Such conversions may help to form side chains with functional groups which may enhance the bioactivities of the parent benzoxazepine molecule.

The structures of all new compounds have been established by ^{1}H-NMR spectroscopy and elemental analyses (Tables 1 and 2).

The present study was sponsored by the Hungarian Academy of Sciences (Grant No. OTKA-1723) for which our gratitude is expressed. Our thanks are due to Mrs. *M. Nagy* for her help in the experimental work.

Experimental Part

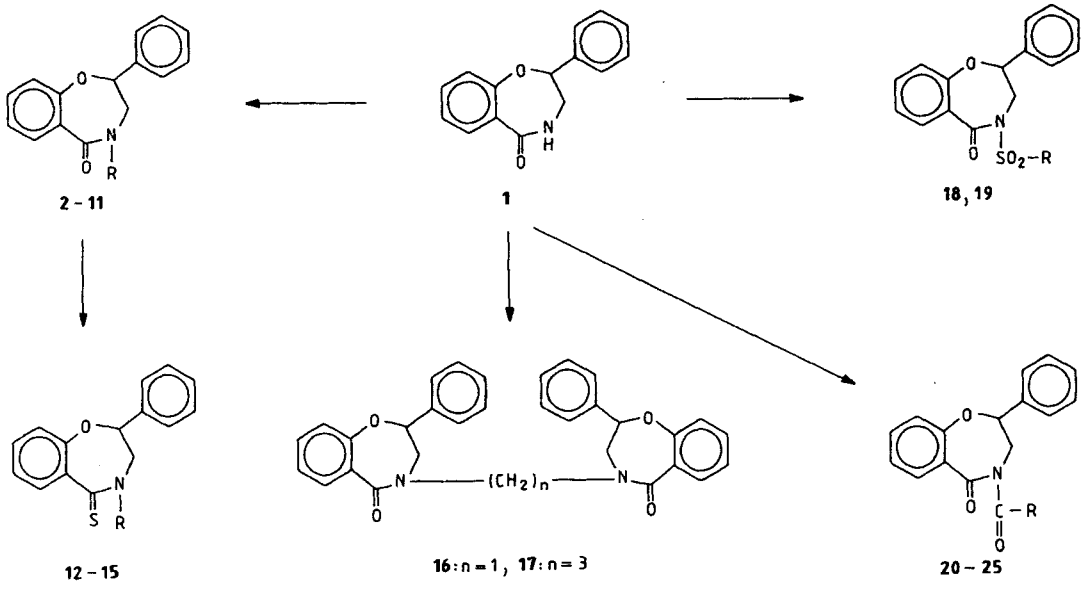
^{1}H-NMR spectra: Bruker WP 200 SY, 200 MHz, $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at room temp.- TLC: Kieselgel 60 F_{254} (Merck), hexane:acetone (7:3 v/v). **1** was prepared as described[5].- Physical constants, analyses data, and ^{1}H-NMR spectroscopic data: Tables 1 and 2.

4-Alkyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4H)-ones **2** - **9**

The appropriate alkyl halide (20.0 mmol) dissolved in anhydrous dimethylformamide (50 ml) was added to a stirred mixture of 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (**1**; 10.0 mmol), anhydrous dimethylformamide (50 ml), and NaH (1.0 g) at 0 °C. The mixture was stirred at room temp. for 16 h, diluted with water, and the precipitate was washed with water, and crystallized from MeOH to afford white crystalline substances **2** - **9**.

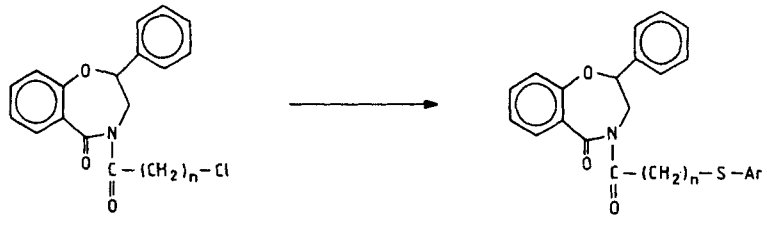
[+] Present address: Alkaloida Chemical Factory, H-4440 Tiszavasvári, Hungary

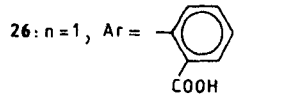
 © VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1993 0365-6233/93/0202-0073 $ 3.50 + .25/0

