Synthesis of 5-Chloro-2-methyl-3-(5-methylthiazol-2-yl)-4(3*H*)-quinazolinone and Related Compounds with Potential Biological Activity [1]

Cyril Párkányi and Duran S. Schmidt [2]

Department of Chemistry and Biochemistry, Florida Atlantic University, 777 Glades Road, P.O. Box 3091, Boca Raton, FL 33431-0991

Received February 16, 1999

Dedicated to the memory of Professor Raymond N. Castle

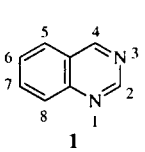
Eight new 2-methyl-4(3*H*)-quinazolinones (**8a-8d, 9c, 9d, 10c, 10d**) with one or two chlorine atoms in the benzene ring and a 5-methyl-1,3-thiazol-2-yl, 4-methyl-1,3-thiazol-2-yl, and 5-ethyl-1,3,4-thiadiazol-2-yl substituent in position 3 of the heterocyclic ring were synthesized and characterized. The two step procedure (Scheme 1) utilizes chlorosubstituted anthranilic acids (**3a-3d**) and acetic anhydride as the starting materials, with the respective chlorosubstituted 2-methyl-4*H*-3,1-benzoxazin-4-ones (**4a-4d**) as the intermediates. The quinazoline derivatives were characterized by their melting points, elemental analyses and the mass, ultraviolet, infrared, and ^{1}H and ^{13}C nmr spectra. The new compounds are expected to be biologically active.

J. Heterocyclic Chem., **37**, 725 (2000).

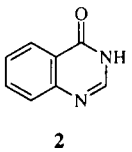
Introduction.

As a continuation of our systematic studies of quinazolines devoted to the various aspects of their chemistry [3-13], we have decided to synthesize a series of novel 3-substituted 2-methyl-4(3*H*)-quinazolinones, with one or two chlorine substituents in the benzene ring and a substituted 1,3-thiazole (referred to as thiazole throughout the text) or 1,3,4-thiadiazole in position 3. This contribution represents a follow-up on our previous work on halosubstituted 4(3*H*)-quinazolinones [13].

Quinazoline (**1**) is an interesting and important aromatic heterocyclic system. Several quinazoline alkaloids are known [6] and 4(3*H*)-quinazolinone (**2**) is an alkaloid [14,15]. Substituted 4(3*H*)-quinazolinones possess a wide range of pharmacological activities. 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone is a potent hypnotic agent and other 4(3*H*)-quinazolinones have been reported to exhibit analgesic, anesthetic, antibacterial, anticancer, anticonvulsant, antihypertensive, anti-inflammatory, antimalarial and antiparasitic, antiviral, bronchodilator, diuretic, muscle relaxant, sedative, and tranquilizing properties (for selected examples, see refs. [16-24]). Several additional studies of quinazolines can be mentioned [25-30].



1



2

Substituted thiazoles and 1,3,4-thiadiazoles are also of interest as biologically active compounds [31-34], with examples of existing applications including their use as fungicides and antibacterial, anticancer, and antiulcer drugs [35-39].

In the present contribution, we describe eight new chlorosubstituted (thiazol-2-yl)- and (1,3,4-thiadiazol-2-yl)-4(3*H*)-quinazolinones, from the respective chloroanthranilic acids (**3a-3c**) and 3,5-dichloroanthanilic acid (**3d**) and acetic anhydride, *via* the intermediate chlorosubstituted 2-methyl-4*H*-3,1-benzoxazin-4-ones (**4a-4d**) which reacted with 2-amino-5-methylthiazole (**5**), 2-amino-5-methylthiazole (**6**), and 2-amino-5-ethyl-1,3,4-thiadiazole (**7**) to yield the desired substituted quinazolines (**8a-8d, 9c, 9d, 10c, 10d**).

Results and Discussion.

Eight new 4(3*H*)-quinazolinones prepared in this work were obtained from chlorosubstituted anthranilic acids and acetic anhydride, through the previously described intermediate substituted 4*H*-3,1-benzoxazinones [40-45] which were reacted with aminosubstituted thiazole and 1,3,4-thiadiazole derivatives. Two alternate mechanisms for the reaction were suggested [46,47].

