SYNTHESIS AND THE SKRAUP REACTION OF AMINO-5 *H*-BENZOTHIOPYRANO[2,3-*b*]PYRIDIN-5-ONES

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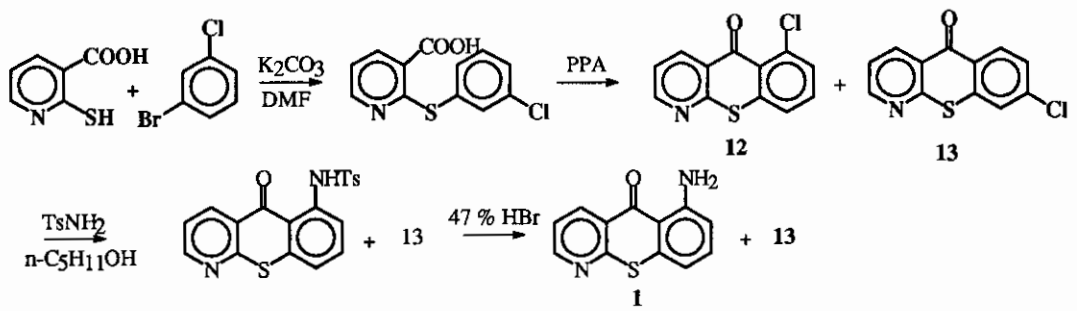
Abstract —— The new amino derivatives of 5 *H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one were synthesized. The Skraup reaction of these amino-5 *H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ones was conducted in the presence of glycerol, fuming sulfuric acid, nitrobenzene, iron (II) sulfate and boric acid. 6-Amino-, 7-amino-, 8-amino- and 9-Amino-5 *H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ones gave 12 *H*-pyrido[3',2':5,6]thiopyrano[2,3-*h*]quinolin-12-one, 12 *H*-pyrido[3',2':5,6]thiopyrano[3,2-*f*]quinolin-12-one, 7 *H*-pyrido[3',2':5,6]thiopyrano-[2,3-*f*]quinolin-7-one and 7 *H*-pyrido[3',2':5,6]thiopyrano-[3,2-*h*]quinolin-7-one, respectively.

In recent years, a number of heteroaromatic antitumor compounds have been prepared with the hope to increase their pharmacological properties or to find new derivatives with lowered side effects.[1-3] DNA intercalating agents, which are very important classes of antitumor drugs, usually possess planar aromatic and heteroaromatic polycyclic systems. Some thioxanthene derivatives are effective against tumors.[4-6] As an extension of our synthetic studies of thioxanthene derivatives, we have planned preparation of thioxanthene analogues consisting of tetracyclic system containing two pyridine ring. This paper describes the synthesis of some amino-5 *H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ones, 6-amino-(**1**), 7-amino-(**2**), 8-amino-(**3**), and 9-amino-5 *H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ones (**4**), and their Skraup reactions[7,8]

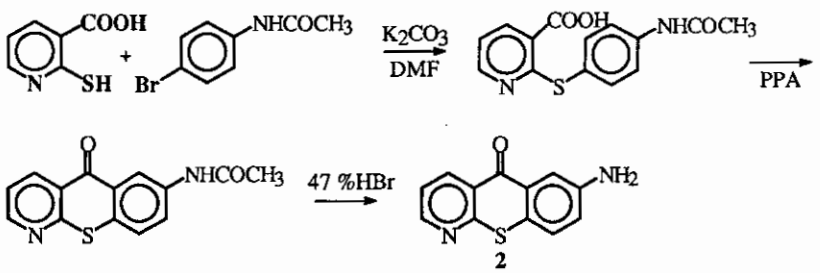
giving 12 *H*-pyrido[3′,2′:5,6]thiopyrano[2,3-*h*]quinolin-12-one(**6**), 12 *H*-pyrido-[3′,2′:5,6]thiopyrano[3,2-*f*]quinolin-12-one(**7**), 7 *H*-pyrido[3′,2′:5,6]thio-pyrano[2,3-*f*]quinolin-7-one(**8**), and 7 *H*-pyrido[3′,2′:5,6]thiopyrano[3,2-*h*]-quinolin-7-one(**9**).

