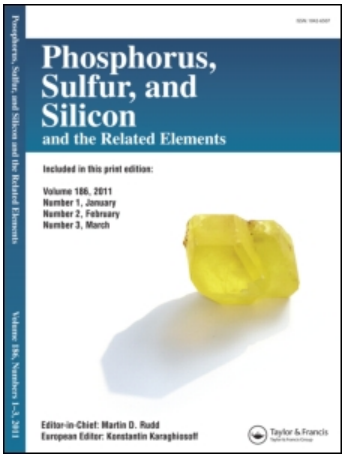


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Antiradiation Activity of Some Sulfur Containing Thiophene Derivatives

A. Y. Hassan; M. M. Ghorab; O. M. Nassar

To cite this Article Hassan, A. Y. , Ghorab, M. M. and Nassar, O. M.(1998) 'Synthesis and Antiradiation Activity of Some Sulfur Containing Thiophene Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 134: 1, 77 — 86
To link to this Article: DOI: 10.1080/10426509808545453
URL: http://dx.doi.org/10.1080/10426509808545453

Phosphorus, Sulfur and Silicon, 1998, Vol. 134/135, pp. 77-86
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND ANTIRADIATION ACTIVITY OF SOME SULFUR CONTAINING THIOPHENE DERIVATIVES

A.Y. HASSAN[a], M.M. GHORAB[b*] and O.M. NASSAR[a]

[a]*Chemistry Department, Faculty of Science, Girls Branch, Al-Azhar University, Nasr City, Cairo, Egypt and* [b]*Department of Drug Radiation Research, National Center for Radiation Research and Technology, Atomic Energy Authority, P.O. Box 29, Nasr City, Cairo, Egypt*

(Received 8 July, 1997; In final form 23 October, 1997)

Condensation of 2-(2,2-dicyano-1-methylvinyl)thiophene (2) with phenylhydrazine furnished the corresponding 2-(1-phenylhydrazonoethyl)-thiophene (4). Compound (4) was obtained also via reaction of (1) with phenylhydrazine. Reaction of (2) with amines gave 2-(2,2-dicyano-1-ethylamino or benzylamino- 1 methylethyl)thiophene (5a,b). Treatment of (2) with elemental sulfur yielded directly the cyclised product 2-(5-amino-4-cyano-3-thienyl)thiophene (6). On the other hand refluxing (2) in pyridine with carbon disulfide gave the pyridine-1,3-dithione derivative (7). Condensation of (2) with phenyl isocyanate and/or phenyl isothiocyanate afforded 6-amino-4-(2-thienyl)-1,2-dihydro-2-oxo- 1-phenylpyridine-5-carbonitrile (9) and/or 5-(2-thienyl)-2,7-dithioxo-3,8-N-phenyl-1,2,3,7,8-pentahydropyrido[2,3-d]pyrimidine-4-imine (11). Also the dicyano derivative (2) when reacted with cinnamonitrile (12) afforded the 2-(3-amino-2,4-dicyano-5-arylphenyl)-thiophenes (15a-d). Conversion of (15b) into the polyazanaphthalene (17) and (18) was affected via cyclocondensation with phenyl isocyanate and/or phenyl isothiocyanate. Compound (15a) showed promising antiradiation activity.

Keywords: Thiophene derivatives; antiradiation activity

INTRODUCTION

Several nitrogen, oxygen and sulfur containing heterocyclic compounds incorporating thiophene residues were found to possess interesting biological properties[1–5]. Recently, we have reported the synthesis and structure activity relationship of a variety of heterocyclic and aromatic derivatives

* To whom correspondence should be addressed.

