ONE-POT SYNTHESES OF NEW SPIRO- AND TRICYCLIC PYRIDAZINO[4,5-*c*]PYRIDAZINONES

Tetsuo Yamasaki, Yuji Yoshihara, Yoshinari Okamoto, Tadashi Okawara, and Mitsuru Furukawa*

Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-hon-machi, Kumamoto 862, Japan

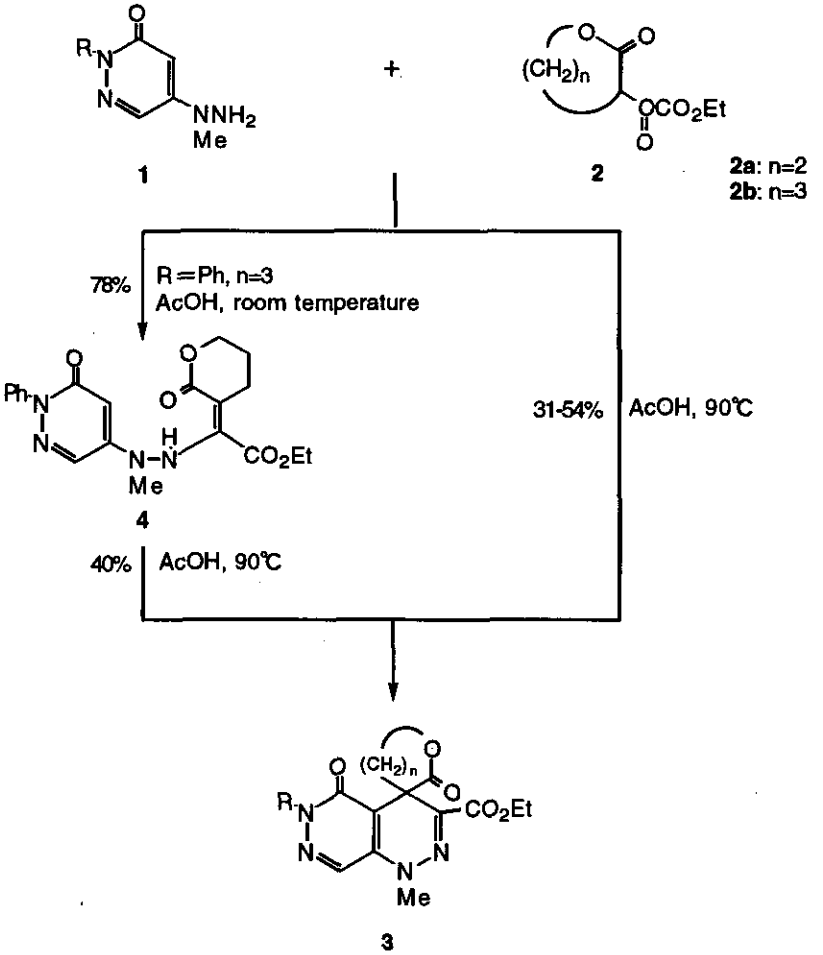
Abstract - New 1,4-dihydropyridazino[4,5-*c*]pyridazine-4-spiro-3'-lactones (**3**) were prepared by one-pot cyclization from 5-hydrazinopyridazinones (**1**), 4-bromo-5-hydrazinopyridazinones (**5**) and α-ethoxalyllactones (**2**). The reaction of **5** with 2-hydroxy-3,5-diethoxycarbonylcyclopent-2-en-1-one (**6**) afforded cyclopenteno[*c*]pyridazino[4,5-*c*]pyridazinone (**7**) and 12a, 13a-diethoxycarbonyl-5,8-dimethyl-1,2,5,8,11,12,12b,13a-octahydro-2,3,5,6,7,8,10,11-octaazadibenzo-[*a*,*i*]fluorene (**8**).

Fused pyridazinones have attracted much attention because of their potential biological and pharmacological activities.[1-3] In the preceding paper, we reported the preparation of 1,4-dihydropyridazino[4,5-*c*]pyridazinones from 5-hydrazinopyridazin-3(2*H*)-ones and α-keto diesters.[4] Recently Chiou reported that one of the 1,4-dihydropyridazino[4,5-*c*]pyridazinones showed pharmacological activity as a non-steroidal anti-inflammatory agent inhibiting endotoxin and interleukin-1 induced uvetis without relation to arachidonate metabolites.[5] The pyridazino[4,5-*c*]pyridazines[6-9] showing diuretic activity were reported, however, anti-inflammatory activity with the same ring system have been found for the first time. This report encouraged us to further study on the preparation of new heterocyclic ring systems containing 1,4-dihydropyridazino[4,5-*c*]pyridazine.