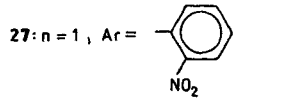


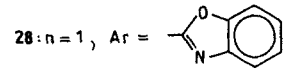
2: R = CH_3
3: R = C_2H_5
4: R = $CH(CH_3)_2$
5: R = $(CH_2)_3CH_3$
6: R = $CH_2C_6H_5$
7: R = CH_2CONH_2
8: R = $CH_2CONHC_6H_5$
9: R = $CH(CH_3)COOH$
10: R = $CH(CH_3)COOCH_3$
11: R = $CH(CH_3)COOC_2H_5$
12: R = CH_3
13: R = C_2H_5
14: R = $(CH_2)_3CH_3$
15: R = $CH_2C_6H_5$
18: R = CH_3
19: R = C_6H_5
20: R = CH_3
21: R = C_2H_5
22: R = $(CH_2)_2CH_3$
23: R = C_6H_5
24: R = CH_2Cl
25: R = $(CH_2)_2Cl$

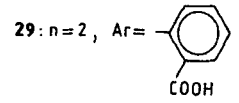
Scheme 1

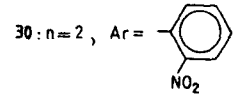












Scheme 2

Table 1: Physical constants and analytical data of compounds **2** - **30**

Compound	M.p. °C	Yield %	Overall formula	Analyses, % Cald. C	H	N	Found C	H	N
2	116-117	84	$C_{16}H_{15}NO_2$	75.87	5.97	5.52	75.63	5.64	5.54
3	127-128	91	$C_{17}H_{17}NO_2$	76.38	6.41	5.23	75.83	6.62	5.18
4	129-130	78	$C_{18}H_{19}NO_2$	76.84	6.80	4.97	76.37	6.67	4.90
5	90-91	74	$C_{19}H_{21}NO_2$	77.26	7.16	4.74	76.94	7.23	4.79
6	136-137	63	$C_{22}H_{19}NO_2$	80.22	5.81	4.25	80.44	5.72	4.26
7	103-104	57	$C_{17}H_{16}N_2O_3$	68.90	5.44	9.44	68.71	5.38	9.35
8	145-146	69	$C_{23}H_{20}N_2O_3$	74.18	5.41	7.51	74.61	5.39	7.60
9	202-203	62	$C_{18}H_{17}NO_4$	69.44	5.50	4.49	69.73	5.62	4.51
10	oil	76	$C_{19}H_{19}NO_4$	70.14	5.88	4.30	70.42	5.93	4.34
11	oil	81	$C_{20}H_{21}NO_4$	70.78	6.24	4.12	70.39	6.19	4.07
12	124-125	71	$C_{16}H_{15}NOS$	71.36	5.61	5.19	71.94	5.89	5.24
13	121-122	56	$C_{17}H_{17}NOS$	72.06	6.05	4.94	71.66	6.14	4.96
14	114-115	84	$C_{19}H_{21}NOS$	73.29	6.80	4.49	73.44	6.95	4.57
15	178-179	57	$C_{22}H_{19}NOS$	76.50	5.54	4.05	76.05	5.67	4.09
16	101-102	53	$C_{31}H_{26}N_2O_4$	75.26	5.34	5.71	75.74	5.27	5.61
17	93-94	46	$C_{33}H_{30}N_2O_4$	76.42	5.83	5.39	76.17	5.65	5.24
18	155-156	76	$C_{16}H_{15}NO_4S$	60.56	4.76	4.44	60.83	4.88	4.27
19	132-133	68	$C_{21}H_{17}NO_4S$	66.48	4.52	3.69	66.91	4.37	3.83
20	89-90	95	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.21	5.49	4.92
21	83-84	91	$C_{18}H_{17}NO_3$	73.19	5.80	4.74	73.50	5.82	4.81
22	78-79	68	$C_{19}H_{19}NO_3$	73.76	6.19	4.53	73.51	6.22	4.58
23	158-159[a]	63	$C_{22}H_{17}NO_3$	76.94	4.99	4.08	76.41	4.82	4.13
24	108-109[b]	97	$C_{17}H_{14}ClNO_3$	64.66	4.47	4.44	64.18	4.38	4.48
25	92-93	59	$C_{18}H_{16}ClNO_3$	65.55	4.89	4.25	65.95	4.98	4.27
26	164-165	51	$C_{24}H_{19}NO_5S$	66.49	4.42	3.23	66.55	4.54	3.21
27	146-147	47	$C_{23}H_{18}N_2O_5S$	63.58	4.17	6.45	63.91	4.33	6.40
28	123-124	44	$C_{24}H_{18}N_2O_4S$	66.95	4.21	6.51	66.43	4.28	6.59
29	145-146	61	$C_{25}H_{21}NO_5S$	66.59	4.69	3.11	66.17	4.60	3.15
30	140-141	52	$C_{24}H_{20}N_2O_5S$	64.27	4.49	6.25	64.59	4.61	6.15