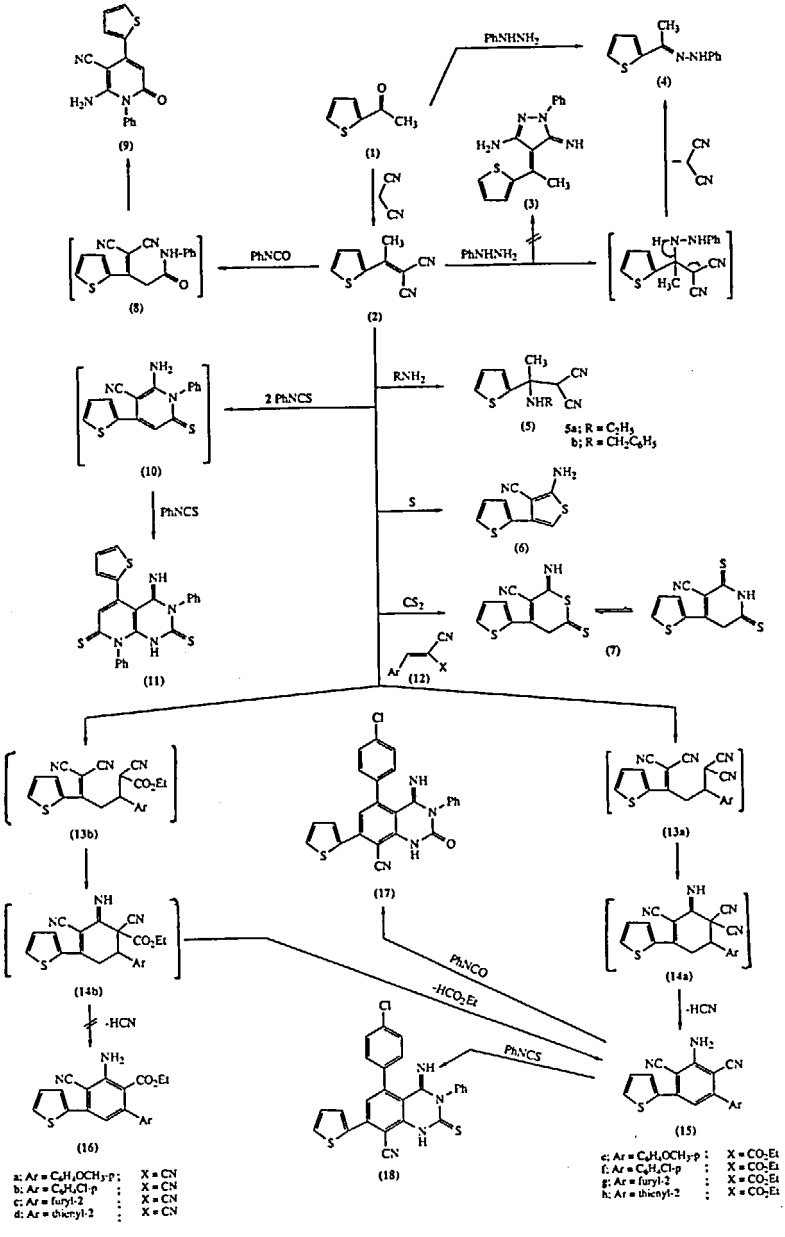
of thienopyrimidines, quinazolinones and thiazolopyrimidines[6–11]. Moreover various sulfur compounds were found to have antiradiation and other biological properties[12–15]. However thiophenes incorporating various heterocyclic unit residues have not yet been studied. Therefore, several thiophene derivatives (2–18) were synthesized and tested for antiradiation activity.

RESULTS AND DISCUSSION

To realize the synthesis of the target antiradiation compounds the following scheme was adopted. In continuation of our work[10,11], it was considered of interest to synthesize new thiophene derivatives which might show the desired activity. Thus, condensation of 2-acetylthiophene (1) with malononitrile using a Dean-Stark trap afforded 2-(2,2-dicyano-1-methylvinyl)thiophene (2)[16]. In contrast to the anticipated formation of the pyrazoline derivative[17] (3), the reaction of (2) with phenylhydrazine in boiling ethanol gave the hydrazone derivative (4). The reaction proceeds via elimination of malononitrile. The proposed structure for (4) was supported by its independent synthesis from (1) by refluxing with phenylhydrazine (m.m.p was not depressed) (Scheme 1). The IR spectrum of (4) showed bands at 3250 cm^{-1} (NH), 2910 cm^{-1} (CH aliphatic), 3100 cm^{-1} (CH aromatic), 1630 cm^{-1} (C=N). The ^{1}H-NMR spectrum of (4 in DMSO-d_6) exhibited signals at δ 2.3 [3H, s, CH_3], 6.6–7.5 [8H, m, Ar-H], 9.2 [1H, s, NH].