The new compounds have well-defined melting points (Table 1) and their structures were established on the basis of their elemental analyses and mass spectral data (Table 2). The infrared spectra of the quinazolines contain characteristic aromatic C-H stretching frequencies at 3074-3240 cm^{-1} (m-s), alkyl C-H stretching frequencies at 2905-2999 cm^{-1} (m), carbonyl group C=O stretching frequencies at 1649-1703 cm^{-1} (s), characteristic C=N stretching frequencies at 1520-1550 cm^{-1} (s), and aromatic substitution frequencies at 763-810 cm^{-1} (s) (Table 3). As a rule, the electronic spectra of the new compounds typically contain two strong absorption bands, at 215-235 nm and at 240-285 nm, respectively, with a third, weaker absorption band at 324 nm in the case of two dichloro derivatives, **8d** and **10d** (Table 3). The ^{1}H and ^{13}C nmr spectra are in agreement with the proposed structures (Table 4). Thus, the ^{1}H nmr spectrum of 5-chloro-2-methyl-3-(5-methylthiazol-2-yl)-4(3*H*)-quinazolinone (**8a**)

Scheme 1

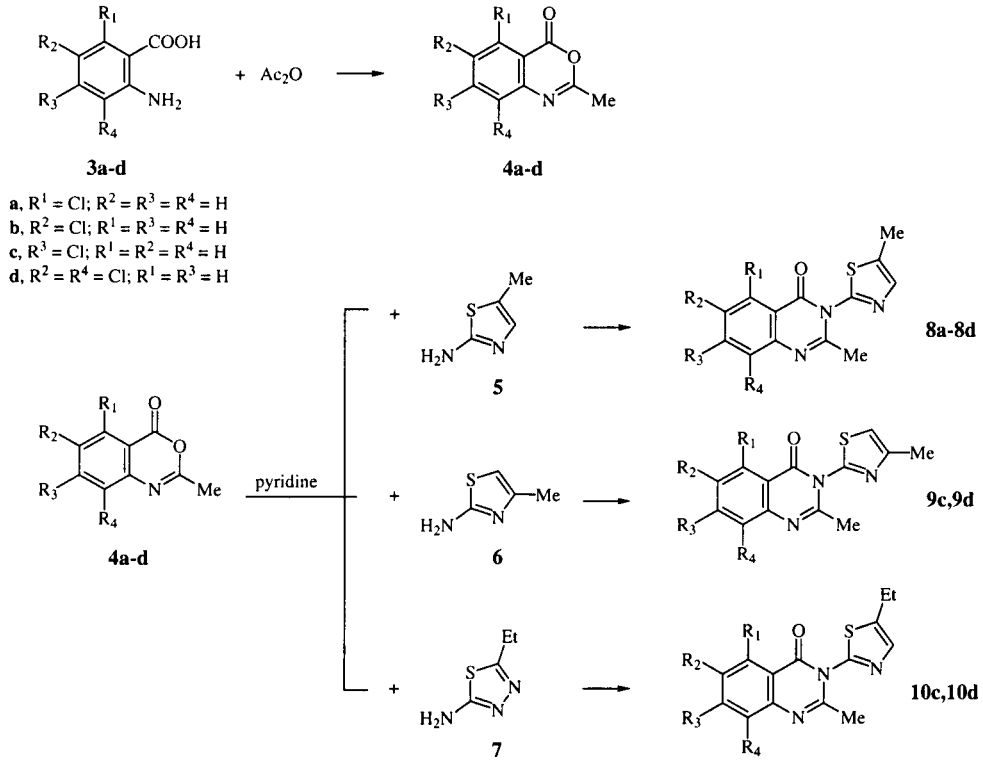


Table 1

Synthesized Substituted 2-Methyl-4(3*H*)-quinazolinones

Compound No.	Substituents [a]	Molecular formula (mol wt)		M.P.	Yield, %
8a	5-Cl-3-(5-MT)	$C_{13}H_{10}ClN_3OS$	(291.8)	217-220	55
8b	6-Cl-3-(5-MT)	$C_{13}H_{10}ClN_3OS$	(291.8)	227-229	42
8c	7-Cl-3-(5-MT)	$C_{13}H_{10}ClN_3OS$	(291.8)	188-190	29
8d	6,8-diCl-3-(5-MT)	$C_{13}H_9Cl_2N_3OS$	(326.2)	165-167	39
9c	7-Cl-3-(4-MT)	$C_{13}H_{10}ClN_3OS$	(291.8)	183-186	47
9d	6,8-diCl-3-(4-MT)	$C_{13}H_9Cl_2N_3OS$	(326.2)	187-190	51
10c	7-Cl-3-(5-ETD)	$C_{13}H_{11}ClN_4OS$	(306.8)	220-223	52
10d	6,8-diCl-3-(5-ETD)	$C_{13}H_{10}C_{l2}N_4OS$	(341.2)	174-177	38

[a] Abbreviations: 5-MT 5-methylthiazol-2-yl; 4-MT 4-methylthiazol-2-yl; 5-ETD 5-ethyl-1,3,4-thiadiazol-2-yl.