We describe here a one-pot synthesis of novel spiro-, tri- and pentacyclic compounds (**3**, **7** and **8**) by cyclization of 5-hydrazinopyridazinones (**1**) and 4-bromo-5-hydrazinopyridazinones (**5**) with α-ethoxalyl-

lactones (**2**) and 2-hydroxycarbonylcyclopent-2-en-1-one (**6**).

Reactions of **1** with **2a** and **2b** in acetic acid at 90°C gave the corresponding pyridazino[4,5-*c*]pyridazine-4-spiro-3'-lactones (**3a-g**) in 31-54% yields (Scheme 1). The results are shown in Tables 1 and 2. The structure of the product (**3**) was assigned by the analytical and spectral data. The ir spectra showed absorptions assignable to ester carbonyl group and lactone carbonyl group at 1760-1720 and 1710-1700 cm^{-1}, respectively. In the ^{1}H-nmr spectra, the methine signal of C-4 on the pyridazinone ring disappeared and the mass spectral data indicated the corresponding molecular ion peak. Moreover, the ^{13}C-nmr of **3b** exhibited the sp^3-quaternary carbon signal at δ 42.0. These data support the assigned structure for the product.



Scheme 1

In order to elucidate the formation pathway of spiro compounds (**3**) from **1** and **2**, the reaction of

compound (**1c**) with lactone (**2b**) was carried out under milder conditions in acetic acid at room temperature, and the dehydrated compound (**4**) was successfully isolated in 78% yield. Heating of **4** at 90°C in acetic acid provided compound (**3g**) in 40% yield. The ir spectrum of **4** showed a carbonyl absorption of lactone ring shifted long wavelength at 1660 cm^{-1} due to conjugation and the ^{1}H-nmr spectrum exhibited the NH signal shifted to the characteristic low-field at δ 9.92. On the basis of these spectral data, the low yield of the conversion of **4** into **3** is supposed to be difficult to approach the negatively charged carbon at C-4 on pyridazinone ring to the positively charged carbon at C-3 of lactone ring due to hydrogen bond between NH and carbonyl group of lactone moiety. Also, we tried the dehydrogenated cyclization of **4** in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or 5%-palladium carbon. But the increase of the yield of **3g** was not recognized.

Table 1: Data of pyridazino[4,5-*c*]pyridazine-4-spiro-3'-lactones (**3a-g**)

Compd No	R	n	Yield(%) (Yield from **5** and **2**)	Mp(℃) (solvent)	Formula	Analysis (%) Calcd. (Found) C H N
3a	H	2	31 (94)	294 (DMF)	$C_{13}H_{14}N_4O_5$	50.98 4.61 18.29 (50.88)(4.73)(18.40)
3b	Me	2	40 (69)	215 (MeOH)	$C_{14}H_{16}N_4O_5$	52.50 5.04 17.49 (52.05)(4.94)(17.19)
3c	Ph	2	54 (72)	188 (EtOH)	$C_{19}H_{18}N_4O_5$	59.68 4.75 14.65 (59.41)(4.79)(14.44)
3d	Bn	2	41 (68)	159-160 (EtOH)	$C_{20}H_{20}N_4O_5$	60.60 5.09 14.13 (60.57)(4.95)(14.23)
3e	H	3	32 (75)	268 (EtOH)	$C_{14}H_{16}N_4O_5$	52.50 5.04 17.49 (52.32)(5.09)(17.37)
3f	Me	3	39 (53)	222 (EtOH)	$C_{15}H_{18}N_4O_5$	53.89 5.43 16.76 (53.70)(5.28)(16.55)
3g	Ph	3	39 (55)	156 (EtOH-$^iPr_2O$)	$C_{20}H_{20}N_4O_5$	60.60 5.09 14.13 (60.46)(5.11)(13.91)

The spiro compounds (**3a-g**) were also obtained in 53-94% yields by the treatment of the bromo compounds (**5**) with **2** in acetic acid at room temperature (Scheme 2).