Lit. m.p.[5] [a]158-159 °C, [b]108-109 °C

Esterification of compound **9**

A mixture of **9** (1.0 g), anhydrous methanol (50 ml) or anhydrous ethanol (50 ml), and conc. H_2SO_4 (2.0 ml) was refluxed for 5 h, then poured into water, and extracted with chloroform. The org. phase was washed with brine, dried with $CaCl_2$, and the solvent was evaporated: colourless oils of **10** and **11**.

4-Alkyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4H)-thiones **12** - **15**

A mixture of **2**, **3**, **5**, and **6** (10 mmol), *Lawesson's* reagent (5.0 mmol), and anhydrous toluene (50 ml) was refluxed for 4 h. Then the solvent was evaporated i.vac. and the residue crystallized from MeOH to obtain pale yellow crystals of **12** - **15**.

Table 2: ^{1}H-NMR spectroscopic data of compounds **2** - **30**

Compound	δ (ppm)
2	2.96 (s, 3H), 3.55 (dd, 1H, J_1=15.6 Hz, J_2=5.3 Hz), 3.70 (dd, 1H, J_1=15.6 Hz, J_2=5.3 Hz), 5.48 (t, 1H, J=7.1 Hz), 7.02-7.84 (m, 9 arom.)
3	1.12 (t, 3H, J=7.2 Hz), 3.12 (m, 1H), 3.64 (ABq, 2H), 3.74 (m, 1H), 5.46 (t, 1H, J=7.1 Hz), 7.00-7.85 (m, 9 arom.)
4	0.98 (d, 3H, J=6.7 Hz), 1.32 (d, 3H, J=6.7 Hz), 3.54 (m, 2H), 5.02 (m, 1H), 5.44 (dd, 1H, J_1=8.3 Hz, J_2=4.0 Hz), 6.96-7.88 (m, 9 arom.)
5	0.90 (t, 3H, J=7.2 Hz), 1.34 (m, 2H), 1.48 (m, 2H), 3.06 (m, 1H), 3.66 (ABq, 2H), 3.74 (m, 1H), 5.47 (dd, 1H, J_1=8.3 Hz, J_2=4.0 Hz), 6.98-7.86 (m, 9 arom.)
6	3.58 (m, 2H), 4.00 (d, 1H, J=14.7 Hz), 5.74 (m, 2H), 6.98-7.92 (m, 14 arom.)
7	3.55 (d, 1H, J=14.6 Hz), 3.87 (ABq, 2H), 4.46 (d, 1H, J=14.6 Hz), 5.60 (t, 1H, J=7.2 Hz), 6.48 (brs, NH_2), 7.04-7.86 (m, 9 arom.)
8	3.68 (d, 1H, J=14.8 Hz), 3.90 (ABq, 2H), 4.53 (d, 1H, J=14.8 Hz), 5.60 (t, 1H, J=5.3 Hz), 7.04-7.87 (m, 14 arom.), 8.78 (s, NH)
9	1.04 (d, 3H, J=7.1 Hz), 3.72 (m, 2H), 4.97 (m, 1H), 5.70 (m, 1H), 6.96-7.78 (m, 9 arom.)
10	1.05 (d, 3H, J=7.2 Hz), 3.71 (m, 2H), 3.76 (s, 3H), 5.38 (m, 1H), 5.65 (m, 1H), 6.92-7.89 (m, 9 arom.)
11	1.10 (d, 3H, J=7.3 Hz), 1.28 (t, 3H, J=7.4 Hz), 3.65 (m, 2H), 3.88 (m, 1H), 4.17 (m, 2H), 5.35 (m, 1H), 6.92-7.91 (m, 9 arom.)
12	3.37 (s, 3H), 3.77 (dd, 1H, J_1=14.8 Hz, J_2=4.3 Hz), 4.12 (dd, 1H, J_1=14.8 Hz, J_2=4.3 Hz), 5.57 (t, 1H, J=4.0 Hz), 6.96-8.07 (m, 9 arom.)
13	1.26 (t, 3H, J=7.6 Hz), 3.41 (m, 1H), 3.88 (m, 2H), 4.33 (m, 1H), 5.56 (t, 1H, J=7.2 Hz), 6.91-8.04 (m, 9 arom.)
14	0.93 (t, 3H, J=7.2 Hz), 1.32 (m, 2H), 1.71 (m, 2H), 3.47 (m, 1H), 3.86 (m, 2H), 4.26 (m, 1H), 5.56 (t, 1H, J=7.3 Hz), 6.90-8.00 (m, 9 arom.)
15	3.80 (d, 2H, J=5.7 Hz), 4.38 (d, 1H, J=14.7 Hz), 5.37 (t, 1H, J=7.4 Hz), 5.99 (d, 1H, J=14.7 Hz), 6.89-8.12 (m, 14 arom.)
16	4.08 (m, 4H), 4.86 (s, 2H), 5.59 (m, 2H), 7.01-7.80 (m, 18 arom.)
17	2.03 (m, 4H), 3.24 (m, 2H), 3.56 (m, 2H), 3.72 (m, 2H), 5.51 (t, 2H, J=7.2 Hz), 7.01-7.80 (m, 18 arom.)
18	3.23 (s, 3H), 4.27 (m, 2H), 5.61 (dd, 1H, J_1=8.2 Hz, J_2=3.1 Hz), 7.02-7.87 (m, 9 arom.)
19	4.17 (dd, 1H, J_1=15.9 Hz, J_2=8.5 Hz), 4.53 (dd, 1H, J_1=15.9 Hz, J_2=3.7 Hz), 5.68 (dd, 1H, J_1=8.6 Hz, J_2=3.7 Hz), 7.06-7.91 (m, 14 arom.)
20	2.61 (s, 3H), 3.96 (dd, 1H, J_1=15.3 Hz, J_2=3.6 Hz), 4.56 (dd, 1H, J_1=8.7 Hz, J_2=3.6 Hz), 5.46 (dd, 1H, J_1=8.7 Hz, J_2=3.6 Hz), 6.95-7.87 (m, 9 arom.)