Table 2

Analytical Data on Substituted 3-Methyl-4(3*H*)-quinazolinones

Compound No.	Molecular formula (mol. wt.)	Analysis, calcd. (found), % C	H	Cl	N	S	Mol. ion, M^+ [a]
8a	$C_{13}H_{10}ClN_3OS{\cdot}H_2O$	50.40	3.90	11.44	13.56	10.35	291 [b]
	(309.8)	(50.28)	(3.84)	- [c]	(13.32)	- [c]	
8b	$C_{13}H_{10}ClN_3OS{\cdot}H_2O$	50.40	3.90	11.44	13.56	10.35	291 [b]
	(309.8)	(50.52)	(3.76)	(10.73)	(13.48)	(10.04)	
8c	$C_{13}H_{10}ClN_3OS{\cdot}H_2O$	50.40	3.90	11.44	13.56	10.35	291 [b]
	(309.8)	(50.15)	(3.59)	- [c]	(13.29)	- [c]	
8d	$C_{13}H_9Cl_2N_3OS$	47.87	2.78	21.74	12.88	9.83	-
	(326.2)	(48.15)	(2.55)	(21.62)	(12.85)	(9.61)	
9c	$C_{13}H_{10}ClN_3OS{\cdot}H_2O$	50.40	3.90	11.44	13.56	10.35	291 [b]
	(309.8)	(50.34)	(3.54)	- [c]	(12.98)	- [c]	

Table 2 (continued)

Compound No.	Molecular formula (mol. wt.)	Analysis, calcd. (found), % C	H	Cl	N	S	Mol. ion, M^+ [a]
9d	$C_{13}H_9Cl_2N_3OS$ (326.2)	47.87 (47.87)	2.78 (2.60)	21.74 (21.60)	12.88 (12.97)	9.83 (10.18)	-
10c	$C_{13}H_{11}ClN_4OS \cdot H_2O$ (324.8)	48.13 (47.97)	4.02 (3.90)	10.95 (10.80)	17.39 (17.34)	9.90 (9.47)	306 [d]
10d	$C_{13}H_{10}Cl_2N_4OS$ (341.2)	[e]					340

[a] Mass spectrum. Complete information on the mass spectra is available upon request. [b] For $C_{13}H_{10}ClN_3OS$ (291.8). [c] Not determined. [d] For $C_{13}H_{11}ClN_4OS$ (306.8). [e] Mass spectrum, important fragments, m/z: 342 (M^+ +2, relative intensity 8), 340 (M^+, molecular ion, 11), 285 (340 - EtCN from 2-ethyl-1,3,4-thiadiazole 96), 258 (285 - MeC, 21), 227 (340 - EtC_2N_2S from 2-ethyl-1,3,4-thiadiazole, base peak, 100), 212 (227 - Me, 15), 200 (212 - C, 9).

exhibits two singlets corresponding to the two methyl groups, at δ 1.97 ppm (3H) and 2.38 ppm (3H), respectively, a singlet at 7.16 ppm (1H), corresponding to H-5 in the thiazole ring, and a doublet at 7.34 ppm (1H), a triplet at 7.43 ppm (1H), and a second doublet at 7.60 ppm (1H) belonging to the three protons in the benzene ring, H-6, H-7, and H-8.

Also, the mass spectra of the synthesized quinazolines are consistent with their proposed structures (Table 2). For example, the principal fragments in the mass spectrum of 6-chloro-2-methyl-3-(5-methylthiazol-2-yl)-4(3*H*)-quinazolinone (**8b**) are at m/z 293 (M^+ + 2, rel. intensity 37); 291 (M^+, molecular ion and base peak, 100); 276 (291 - Me, 3);