Furthermore, we examined the cyclization of hydrazinopyridazinones (**5**) with cyclopentenone (**6**) under the similar conditions. Many spots were observed on tlc. We were able to isolate the corresponding

cyclopentano[*c*]pyridazino[4,5-*c*]pyridazinones (**7a,b**) along with very low yield of pentacyclic compounds (**8a,b**) by silica gel column chromatography, but the other compounds could not be isolated (Scheme 3, Tables 3 and 4). In the ^{1}H-nmr spectra of **7a,b**, geminal coupling signals of methylene protons on cyclopentene ring were observed at δ 3.27, 3.64 (*J*=16.9 Hz) and at δ 3.32, 3.65 (*J*=16.2 Hz), respectively. On the other hand, those of **8a,b** exhibited the methylene signal at δ 3.11, 4.50 (*J*=14.7 Hz) and δ 3.20, 4.52 (*J*=15.0 Hz), respectively. This lower-field shift of the methylene protons on compound (**8**) seems to be caused by anisotropic effect of two ester carbonyl groups. Probably, the configuration of

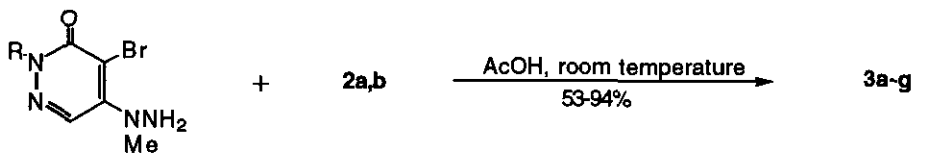
Table 2: Spectral data of pyridazino[4,5-*c*]pyridazine-4-spiro-3'-lactones (**3a-g**)

Compd No	Ir(cm^{-1}) (C=O)	Ms *m/z*	^{1}H-Nmr(solvent) δ, *J* (Hz)
3a	3140 1760 1700 1640	307 (M^++1)[a]	(DMSO-d_6) 1.24(3H, t, CH_3, *J*=7.2), 2.35(2H, t, CH_2, *J*=7.2), 3.60(3H, s, NCH_3), 4.00-4.80(4H, m, CH_2 x 2), 8.04(1H, s, CH=), 13.05(1H, s, NH)
3b[b]	1750 1700 1650	320 (M^+)	($CDCl_3$) 1.35(3H, t, CH_3, *J*=7.2), 2.41(2H, t, CH_2, *J*=7.8), 3.63(3H, s, NCH_3), 3.73(3H, s, NCH_3), 4.15-4.80(4H, m, CH_2 x 2), 7.66(1H, s, CH=)
3c	1755 1710 1650	382 (M^+)	($CDCl_3$) 1.36(3H, t, CH_3, *J*=7.2), 2.44(2H, t, CH_2, *J*=7.0), 3.67(3H, s, NCH_3), 4.15-4.90(4H, m, CH_2 x 2), 7.25-7.75(5H, m, Ph), 7.82(1H, s, CH=)
3d	1750 1705 1640	396 (M^+)	($CDCl_3$) 1.36(3H, t, CH_3, *J*=7.2), 2.41(2H, t, CH_2, *J*=7.0), 3.60(3H, s, NCH_3), 4.29-4.72(4H, m, CH_2 x 2), 5.18(1H, d, C<u>H</u>H, *J*=13.9), 5.35(1H, d, CH<u>H</u>, *J*=13.9), 7.27-7.38(5H, m, Ph), 7.66(1H, s, CH=)
3e	3140 1720 1705 1640	321 (M^++1)[a]	(DMSO-d_6) 1.25(3H, t, CH_3, *J*=7.2), 1.70-2.40(4H, m, CH_2 x 2), 3.63(3H, s, NCH_3), 4.00-4.90(4H, m, CH_2 x 2), 8.06(1H, s, CH=), 13.00(1H, s, NH)
3f	1720 1700 1640	334 (M^+)	(DMSO-d_6) 1.36(3H, t, CH_3, *J*=7.2), 1.80-2.50(4H, m, CH_2 x 2), 3.69(3H, s, NCH_3), 3.75(3H, s, NCH_3), 4.15-5.00(4H, m, CH_2 x 2), 7.70(1H, s, CH=)
3g	1715 1700 1650	396 (M^+)	(DMSO-d_6) 1.36(3H, t, CH_3, *J*=7.2), 1.80-2.50(4H, m, CH_2 x 2), 3.69(3H, s, NCH_3), 4.15-5.00(4H, m, CH_2 x 2), 7.20-7.80(5H, m, Ph), 7.87(1H, s, CH=)

[a]The parent ion was determined with CI-ms.