RESULTS AND DISCUSSION

The synthesis of 6-amino-5 *H*-benzothiopyrano[2,3-*b*]pyridin-5-ones(**1**) was previously described (**Scheme 1**).[9]



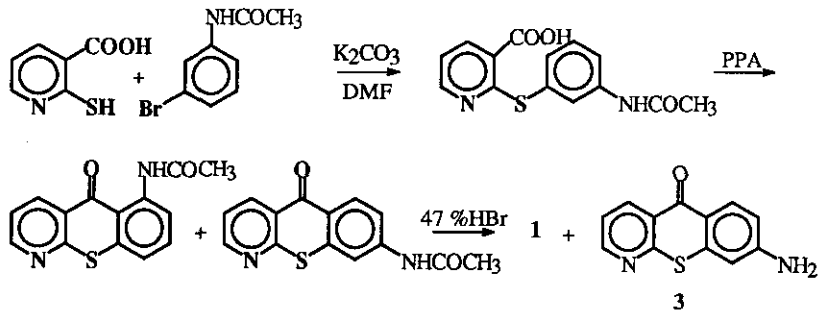
Scheme 1



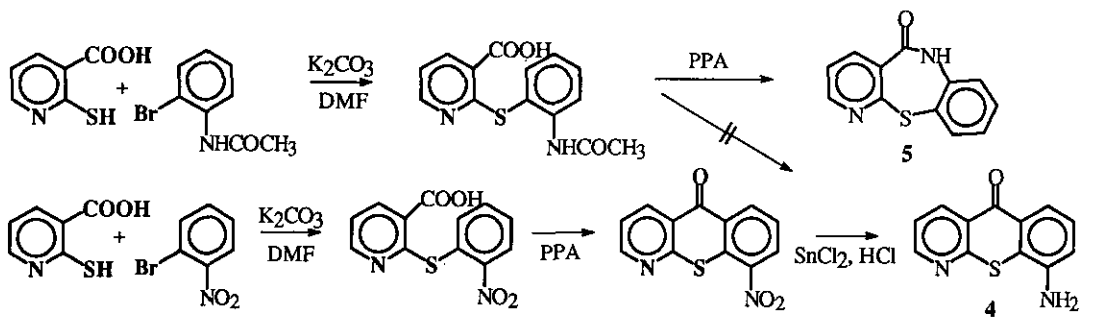
Scheme 2

The synthetic route of 7-amino-5 *H*-benzothiopyrano[2,3-*b*]pyridin-5-ones(**2**) was summarized in Scheme 2. The Ullmann reaction of 2-mercaptonicotinic acid with 4-bromoacetanilide in the presence with K_2CO_3 in dimethylformamide(DMF) under reflux for 14 h gave 2-(4-acetaminophenylthio)nicotinic acid . This was heated with polyphosphoric acid (PPA) at 120°C for 3 h and then hydrolyzed with hydrobromic acid

in the presence with phenol for 1 h to give 7-amino-5*H*-benzothiopyrano[2,3-*b*]-pyridin-5-ones (**2**). In a similar way, the reaction of 2-mercaptonicotinic acid with 3-bromoacetanilide afforded 2-(3-acetaminophenylthio)nicotinic acid, which was cyclized with PPA and then hydrolyzed with hydrobromic acid to give 5- (**1**) and 8-amino-5*H*-benzothiopyrano[2,3-*b*]pyridin-5-ones (**3**) (**Scheme 3**). 9-Amino-5*H*-benzothio-pyrano[2,3-*b*]pyridin-5-one (**4**) was synthesized by the Ullmann reaction of 2-mercaptonicotinic acid and 2-bromonitrobenzene in DMF, cyclization with PPA, and reduction. The reaction requirement from 2-mercaptonicotinic acid and 2-bromo-acetanilide gave pyrido[2,3-*b*][1,5]benzothiazepin-5-one in good yield, **4** being not produced (**Scheme 4**).