Table 3

Infrared and Ultraviolet Absorption Spectra of the Quinazolines

Compound No.	Infrared spectrum, $\tilde{\nu}$ (cm^{-1}) [a]	Ultraviolet spectrum, λ_{max}(nm)(log ε) [b]
8a	3240, 2960, 1695, 1525, 785	220 (3.79), 240 (4.09)
8b	3110, 2999, 1690, 1540, 782	215 (4.16), 240 (4.09)
8c	3099, 2997, 1668, 1520, 769	220 (4.06), 280 (4.11)
8d	3072, 2922, 1703, 1530, 810	236 (4.47), 276 (4.22), 324 (4.61)
9c	3188, 2939, 1676, 1520, 823	220 (3.78), 285 (3.93)
9d	3140, 2905, 1699, 1550, 810	235 (4.48), 276 (4.22)
10c	3115, 2905, 1649, 1525, 763	220 (3.81), 270 (3.81)
10d	3074, 2980, 1703, 1550, 810	235 (4.04), 276 (4.01), 324 (3.49)

[a] In KBr disk. The sequence of the characteristic frequencies shown is: aromatic CH (m-s), aliphatic CH (m), C=O (s), C=N (s), aromatic substitution (s). [b] In methanol.

Table 4

^1H and ^{13}C nmr Spectra of the Quinazolines

Compound No.	^1H nmr spectrum (δ, ppm, DMSO-d_6) ^{13}C nmr spectrum (δ, ppm, DMSO-d_6)
8a	^1H: 1.97 s, 3H (Me); 2.38 s, 3H (Me); 123.8; 7.16 s, 1H (thiazole); 7.34 d, 1H (Ar); 7.43 t, 1H (Ar); 7.43 t, 1H (Ar); 7.60 d, 1H (Ar) ^{13}C: Me: 9.9; 23.7; other C: 122.2; 123.8; 126.5; 126.0; 129.0; 130.2; 134.0; 136.5; 156.0; 163.0; 169.0
8b	^1H: 2.10 s, 3H (Me); 2.34 s, 3H (Me); 7.25 s, 1H (thiazole); 7.55 d, 1H (Ar); 7.96 s, 1H (Ar); 8.17 d, 1H (Ar) ^{13}C: Me: 11.0; 24.5; other C: 122.4; 123.5; 125.0; 126.5; 129.5; 132.0; 141.0; 161.0 [a]; 168.0 [a]; 168.5
8c	^1H: 2.13 s, 3H (Me); 2.34 s, 3H (Me); 7.20 d, 1H (Ar); 7.25 s, 1H (thiazole); 8.00 d, 1H (Ar); 8.35 s, 1H (Ar) ^{13}C: Me: 11.5; 25.5; other C: 120.0; 121.0; 121.5; 122.0; 125.0; 128.0; 128.5; 131.0; 136.5; 140.0; 168.5
8d	^1H: 2.26 d, 3H (Me); 2.54 s, 3H (Me); 7.63 s, 1H (thiazole); 8.02 s, 1H (Ar); 8.19 s, 1H (Ar) ^{13}C: Me: 12.0; 23.0; other C: 122.0; 124.0; 130.5; 132.0; 134.5; 138.0; 138.5; 142.0; 154.0; 155.0; 160.0
9c	^1H: 2.14 s, 3H (Me); 2.34 s, 3H (Me); 7.22 d, 1H (Ar); 7.26 s, 1H (thiazole); 8.01 d, 1H (Ar); 8.38 s, 1H (Ar) ^{13}C: Me: 16.5; 25.0; other C: 107.0; 120.0; 121.0; 123.0; 126.5; 128.0; 128.5; 131.0; 140.0; 140.5; 168.5
9d	^1H: 2.24 s, 3H (Me); 2.41 s, 3H (Me); 7.59 s, 1H (thiazole); 8.01 s, 1H (Ar); 8.18 s, 1H (Ar) ^{13}C: Me: 16.8; 23.0; other C: 118.5; 121.5; 122.0; 124.0; 131.0; 132.0; 134.0; 142.0; 150.0; 155.5; 160.0
10c	^1H: 0.86 t, 3H (Me in Et); 1.64 s, 3H (Me); 2.53 q, 2H (CH_2 in Et); 6.82 d, 1H (Ar); 7.45 s, 1H (Ar); 7.73 s, 1H (Ar) ^{13}C: Me: 14.0; 22.5; CH_2: 23.5; other C: 124.0; 125.5; 128.5; 129.5; 130.0; 137.0; 158.0; 163.0; 166.0; 169.0
10d	^1H: 1.38 t, 3H (Me in Et): 2.28 s, 3H (Me); 3.21 q, 2H (CH_2 in Et); 8.04 s, 1H (Ar); 8.23 s, 1H (Ar) ^{13}C: Me: 13.0; 23.0; CH_2: 23.5; other C: 124.5; 130.5; 132.0; 134.0; 134.5; 142.0; 154.5; 158.0; 160.0; 176.5

[a] Indistinct.