[b]**3b** had ^{13}C-nmr(DMSO-d_6): δ 14.1(CH_3), 39.9(NCH_3), 41.2(NCH_3 and CH_2), 42.0(C), 62.3(CH_2), 67.6 (CH_2), 113.3(C), 124.6(-CH_2=), 134.8(C), 135.8(C), 158.7(C=O), 162.7(C=O), 176.0(C=O).

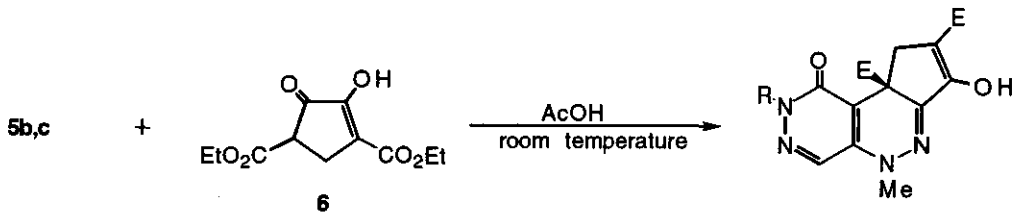
two ester carbonyl groups of **8** is assumed to be cis form.



5

5a: R=H
5b: R=Me
5c: R=Ph
5d: R=Bn

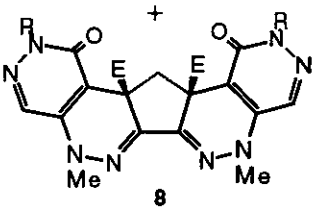
Scheme 2



6

7

7, 8	R	E
a	Me	CO_2Et
b	Ph	CO_2Et



8

Scheme 3

Table 3: Data of cyclopentano[*c*]pyridazino[4,5-*c*]pyridazinones (**7a,b**) and octaazadibenzo-[*a*, *i*]fluorenes (**8a,b**)

Compd No	R	E	Yield(%)	Mp(℃) (solvent)	Formula	Analysis (%) Calcd. (Found) C H N
7a	Me	CO_2Et	13	130 (CH_2Cl_2-$^iPr_2O$)	$C_{17}H_{20}N_4O_6$	54.25 5.36 14.89 (54.01)(5.38)(14.63)
7b	Ph	CO_2Et	34	114 (CH_2Cl_2-$^iPr_2O$)	$C_{22}H_{22}N_4O_6$	60.27 5.06 12.78 (59.99)(5.05)(12.70)
8a	Me	CO_2Et	2	298 (CH_2Cl_2-$^iPr_2O$)	$C_{23}H_{26}N_8O_6$	54.11 5.13 21.95 (54.08)(5.19)(21.90)
8b	Ph	CO_2Et	1	268 (DMF)	$C_{33}H_{30}N_8O_6$	62.45 4.77 17.66 (62.02)(4.68)(17.69)

Table 4: Spectral data of cyclopentano[*c*]pyridazino[4,5-*c*]pyridazinones (**7a,b**) and octaazadibenzo[*a*, *i*]fluorenes (**8a,b**)