Bis[2,3-dihydro-1-phenyl-1,4-benzoxazepin-5(4H)-onyl]-alkanes **16** *and* **17**

1 was reacted with CH_2I_2 or 1,3-dibromopropane as described for compounds **2** - **9** to yield white crystals of **16** and **17**.

Acylation of **1** *with mesyl chloride and benzene-sulfonyl chloride*

1 (5.0 mmol) was acylated with mesyl chloride (10 mmol) or benzenesulfonyl chloride (10 mmol) under conditions described for the preparation of **2** - **9** to afford compounds **18** and **19**.

N-Acyl-derivatives of **1** *(***20** - **23***) (***24** *and* **25***)*

A mixture of **1** (10 mmol), the appropriate carboxylic acid anhydride (30 mmol), and anhydrous pyridine (10 ml) was heated at 80 °C for 5 h and poured into water. The precipitate was washed with water and crystallized from MeOH to yield white crystals of **20** - **23**.- A mixture of **1** (10 mmol), chloroacetyl chloride (30 mmol) or 3-chloropropionyl chloride (30 mmol), K_2CO_3 (5.0 g), and anhydrous acetone (100 ml) was refluxed for 2 h, the inorganic salt filtered off and the solvent evaporated *i.vac.* The residue was crystallized from MeOH to obtain white crystals of **24** and **25**, respectively.