Interaction of (2) with ethylamine and/or benzylamine in boiling ethanol furnished 2-(2,2-dicyano-1-ethylamino or benzylamino- 1-methylethyl)thiophene (5a,b), resulting from initial attack of the nucleophile at C-B of the olefinic bond of the dicyano derivative (2) (Scheme 1). The IR spectrum of (5b) revealed bands at 3230 cm^{-1}(NH), 2920 cm^{-1} (CH aliphatic), 3100 cm^{-1} (CH aromatic), 2195, 2160 cm^{-1} (2C≡N). The ^{1}H-NMR spectrum of (5b in DMSO-d_6) exhibited signals at δ 2.6 [3H, s, CH_3], 4.1 [2H, s, CH_2], 7.1–7.8 [8H, m, Ar-H], 9.7 [1H, s, NH].

The reaction of (2) with sulfur via a Gewald reaction[18] produced the thienyl derivative (6). On the other hand refluxing (2) in pyridine with carbon disulfide gave the dithione derivative (7). The IR spectrum of (6) showed bands at 3300, 3200 cm^{-1} (NH_2), 3080 cm^{-1} (CH aromatic) and



SCHEME I

2200 cm^{-1} (C≡N) and the IR spectrum of (7) exhibited bands at 3320 cm^{-1} (NH), 3100 cm^{-1} (CH aromatic), 2220 cm^{-1} (C≡N), 1270 cm^{-1} (C=S).

Gewald *et al*[19], reported that the reaction of the crotononitrile derivative (2) with phenyl isocyanate and/or phenyl isothiocyanate yielded 2H-pyran and pyridinethione derivatives respectively. Accordingly the reaction of (2) with phenyl isocyanate furnished 6-amino-4-(2-thienyl)-1,2-dihydro-2-oxo-1-phenylpyridine-5-carbonitrile (9). It's structure was confirmed by its IR, ^{1}H-NMR, and mass spectra. The IR spectrum showed absorption bands at 3350, 3240 cm^{-1} (NH_2), 3100 cm^{-1} (CH aromatic), 2210 cm^{-1} (C≡N), 1650 cm^{-1} (C=O). The ^{1}H-NMR spectrum of (9 in DMSO-d_6) exhibited signals at δ 6.7 [1H, s, CH], 7.1–8.6 [8H, m, Ar-H], 10.4 [2H, s, NH_2]. The Mass spectrum of (9) showed a molecular ion peak m/z 293 (M^+. 5.25%), with a base peak at 93 (100%); other significant peaks were at 167 (2.34%), 183 (6.31%); 212 (16.39%), 265 (7.59%).

The reaction of (2) with phenyl isothiocyanate in a 1:1 molar ratio under the previous conditions[19] yielded a product of molecular formula ($C_{23}H_{16}N_4S_3$) (11). This compound was also obtained by using a 1:2 molar ratio. It is assumed to proceeds via the intermidiate (10) which reacts with another mole of phenyl isothiocyanate to give (11). It's IR spectrum indicates absence of the carbonitrile absorption band, presence of bands at 3320, 3200 cm^{-1} (2NH), 1320, 1240 cm^{-1} (2C=S) and it's ^{1}H-NMR spectrum with absorptions at δ 6.1 [1H, s, CH], 6.2, 6.8 [2H, 2s, 2NH), 7.3–8.9 [13H, m, Ar-H], is in agreement with the assigned structure.