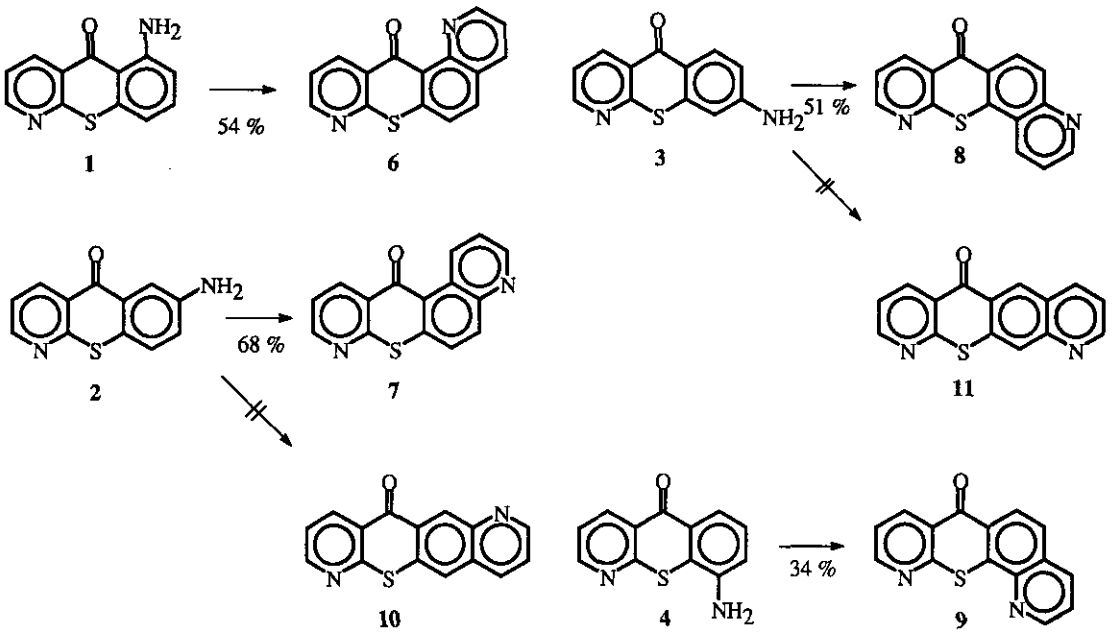
Scheme 3



Scheme 4

Skraup reactions of amino-5*H*-benzothiopyrano[2,3-*b*]pyridin-5-ones with glycerol, fuming sulfuric acid, and nitrobenzene were conducted in the presence of iron (II) sulfate and boric acid, and all products obtained were found to have the molecular

formula $C_{15}H_8N_2OS$ based on elemental analytical data and mass spectrum (ms) [*m/z* 264 ($M^{+\cdot}$)]. The Skraup reaction products were summarized in Scheme 5.



reaction condition: $H_2SO_4 \cdot SO_3$, nitrobenzene, $FeSO_4 \cdot 7H_2O$, H_3BO_3, 130°C, 5 h

Scheme 5

The Skraup reaction of **1** gave 12*H*-pyrido[3′,2′:5,6]thiopyrano[2,3-*h*]quinolin-12-one (**6**) in 54 % yield. The structure of **6** was determined by ^{1}H-nmr spectroscopy. The ^{1}H-nmr spectrum showed proton signals of the new pyridine ring at δ 7.54 (dd, *J*=4.4, 8.3 Hz, 3-H), δ 8.20 (dd, *J*=1.9, 8.3 Hz, 4-H) and δ 9.23 (dd, *J*=1.9, 4.4 Hz, 2-H) ppm, and proton signals of the 5*H*-benzothiopyrano[2,3-*b*]pyridin- 5-one skeleton at δ 7.67 (d, *J*=8.3 Hz, 6-H) and δ 7.98 (d, *J*=8.3 Hz, 5-H) ppm. The Skraup reaction of **2** afforded only 12*H*-pyrido[3′,2′:5,6]thiopyrano[3,2-*f*]quinolin-12-one (**7**) in 68% yield, another isomer, 12*H*-pyrido[3′,2′:5,6]thiopyrano[2,3-*g*]-quinolin-12-one (**10**) being not noticed at all. The ^{1}H-nmr spectrum of **7** demonstrated the new pyridine ring and two doublet proton signals of the 5*H*-benzothiopyrano-[2,3-*b*]pyridin-5-one skeleton as in the case of **2**. Similarly, the Skraup reaction

of **3** has possibility to give two products, 7*H*-pyrido[3',2':5,6]thiopyrano[2,3-*f*]quinolin-7-one (**8**) and 12*H*-pyrido[3',2':5,6]thiopyrano[3,2-*g*]quinolin-12-one (**11**). But that of **3** produced only product (**8**) in 51 % yield, and the structure of **8** was confirmed by the ^{1}H-nmr spectrum as the case of **7**. Based on the present results, the Skraup reaction of **3** affords the corresponding angular-type product (**8**) without the linear-type product (**11**). Skraup reaction of **4** gave 7*H*-pyrido[3',2':5,6]-thiopyrano[3,2-*h*]quinolin-7-one (**9**) in 34 % yield.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H-Nmr spectra were measured on a JEOL FX-400 instrument using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Ms were taken with a Hitachi RMU-7MG spectrometer.