263 (291 – CO, 15); 177 (263 – SC(Me)CHN from 5-methylthiazole, 25); 151 (177 – CN, 17); 140 (291 – 151, 14); 110 (151 – NCMe, 36) 75 (110 – Cl, 42).

The new compounds are expected to be biologically active and will be tested for their potential anticancer and antiviral activity at the National Cancer Institute, Bethesda, MD.

EXPERIMENTAL

All melting points were determined on a Mel-Temp II capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a General Electric QE300 (300 MHz) spectrometer in deuterated dimethyl sulfoxide. The infrared spectra were measured on a Mattson Model 4020 (Galaxy) FT infrared spectrometer in potassium bromide disks (intensity of the absorption: s-strong, m-medium, w-weak). The ultraviolet absorption specrtra were taken on a Varian Cary 3 uv-visible spectrophotometer in methanol. The mass spectra were recorded on a 5980 Hewlett-Packard mass spectrometer; the ionizing voltage was 70 eV. In the GC, the initial oven temperature was 50° for 3 minutes, followed by an increase from 50° to 350° with a linearly programmed gradient of 25°/minute. The purity of all compounds was checked by thin-layer chromatography (TLC) on silica gel 60 F-254 precoated plates and the spots were located in the ultraviolet light. Elemental analyses were carried out by Desert Analytics, Tucson, AZ. Commercial reagents were purchased from Aldrich Chemical Co., Milwaukee, WI, and used without further purification. All solvents were reagent grade except for the deuterated dimethyl sulfoxide used for spectroscopic measurements (spectrophotometric grade).

5-Chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**4a**) [40-42].

6-Chloroanthranilic acid (**3a**, 2.0 g, 0.012 mol) was refluxed with acetic anhydride (10 ml, 10.8 g, 0.106 mol) for 40 minutes. The solution was cooled to room temperature and excess acetic acid was removed by flow of nitrogen gas over the solution. The resulting solid (2.0 g, 88%) was recrystallized from methanol to give white crystals of **4a** (0.71 g, 32%), ^1H nmr spectrum (DMSO-d_6); δ (ppm) 1.50 s, 3H (Me); 6.55 d, 1H (Ar); 6.70 d, 1H (Ar); 6.90 t, 1H (Ar); mass spectrum, principal fragments; m/z 197 ($M^+ + 2$, rel. intensity 30); 195 (M^+, molecular ion, 87); 180 (M^+ - Me, base peak, 100); 151 (M^+ - CO, 65); 124 (M^+ - OCOCMe, 37); 110 (C_6H_3Cl, 12).

Chlorosubstitued 2-methyl-4*H*-3,1-benzoxazin-4-ones (**4b-4d**).

The above procedure was also used to obtain the previously described 6-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**4b**) [43,44] from 5-chloroanthranilic acid (**3b**), 7-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**4c**) [41,42,44] from 4-chloroanthranilic acid (**3c**), and 6,8-dichloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**4d**) [45] from 3,5-dichloroanthranilic acid (**3d**), by refluxing a solution of the respective acid in acetic anhydride for 30-45 minutes. The products, **4b-4d**, were recrystallized from methanol, ethanol, or acetone, and were used to obtain the corresponding 3-substituted 2-methyl-4(3*H*)-quinazolinones as described in the next step.

5-Chloro-2-methyl-3-(5-methylthiazol-2-yl)-4(3*H*)-quinazolinone (**8a**).

Equimolar amounts of 5-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (**4a**, 1.08 g, 5.5 mmol) and 2-amino-5-methylthiazole (**5**, 0.63 g, 5.5 mmol) were thoroughly mixed and refluxed for 30 hours in dry pyridine (15 ml) under anhydrous conditions. The solution was allowed to cool to room temperature and pyridine was removed by a slow stream of nitrogen gas passed over the solution. The residue was purified by recrystallization from methanol giving **8a** (0.88 g, 55%), mp 217-220° (for additional experimental data on this compound, see Tables 1-4).

3-Substituted 2-methyl-4(3*H*)-quinazolinones.