Recently the condensation of (2) with various substituted α-cyanocinnamonitrile (12a-d) was found to be a new general route for the synthesis of polysubstituted aromatic amines 2-(3-amino-2,4-dicyano-5-arylphenyl)thiophenes (15a-d). The formation of (15) from the reaction of (2) and (12) is assumed to proceed via a Michael-type addition of the methyl group in (2) to the activated double bond to yield the acyclic Michael adduct (13a) which then cyclizes into compound (14a). The latter readily looses HCN to yield the final stable compounds (15a-d).

In contrast to the anticipated formation of the ester (16), the reaction of (2) with various substituted α-cyanocinnamonitriles (12e-h) afforded the derivetives (15a-d). Their formation is assumed to proceed via elimination of ethyl formate from the intermediate (14b). The IR spectrum of (15b) showed bands at 3350, 3300 cm^{-1} (NH_2), 3100 cm^{-1} (CH aromatic), 2220 cm^{-1} (C≡N), 760 cm^{-1} (C-Cl), also the IR spectrum of (15d) exhibited

bands at 3400, 3350 cm^{-1} (NH_2), 3095 cm^{-1}(CH aromatic), 2210 cm^{-1} (C≡N). The ^{1}H-NMR spectrum (15a in DMSO-d_6) possesses peaks at δ 3.8 [3H, s, OCH_3], 6.9 [2H, br, NH_2], 7.2–8.1 [8H, m, Ar-H].

TABLE I Characterization data of newly synthesized compounds

Compd. No.	*M.P °C*	*Yield %*	*Mol.-formula*	*Analysis Required/ (Found)%*			
				C	*H*	*N*	*S*
4	103–105	88	$C_{12}H_{12}N_2S$	66.66	5.55	12.96	14.81
				(66.90)	(5.20)	(12.50)	(15.10)
5a	160–62	72	$C_{11}H_{13}N_3S$	60.27	5.93	19.17	14.61
				(60.50)	(5.60)	(19.40)	(14.50)
5b	120–22	70	$C_{16}H_{15}N_3S$	68.32	5.33	14.94	11.38
				(68.10)	(5.50)	(15.20)	(11.60)
6	>340	82	$C_9H_6N_2S_2$	52.42	2.91	13.59	31.06
				(52.10)	(2.60)	(13.70)	(31.30)
7	>340	65	$C_{10}H_6N_2S_3$	48.00	2.40	11.20	38.40
				(47.70)	(2.10)	(11.50)	(38.70)
9	250–52	86	$C_{16}H_{11}N_3OS$	65.52	3.75	14.33	10.92
				(65.80)	(3.90)	(14.10)	(10.60)
11	>340	70	$C_{23}H_{16}N_4S_3$	62.16	3.60	12.61	21.62
				(62.40)	(3.80)	(12.90)	(21.40)
15a	300–302	85	$C_{19}H_{13}N_3OS$	68.88	3.92	12.68	9.66
				(68.60)	(4.20)	(12.90)	(9.30)
15b	272–74	91	$C_{18}H_{10}N_3SCl$	64.38	2.98	12.51	9.53
				(64.10)	(2.60)	(12.20)	(9.70)
15c	280–82	72	$C_{16}H_9N_3OS$	65.97	3.09	14.43	10.99
				(65.70)	(3.40)	(14.60)	(10.60)
15d	260–62	84	$C_{16}H_9N_3S_3$	62. 54	2.93	13.68	20.84
				(62.10)	(2.60)	(13.90)	(20.40)
17	>340	74	$C_{25}H_{15}N_4OSCl$	66.00	3.30	12.32	7.04
				(66.30)	(3.60)	(12.10)	(7.20)
18	160–62	69	$C_{25}H_{15}N_4S_2Cl$	63.76	3.18	11.90	13.60
				(63.50)	(3.40)	(11.50)	(13.80)