Compd No	Ir(cm^{-1}) (C=O)	Ms (M^+) *m/z*	^{1}H-Nmr ($CDCl_3$) δ, *J* (Hz)	^{13}C-Nmr (solvent) δ
7a	1720 1660(sh) 1635	376	1.15(3H, t, CH_3, *J*=7.2), 1.32(3H, t, CH_3, *J*=7.2), 3.27(1H, d, CHH, *J*=16.9), 3.64(1H, d, CHH, *J*=16.9), 3.71(3H, s, NCH_3), 3.78(3H, s, NCH_3), 3.90-4.55(4H, m, CH_2 x 2), 7.77(1H, s, CH=), 10.00(1H, s, OH)	(DMSO-d_6) 13.7(CH_3), 14.2(CH_3), 35.9(CH_2), 39.1(NCH_3), 40.6(NCH_3), 59.8(OCH_2), 61.6(OCH_2), 104.5(C), 108.6(C), 126.0(CH), 137.8(C), 144.3 (C), 157.3(C), 158.6(C), 165.2(C), 169.1(C)
7b	1725 1670(sh) 1660(sh) 1635	438	1.16(3H, t, CH_3, *J*=7.2), 1.31(3H, t, CH_3, *J*=7.2), 3.32(1H, d, CHH, *J*= 16.2), 3.65(1H, d, CHH, *J*=16.2), 3.76(3H, s, NCH_3), 3.90-4.55(4H, m, CH_2 x 2), 7.20-7.70(5H, m, Ph), 7.94 (1H, s, CH=), 10.01(1H, s, OH)	(DMSO-d_6) 13.7(CH_3), 14.2(CH_3), 36.1(CH_2), 40.7(NCH_3), 43.7(C), 59.8 (OCH_2), 61.7(OCH_2), 104.9(C), 108.8 (C), 125.5(CH), 127.6(CH), 127.8 (CH), 128.5 (CH), 137.5(C), 141.3(C), 144.8 (C), 157.2(C), 158.3(C), 165.2 (C), 169.1(C)
8a	1730 1640	510	1.17(6H, t, CH_3 x 2, *J*=7.2), 3.11(1H, d, CHH, *J*=14.7), 3.69(6H, s, NCH_3 x 2), 4.10(4H, q, CH_2 x 2, *J*=7.2), 4.50(1H, d, CHH, *J*=14.7), 7.66(2H, s, CH=x 2)	($CDCl_3$) 13.9(CH_3), 39.8(NCH_3), 40.8(CH_2), 40.8(NCH_3), 47.6(C), 62.0(OCH_2), 107.1(C), 124.4(CH), 138.5(C), 141.6(C), 158.8(C), 169.3(C)
8b	1720 1655 1640(sh)	634	1.18(6H, t, CH_3 x 2, *J*=7.2), 3.20(1H, d, CHH, *J*=15.0), 3.75(6H, s, NCH_3 x 2), 4.13(4H, q, CH_2 x 2, *J*=7.2), 4.52(1H, d, CHH, *J*=15.0), 7.22-7.78 (10H, m, Ph x 2), 7.83(2H, s, CH= x 2)	(DMSO-d_6) 13.7(CH_3), 40.3(CH_2), 40.8(NCH_3), 47.6(C), 61.5(OCH_2), 105.9(C), 125.5(CH), 127.5(CH), 127.8(CH), 128.5(CH), 137.9(C), 140.4(C),141.2(C), 157.6(C), 169.2(C)

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO IRA-1 grating ir spectrophotometer. The ^{1}H- and ^{13}C-nmr spectra were measured with a HITACHI R-600 spectrometer and a JEOL JNM-GX 400 spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained with a JEOL JMS-DX 303 mass spectrometer.

The hydrazinopyridazinones (**1a-d**) and (**5a-d**) were prepared according to literature procedure.[10, 11]

General Procedure for the Preparation of Pyridazino[4,5-*c*]pyridazine-4-spiro-3'-lactones (3a-g) from 5-(1-Methylhydrazino)pyridazin-3(2*H*)-ones (1a-d) and α-Ethoxalyllactones (2a,b) ---- α-Ethoxalyllactone[12] (**2a,b**; 5 mmol) was added dropwise to a stirred solution of 5-(1-methylhydrazino)pyridazin-3(2*H*)-ones (**1a-d**; 5 mmol) in acetic acid (15 ml). The mixture

was heated at 90°C for 7 days. After evaporation of acetic acid under reduced pressure, the residue was purified by silica gel column chromatography using $CHCl_3$ / MeOH (20 : 1) as an eluent to give compounds (**3a-g**). Analytical samples were purified by recrystallization from appropriate solvent (Tables 1 and 2).

Dehydration of 5-(1-Methylhydrazino)-2-phenylpyridazin-3(2*H*)-one (1c) with α-Ethoxalyllactone (2b) ---- α-Ethoxalyl-δ-valerolactone (**2b**; 2.00 g, 10 mmol) was added dropwise to a stirred solution of 5-(1-methylhydrazino)-2-phenylpyridazin-3(2*H*)-one (**1c**; 2.16 g, 10 mmol) in acetic acid (20 ml) at room temperature. After stirring for seven days, water (400 ml) was poured into the reaction mixture and the aqueous solution was extracted with CH_2Cl_2 (80 ml x 6). The extract was dried over anhydrous magnesium sulfate and CH_2Cl_2 was evaporated *in vacuo*. The residue was recrystallized from EtOH / *n*-hexane to give the dehydrated compound (**4**). mp 182°C; Yield 3.10 g (78 %); ir (KBr) ν 3250 (NH), 1720, 1660, 1640 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$, TMS) δ 1.23 (3H, t, $OCH_2C\underline{H}_3$, *J*=7.2 Hz), 1.85-2.10 (2H, m, $OCH_2C\underline{H}_2CH_2$), 2.47 (2H, t, $OCH_2CH_2C\underline{H}_2$, *J*=6.9 Hz), 3.14 (3H, s, NCH_3), 4.10-4.43 (4H, m, $OC\underline{H}_2CH_2CH_2$ and $OC\underline{H}_2CH_3$), 6.02 (1H, d, CH=, *J* =1.9 Hz), 7.25-7.80 (5H, m, Ph), 7.98 (1H, d, CH=, *J*=1.9 Hz), 9.92 (1H, br, NH). Ms (EI): *m/z* 398 (M^+). *Anal.* Calcd for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.56; N, 14.06. Found: C, 60.02; H, 5.56; N, 13.99.