As described above, the chlorosubstituted 2-methyl-4*H*-3,1-benzoxazin-4-ones (**4a-4d**) were refluxed with equimolar amounts of 2-amino-5-methylthiazole (**5**), 2-amino-4-methylthiazole (**6**), or 2-amino-5-ethyl-1,3,4-thiadiazole (**7**) and yielded the desired products **8b**, **8c**, **8d**, **9c**, **9d**, **10c**, and **10d**. The information on their melting points and yields is in Table 1, elemental analyses and mass spectral data (molecular ion) are given in Table 2. The infrared and electronic absorption spectra are presented in Table 3 and the ^1H and ^{13}C nmr spectra are summarized in Table 4.

Acknowledgements.

The authors wish to thank Professor Manfred G. Reinecke (Texas Christian University, Ft. Worth, TX) and Dr. J. William Louda (Florida Atlantic University) for their help with the mass spectra.

REFERENCES AND NOTES

[1] Presented, in part, at the 35th National Organic Chemistry Symposium, American Chemical Society, San Antonio, TX, June 22-26, 1997, and at the 16th International Congress of Heterocyclic Chemistry, Bozeman, MT, August 10-15, 1997.

[2] This work is described in the thesis submitted by Duran S. Schmidt in partial fulfillment of the requirements for an M.S. degree in Chemistry (Florida Atlantic University, 1997).

[3] C. Párkányi and A. Vystrčil, *Collect Czech. Chem. Commun.*, **21**, 1007 (1956); *Chem. Listy*, **50**, 106 (1956).

[4] C. Párkányi and A. Vystrčil, *Collect. Czech. Chem. Commun.*, **21**, 689 (1956); *Chem. Listy*, **50**, 62 (1956).

[5] C. Párkányi and A. Vystrčil, *Collect. Czech. Chem. Commun.*, **21**, 1657 (1956); *Chem. Listy*, **50**, 666 (1956).

[6] C. Párkányi, *Česk. Farm.*, **5**, 370 (1956).

[7] C. Párkányi, *Collect. Czech. Chem. Commun.*, **23**, 63 (1958); *Chem. Listy*, **51**, 709 (1957).

[8] C. Párkányi, *Collect. Czech. Chem. Commun.*, **26**, 998 (1961).

[9] A. S. Shawali, M. Sami, S. M. Sherif and C. Párkányi, *J. Heterocyclic Chem.*, **17**, 877 (1980).

[10] A. O. Abdelhamid, C. Párkányi, A. S. Shawali and M. A. Abdalla, *J. Heterocyclic Chem.*, **21**, 1049 (1984).

[11] N. S. Cho, K. Y. Song and C. Párkányi, *J. Heterocyclic Chem.*, **26**, 1807 (1989).

[12] J. J. Aaron, A. Tine, M. D. Gaye, C. Párkányi, C. Boniface and T. W. N. Bieze, *Spectrochim. Acta*, **47A**, 419 (1991).

[13] C. Párkányi, H. L. Yuan, B. H. E. Strömberg and A. Evenzahav, *J. Heterocyclic Chem.*, **29**, 749 (1992).

[14] C. S. Jang, F. Y. Wu, K. C. Huang and C. Y. Wang, *Nature*, **161**, 400 (1948).

[15] T. Q. Chou, F. Y. Wu and Y. S. Kao, *J. Am. Chem. Soc.*, **70**, 1765 (1948).

[16] L. Neipp, W. Kunz and R. Meier, *Schweiz. Z. Allgem. Pathol. Bakteriol.*, **19**, 331 (1956); *Chem. Abstr.*, **50**, 15700a (1956).

[17] W. L. F. Armarego, *Advan. Heterocycl. Chem.*, **1**, 253 (1963).

[18] B. M. Gupta, U. Agarwal and S. K. Khan, *Indian J. Exp. Biol.*, **1**, 61 (1963); *Chem. Abstr.*, **58**, 14477e (1963).

[19] A. H. Amin, D. R. Mehta and S. S. Samarth, *Fortschr. Arzneimittelforsch.*, **14**, 218 (1970).

[20] I. R. Ager, D. R. Harrison, P. D. Kennewell and J. B. Taylor, *J. Med. Chem.*, **20**, 379 (1977).

[21] S. K. Shukla, A. K. Agnihotri and B. L. Chowdhary, *Indian Drugs*, **19**, 59 (1981); *Chem. Abstr.*, **96**, 97196m (1982).