Table 2: continued

Compound	δ(ppm)
21	1.17 (t, 3H, J=7.1 Hz), 3.06 (q, 2H, J=7.1 Hz), 4.02 (dd, 1H, J_1=15.3 Hz, J_2=3.6 Hz), 4.57 (dd, 1H, J_1=8.8 Hz, J_2=3.6 Hz), 5.49 (dd, 1H, J_1=8.8 Hz, J_2=3.7 Hz), 6.97-7.90 (m, 9 arom.)
22	0.96 (t, 3H, J=7.3 Hz), 1.68 (m, 2H), 2.99 (t, 2H, J=7.7 Hz), 4.02 (dd, 1H, J_1=15.4 Hz, J_2=3.7 Hz), 4.54 (dd, 1H, J_1=8.4 Hz, J_2=3.7 Hz), 5.47 (dd, 1H, J_1=8.4 Hz, J_2=3.7 Hz), 6.97-7.90 (m, 9 arom.)
23	4.29 (dd, 1H, J_1=15.3 Hz, J_2=4.0 Hz), 4.59 (dd, 1H, J_1=7.3 Hz, J_2=4.0 Hz), 5.57 (dd, 1H, J_1=7.3 Hz, J_2=4.0 Hz), 7.06-7.85 (m, 14 arom.)
24	4.02 (dd, 1H, J_1=15.0 Hz, J_2=3.5 Hz), 4.63 (dd, 1H, J_1=8.5 Hz, J_2=3.5 Hz), 5.52 (dd, 1H, J_1=8.5 Hz, J_2=3.5 Hz), 6.98-7.87 (m, 9 arom.)
25	3.52 (m, 2H), 3.79 (m, 2H), 4.03 (dd, 1H, J_1=15.2 Hz, J_2=3.7 Hz), 4.56 (dd, 1H, J_1=8.5 Hz, J_2=3.7 Hz), 5.47 (dd, 1H, J_1=8.5 Hz, J_2=3.7 Hz), 6.98-7.88 (m, 9 arom.)
26	4.04 (dd, 1H, J_1=15.0 Hz, J_2=3.7 Hz), 4.52 (ABq, 2H), 4.57 (dd, 1H, J_1=8.8 Hz, J_2=3.7 Hz), 5.41 (dd, 1H, J_1=8.8 Hz, J_2=3.7 Hz), 6.98-8.12 (m, 13 arom.)
27	4.11 (dd, 1H, J_1=15.1 Hz, J_2=3.6 Hz), 4.52 (ABq, 2H), 4.56 (dd, 1H, J_1=8.3 Hz, J_2=3.6 Hz), 5.42 (dd, 1H, J_1=8.3 Hz, J_2=3.6 Hz), 7.00-8.50 (m, 13 arom.)
28	4.01 (dd, 1H, J_1=15.0 Hz, J_2=3.5 Hz), 4.67 (dd, 1H, J_1=8.9 Hz, J_2=3.5 Hz), 4.86 (ABq, 2H), 5.53 (dd, 1H, J_1=8.9 Hz, J_2=3.5 Hz), 7.00-7.92 (m, 13 arom.)
29	3.28 (m, 2H), 3.49 (m, 2H), 4.08 (dd, 1H, J_1=15.2 Hz, J_2=3.6 Hz), 4.57 (dd, 1H, J_1=8.5 Hz, J_2=3.6 Hz), 5.53 (dd, 1H, J_1=8.5 Hz, J_2=3.6 Hz), 6.97-8.14 (m, 13 arom.)
30	3.27 (m, 2H), 3.45 (m, 2H), 4.12 (dd, 1H, J_1=15.0 Hz, J_2=3.7 Hz), 4.54 (dd, 1H, J_1=8.2 Hz, J_2=3.7 Hz), 5.52 (dd, 1H, J_1=8.2 Hz, J_2=3.7 Hz), 6.99-8.26 (m, 13 arom.)

Thiophenol-ethers **26** - **30**

A mixture of **24** or **25** (5.0 mmol), respectively, anhydrous toluene (100 ml), the appropriate thiophenol (6.0 mmol), and DBU (0.8 ml) was stirred at room temp. for 24 h. Then the solvent was evaporated i.vac. and the residue crystallized from MeOH to afford compounds **26** - **30**.

References

1 Part XXVI: A. Lévai, T. Timár, L. Frank, and S. Hosztafi, Heterocycles, *34*, 1523 (1992).
2 I.M. Lockhart, Chem. Ind. (London) *1968*, 1844.
3 D. Misiti and V. Rimatori, Tetrahedron Lett. *1970*, 947.
4 D. Misiti and V. Rimatori, Ann. Ist. Super. Sanita *9*, 150 (1973); C.A. *81*, 37539 (1974).
5 A. Lévai and R. Bognár, Acta Chim. Acad. Sci. Hung. *97*, 77 (1978).
6 Gy. Litkei and T. Patonay, Acta Chim. Acad. Sci. Hung. *114*, 47 (1983).
7 H. Duddeck and A. Lévai, Arch. Pharm. (Weinheim) *316*, 100 (1983).
8 D. Huckle, I.M. Lockhart, and M. Wright, J. Chem. Soc., Perkin Trans. I *1972*, 2425.
9 T. Hashiyama, A. Watanabe, H. Inoue, M. Konda, M. Takeda, S. Murata, and T. Nagao, Chem. Pharm. Bull. *33*, 634 (1985).

[Ph70]