7-Amino-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (2): A mixture of 2-mercaptonicotinic acid, 4-bromoacetoanilide, potassium carbonate, copper, cuprous iodide, and DMF was stirred at reflux for 14 h, cooled and filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and acidified with 10% hydrochloric acid. The resulting precipitate was collected and was heated with PPA at 130°C for 6 h. The hot solution was poured into ice-water. The resulting precipitate was collected, and heated with 47% hydrobromic acid and phenol at reflux for 2 h. After cooling, the mixture was alkalinized with 10% aqueous sodium hydroxide to give a yellow solid which was recrystallized from methanol to afford **2** (yield 54 %) as yellow needles (from MeOH), mp 256-257°C. *Anal*. Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.15; H, 3.45; N, 12.15. Ir (KBr): 1600, 1620 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 7.08 (1H, dd, J= 2.4, 8.3 Hz, 8-H), 7.40 (1H, dd, J=4.4, 8.3 Hz, 3-H), 7.47 (1H, d, J=8.3 Hz, 9-H), 7.86 (1H, d, J=2.4, 6-H), 8.77 (1H, dd, J=2.0, 4.4 Hz, 2-H), 8.83 (1H, dd, J=2.0, 8.3 Hz, 4-H). Ms: m/z 228 ($M^{+\cdot}$).

8-Amino-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (3): A mixture of **1** and **3** was prepared from 2-mercaptonicotinic acid and 3-bromoacetanilide in a manner similar to that described for the preparation of **2**. The obtained mixture was separated by silica gel column chromatography ($CHCl_3$) to afford **1** and **3**. Compound (**3**) : Yield 54 %. Yellow needles (from MeOH); mp 296-297°C. *Anal* . Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.03; H, 3.31; N, 12.11. Ir (KBr): 1585, 1620 cm^{-1}. ^{1}H-Nmr ($CDCl_3$)δ : 6.76 (1H, d, *J*= 2.0 Hz, 9-H), 6.78 (1H, dd, *J*=2.0, 8.3 Hz, 7-H), 7.39 (1H, dd, *J*=4.4, 8.3 Hz, 9-H), 8.42 (1H, d, *J*=8.3 Hz, 6-H), 8.72 (1H, dd, *J*=2.0, 4.4 Hz, 2-H), 8.80 (1H, dd, *J*=2.0, 8.3 Hz, 4-H). Ms: m/z 228 ($M^{+\cdot}$).

9-Amino-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (4): A mixture of 2-mercaptonicotinic acid, 2-bromonitrobenzene, potasium carbonate, copper, cuprous iodide in DMF was stirred under reflux for 14 h. After removal of solvent under reduced pressure, the residue was dissolved in hot water and then filtered. The filtrate was acidified with 10% hydrochloric acid. The resulting precipitate was collected by filtration, dried. The solid was cyclized with PPA to give 9-nitro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one. The nitro compound was dissolved in acetic acid and then added into stanic chloride in concentrate hydrochloric acid. the reaction mixture was heated on a steam bath for 1 h. After cooling, the reaction solution was poured into 10% sodium hydroxide. The precipitate were collected and recrystallized from methanol to give **4** (yield 54 %) as yellow needles, mp 285-286°C. *Anal* . Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.23; H, 3.43; N, 12.21. Ir (KBr): 1580, 1650 cm^{-1}. ^{1}H-Nmr($CDCl_3$)δ : 7.08 (1H, dd, *J*= 1.5, 8.3 Hz, 8-H), 7.38 (1H, t, *J*=8.3 Hz, 7-H), 7.45 (1H,dd, *J*=4.9, 7.8 Hz, 3-H), 8.11 (1H, dd, *J*=1.5, 7.8 Hz, 6-H), 8.80 (1H, dd, *J*=2.0, 4.4 Hz, 2-H), 8.84 (1H, dd, *J*=2.0, 7.8 Hz, 4-H). Ms: m/z 228 ($M^{+\cdot}$).