[22] A. K. Agnihotri and S. K. Shukla, *Arch. Pharm.*, **315**, 701 (1982).

[23] S. K. Shukla and A. K. Agnihotri, *Ind. J. Forestry*, **7**, 151 (1984); *Chem. Abstr.*, **102**, 42727x (1985).

[24] A. R. El-Naser Ossman and S. El-Sayed Bakarat, *Saudi Pharm. J.*, **2**, 21 (1994); *Chem. Abstr.*, **121**, 179538y (1994).

[25] I. J. Pachter, R. F. Raffauf, G. E. Ullyot and O. Ribeiro, *J. Am. Chem. Soc.*, **82**, 5187 (1960).

[26] D. R. Mehta, J. S. Naravane and R. M. Desai, *J. Org. Chem.*, **28**, 445 (1963).

[27] D. G. O'Donovan and H. Horan, *J. Chem. Soc. C*, 2466 (1970).

[28] I. Husain, S. N. Misra and S. R. Yadav, *J. Indian Chem. Soc.*, **57**, 924 (1980).

[29] M. R. Chaurasia and S. K. Sharma, *J. Nepal Chem. Soc.*, **1**, 11 (1981); *Chem. Abstr.*, 103, 136975z (1985).

[30] M. R. Chaurasia and J. K. Sharma, *J. Indian Chem. Soc.*, **59**, 370 (1982).

[31] C. Párkányi, H. L. Yuan, N. S. Cho, J.-H. J. Jaw, T. E. Woodhouse and T. L. Aung, *J. Heterocyclic Chem.*, **26**, 1331 (1989).

[32] N. S. Cho, H. I. Shon and C. Párkányi, *J. Heterocyclic Chem.*, **28**, 1645 (1991).

[33] N. S. Cho, H. I. Shon and C. Párkányi, *J. Heterocyclic Chem.*, **28**, 1725 (1991).

[34] N. S. Cho, G. N. Kim and C. Párkányi, *J. Heterocyclic Chem.*, **30**, 397 (1993).

[35] S. K. V. Seshavataram and N. V. Subba Rao, *Proc. Indian Acad. Sci.*, **49A**, 96 (1959).

[36] A. Shaffie, I. Lalezari and A. Pournorouz, *J. Pharm. Sci.*, **62**, 839 (1973).

[37] G. R. Revankar and R. K. Robins (ICN Pharmaceutics), U. S. Pat. 4,093,624 (1978); *Chem. Abstr.*, **89**, 180309b (1978).

[38] S. Takano, H. Imaizumi, T. Kajita, K. Takashima, K. Takezawa, M. Yotsutsui, T. Yasuda, A. Yotsutsui, H. Sakai and I. Saikawa (Kokai Tokkyo Koho), Jap. Pat. 62,178,590 (1987); *Chem. Abstr.*, **108**, 112450b (1988).

[39] R. B. Boar, A. J. Cross, D. A. Gray and A. R. Green (Astra AB), PCT Int. WO 95 01 968 (1995); SE 93/2 334 (1993); *Chem. Abstr.*, **122**, 239691a (1995).

[40] E. Reeder, L. H. Sternbach, O. Kell, N. Steiger, A. Stempel, R. I. Fryer, G. Saucy and G. H. Sach (Hoffmann-LaRoche), Ger. Pat. 1,145, 626 (1963); *Chem. Abstr.*, **60**, 12033h (1964).

[41] E. Reeder and L. H. Sternbach (Hoffmann-LaRoche), U.S. Patent 3,136,815 (1964); *Chem. Abstr.*, **61**, 9515f (1964).

[42] E. Reeder and L. H. Sternbach (Hoffmann-LaRoche), U.S. Patent 3,239,564 (1966); *Chem. Abstr.*, **64**, 19498a (1966).

[43] A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **70**, 2423 (1948).

[44] D. R. Desai, V. S. Patel and S. R. Patel, *J. Indian Chem. Soc.*, **43**, 351 (1966); *Chem. Abstr.*, **65**, 8906d (1966).

[45] W. Ried and J. Valentin, *Chem. Ber.*, **101**, 2106 (1968).

[46] L. A. Errede, J. J. McBrady and H. T. Oien, *J. Org. Chem.*, **41**, 1763 (1976).

[47] H. Asakawa, M. Matano and Y. Kawamatsu, *Chem. Pharm. Bull.*, **27**, 287 (1979).