***Cyclization of Dehydrated Compound* (4)** ---- A solution of **4** (3.19 g, 8 mmol) in acetic acid (20 ml) was heated at 90 °C for 7 days. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give **3g** (1.36 g, 43 %).

General Procedure for the Preparation of 3a-g from 4-Bromo-5-(1-methylhydrazino)-pyridazin-3(2*H*)-ones (5a-d) and 2a,b ---- To a stirred solution of compound (**5**; 10 mmol) in acetic acid (20 ml) was added dropwise **2** (10 mmol) at room temperature. After being stirred for 3 days, the reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using $CHCl_3$ / MeOH (40 : 1) as an eluent to give compounds (**3a-g**) (Table 1).

General Procedure for the Preparation of Cyclopenteno[*c*]pyridazino[4,5-*c*]pyridazinones (7a,b) and 12a,13a-Diethoxycarbonyl-5,8-dimethyl-1,2,5,8,11,12,12b,13a-octahydro-2,3,5,6,7,8,10,11-octaazadibenzo[*a*,*i*]fluorenes (8a,b) ---- 2-Hydroxy-3,5-diethoxycarbonyl-cyclopent-2-en-1-one[13] (**6**; 2.42 g, 10 mmol) was added to a stirred solution of 4-bromo-5-(1-methyl-

hydrazino)pyridazinones (**5b,c**; 10 mmol) in acetic acid (20 ml) at room temperature. After stirring for 3 days, water (600 ml) was poured into the reaction mixture and the aqueous solution was extracted with CH_2Cl_2 (100 ml x 6). The extract was dried over anhydrous magnesium sulfate and the CH_2Cl_2 was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel using $CHCl_3$ /MeOH (60 : 1) as an eluent to give compounds (**7**) and (**8**). Analytical samples were purified by recrystallization from appropriate solvent (Tables 3 and 4).

REFERENCES

1. B. D. G. Haylor and P. H. G. Smith, Eur. Pat. Appl. EP 634, 413, 1995 (*Chem. Abstr.*, 1995, **122**, 214088).
2. D. A. Berry, L. L. Wotring, J. C. Drach, and L. B. Townsend, *Nucleosides Nucleotides*, 1994, **13**, 2001.
3. P. G. Baraldi, A. Bigoni, B. Cacciari, C. Caldari, S. Manfredini, and G. Spalluto, *Synthesis*, **1994**, 1158.
4. T. Yamasaki, Y. Yoshihara, Y. Okamoto, T. Okawara, and M. Furukawa, *J. Heterocycl. Chem.*, 1992, **29**, 1313.
5. G. C. Chiou, Q. S. Yao, and T. Okawara, *J. Ocular Pharmacol.*, 1994, **10**, 577.
6. P. Singh and S. P. Gupta, *Indian J. Med. Res.*, 1979, **69**, 804.
7. K. Nishikawa, H. Shimakawa, Y. Inada, Y. Shibuta, S. Kikuchi, S. Yurugi, and Y. Oka, *Chem. Pharm. Bull.*, 1976, **24**, 2057.
8. S. Yurugi and S. Kikuchi, Japan Kokai 73 34, 198, 1973 (*Chem. Abstr.*, 1973 **79**, 320739).
9. M. Hieda, K. Omura, and S. Yurugi, *Yakugaku Zasshi*, 1972, **92**, 1327.
10. T. Yamasaki, E. Kawaminami, T. Yamada, T. Okawara, and M. Furukawa, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 991.
11. K. Kaji, H. Nagashima, Y. Hirose, and H. Oda, *Chem. Pharm. Bull.*, 1985, **33**, 982.
12. G. M. Ksander, J. E. McMurry, and M. Johnson, *J. Org. Chem.*, 1977, **42**, 1180.
13. M. A. Giantnrco and P. Friedel, *Tetrahedron*, 1963, **19**, 2039.

Received, 16th January, 1996