Pyrido[2,3-*b*][1,5]benzothiazepin-5-one(5): This compound was prepered from 2-mercaptonicotinic acid and 2-bromoacetanilide in a manner similar to that described for the preparation of **2**. Compound (**5**):Yield 76%. Pale yellow needles, mp 262-263°C.

Anal. Calcd for $C_{12}H_8N_2OS$: C,63.14; H, 3.53; N, 12.27. Ir (KBr): 1580, 1670 cm^{-1}. ^{1}H-Nmr ($CHCl_3$)δ : 6.74 (1H, dd, *J*=4.9, 7.8 Hz, 3-H), 6.78 (1H, t, *J*=7.8 Hz, 9-H), 7.23 (1H, t, *J*=7.8 Hz, 8-H), 7.37 (1H, dd, *J*=1.5, 7.8 Hz, 10-H), 8.23(1H, dd, *J*=2.0, 7.8 Hz, 4-H), 8.31 (1H, dd, *J*=2.0, 4.9 Hz, 2-H), 8.42 (1H, dd, *J*=1.5, *J*=8.3 Hz, 7-H), 10.72 (1H, s, 6-H). Ms: m/z 228 ($M^{+\cdot}$).

General procedure for the Skraup reaction of amino-5*H*-benzothiopyrano[2,3-*b*]-pyridin- 5-ones (1-4)

A mixture of H_2SO_4 SO_3 (6.0 g, 50 mmol), nitrobenzene (1.23 g, 10 mmol), $FeSO_4$ $7H_2O$ (0.28 g, 1.0 mmol), and H_3BO_3 (0.31 g, 5.0 mol) was chilled to 0-5°C, and glycerol (1.84 g, 20 mmol), amino-5*H*-benzothiopyrano[2,3-*b*]pyridin-5-one (1.06 g, 5 mmol) and water (2.5 ml) were successively added. The mixture was heated at 130°C for 5 h. The reaction mixture was neutralized with 28 % NH_4OH and the resulting precipitate was collected by filtration, and the precipitate extracted with $CHCl_3$. The extract was dried over Na_2SO_4, the solvent was evaporated and the residue was recrystallized from MeOH to give the corresponding pyrido[3',2':5,6]thiopyrano-quinoline derivative.

12*H*-Pyrido[3',2':5,6]thiopyrano[2,3-*h*]quinolin-12-one(6): Pale yellow needles, mp 166-167°C. Yield 54 %. *Anal*. Calcd for $C_{15}H_8N_2OS$: C, 68.17; H, 3.05; N, 10.60. Found: C, 67.68; H, 3.13; N, 10.45. Ir (KBr): 1580, 1600, 1640 cm^{-1}. ^{1}H-Nmr($CDCl_3$)δ : 7.50 (1H, dd, *J*=4.4, 8.1 Hz, 10-H), 7.54 (1H, dd, *J*=4.4, 8.3 Hz, 3-H), 7.67 (1H, d, *J*=8.6 Hz, 6-H), 7.98 (1H, d, *J*=8.6 Hz, 5-H), 8.20 (1H, dd, *J*=1.9, 8.3 Hz, 4-H), 8.79 (1H, dd, *J*=1.9, 4.4 Hz, 9-H), 8.85 (1H, dd, *J*=1.9, 8.1 Hz, 11-H), 9.23 (1H, dd, *J*=1.9, 4.4 Hz, 2-H). Ms: m/z 264 ($M^{+\cdot}$).

12*H*-Pyrido[3',2':5,6]thiopyrano[3,2-*f*]quinolin-12-one(7): Pale yellow needles, mp 226-227°C. Yield 69 %. *Anal*. Calcd for $C_{15}H_8N_2OS$: C, 68.17; H, 3.05; N, 10.60. Found: C, 68.24; H, 2.88; N, 10.55. Ir (KBr): 1580, 1600, 1620 cm^{-1}. ^{1}H-Nmr($CDCl_3$)δ : 7.55 (1H, dd, *J*=4.4, 8.3 Hz, 10-H), 7.66 (1H, dd, *J*=4.4, 8.8 Hz,

2-H), 7.86 (1H, d, J=8.8 Hz, 6-H), 8.37 (1H, d, J=8.8 Hz, 5-H), 8.84 (1H, dd, J=2.0, 4.4 Hz, 9-H), 8.89 (1H, dd, J=2.0, 8.3 Hz, 11-H), 9.00 (1H, d, J=1.0, 4.4 Hz, 3-H), 10.27 (1H, d, J=1.0, 8.8 Hz, 1-H). Ms: m/z 264 ($M^{+\cdot}$).

7*H*-Pyrido[3',2':5,6]thiopyrano[2,3-*f*]quinolin-7-one (8): Pale yellow needles, mp 260-261°C. Yield 51 %. *Anal*. Calcd for $C_{15}H_8N_2OS$: C, 68.17; H, 3.05; N, 10.60. Found: C, 68.45; H, 3.14; N, 10.53. Ir (KBr): 1580, 1600, 1640 cm^{-1}. ^{1}H-Nmr($CDCl_3$)δ : 7.54 (1H, dd, J=4.4, 7.8 Hz, 9-H), 7.64 (1H, dd, J=4.4, 8.8 Hz, 2-H), 8.15 (1H, d, J=8.8 Hz, 5-H), 8.78 (1H, d, J=8.8 Hz, 6-H), 8.82 (1H, dd, J=2.0, 8.8 Hz, 1-H), 8.88 (1H, dd, J=2.0, 4.4 Hz, 10-H), 8.90 (1H, dd, J=2.0, 7.8 Hz, 8-H), 9.13 (1H, dd, J=2.0, 4.4 Hz, 3-H). Ms: m/z 264 ($M^{+\cdot}$).

7*H*-Pyrido[3',2':5,6]thiopyrano[3,2-*h*]quinolin-7-one (9): Pale yellow needles, mp 245-246°C. Yield 34 %. *Anal*. Calcd for $C_{15}H_8N_2OS$: C, 68.17; H, 3.05; N, 10.60. Found: C, 67.79; H, 2.77; N, 10.57. Ir (KBr): 1580, 1600, 1630 cm^{-1}. ^{1}H-Nmr (acetone-d_6) δ : 7.68 (1H, d, J=8.8 Hz, 5-H), 7.85(1H, dd, J=4.2, 8.3 Hz, 3-H), 8.07 (1H, d, J=8.8 Hz, 5-H), 8.56 (1H, dd, J=1.7, 8.3 Hz, 4-H), 8.58 (1H, d, J=8.8 Hz, 6-H), 8.86 (1H, dd, J=2.0, 8.1 Hz, 8-H), 8.95 (1H, dd, J=2.0, 4.4 Hz, 10-H), 9.11 (1H, dd, J=1.7, 4.2 Hz, 2-H). Ms: m/z 264 ($M^{+\cdot}$).

REFERENCES

1. W. A. Denny, B. F. Cain, G. J. Atwell, C. Hansch, A. Panthananickal, and A. Leo, *J. Med. Chem.*, 1982, **25**, 276.
2. I. Antonini and S. Martelli, *J. Heterocycl. Chem.*, 1992, **29**, 471.
3. W. M. Cholody, S. Martelli, and J. Konopa, *J. Med. Chem.*, 1992, **35**, 378.
4. S. Archer, L. Pica-Mattoccia, D. Cioli, A. Seyed-Mozaffari, and A.-H. Zayed, *J. Med. Chem.*, 1988, **31**, 254.
5. H. D. H. Showalter, M. M. Angelo, E. M. Berman, G. D. Kanter, D. F.Ortwine, S. G. Ross-Kesten, A. D. Sercel, W. R. Turner, L. M. Werbel, D. F. Worth, E. F. Elslager,

W. R. Leopold, and J. L. Shillis, *J. Med. Chem.*, 1988, **31**, 1527.

6. S. Archer, K. J. miller, R. Rej, C. Periana, and L. Fricker, *J. Med. Chem.*, 1982, **25**, 220.

7. I. Takeuchi, Y. Hamada, and K. Okamura, *Heterocycles*, 1989, **29**, 2109.

8. I. Takeuchi and Y. Hamada, *Chem. Pharm. Bull.*, 1976, **24**, 1813.

9. H. Fujiwara and I. Okabayashi, *Heterocycles*, 1993, **36**, 1105.

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