Compound (15b) could readily be converted into polyazanaphthalene when reacted with phenyl isocyanate and/or phenyl isothiocyanate to yield the 4-imino-2-oxo-1,2,3-trihydro-3-phenyl-5-(4-chlorophenyl)-7-(2-thienyl) quinazoline-8-carbonitrile (17) and/or the 4-imino-2-thioxo-1,2,3-trihydro-3-phenyl-5-(4-chlorophenyl)-7-(2-thienyl)-quinazoline-8-carbonitrile (18), respectively. The IR and ^{1}H-NMR spectra of (17) and (18) are in good agreement with the proposed structure. The IR spectrum of (17) showed bands at 3420, 3350 cm^{-1} (2NH), 2210 cm^{-1} (C≡N), 3100 cm^{-1} (CH aromatic), 1690 cm^{-1} (C=O), and the IR spectrum of (18) exhibited bands at 3300, 3220 cm^{-1} (2NH), 2230 cm^{-1} (C≡N), 3080 cm^{-1} (CH aromatic), 1310 cm^{-1} (C=S). The ^{1}H-NMR spectrum of (17 in DMSO-d_6) exhibited signals at δ 6.9–7.5 [13H, m, Ar-H]; 8.9 [2H, s, 2NH], and the ^{1}H-NMR spectrum of (18 in DMSO-d_6) showed signals at δ 7.2–8.0 [13H, m, Ar-H], 9.3 [2H, s, 2NH].

Antiradiation activity

Exploratory test for the antiradiation activity of some of the synthesized compounds was achieved by intraperitoneal injection of the experimental animals with the dithione derivative (7) at a dose of (200 mg/kg), which represend in a survival rate of 0 % after 48 hr.

TABLE II Antiradiation activity[a]

Compd. No.	*Dose mg/kg*	*Survival[b] %*	*Protective Index[c]*	*Rating[d]*
7	200	0	0	-
9	200	50	3	+
15a	200	66	5	+

[a]The antiradiation data generally represent the lowest dose of a drug for which a high rate of survival was obtained.
[b]The percent survival (30 days) of the tested animals is given for the dose specified.
[c]Protective index = (protection factor) × LD_{50}/minimum effective dose), where doses are in mg/kg and the protection factor is 1.3 for 30% survival, 1.4 for 40% survival.
[d]Ratings are based on the following ranges of protective indices:- (-), 0–1; (+), 2–5; (++), 6–10, (+++), 11–15; (++++), 16–29. The ratings are a measure of the lowest drug dose for which some protection was obtained. A high survival rate and a low rating (low protective index) indicates that the compounds did not protect well at doses lower than those shown.

Analogously compounds (9) and (15a) were tested in groups of male rats each of 12 (100–120 gm) for antiradiation activity by the reported

method[20]. The tested compounds, dissolved in dimethylsulfoxide were orally administred at a dose of 200 mg/kg 30 minutes before exposing the animals to a gamma irradiation (6.5 Gy)* at a dose rate of 1.2 rad/sec (Table II). The doses used were determined as employed in previous experiment[13] on analogous compounds which showed LD_{50} of about 430, 380, 600 mg/kg for compounds (7), (9) and (15a), respectively.

A comparison of the antiradiation activity of the tested compounds revealed that compound (15a) (protective index = 5; survival rate of 66%) showed a promising activity greater than compound (9) (protective index = 3; survival rate 50%).

The promising activity of compound (15a) may be attributed to the presence of the amino group (NH_2); the methoxy group and the thiophene ring. Such groups when incorporated in known antiradiation[7,13,21] drugs apparently are responsible for the protection.

EXPERIMENTAL

All m.p.,s are uncorrected. Elemental analyses were carried out at the microanalytical laboratories of the Faculty of Science, Cairo University. The IR spectra (KBr) were measured on a Shimadzu IR 440 spectrophotometer, the ^{1}H-NMR spectra were obtained on a Jeol Fx 90 Q (90 MHz) spectrometer and the mass spectra on a Shimadzu Gc-Ms-Qp 1000 Ex using the direct inlet system.

Reaction of 2-(2,2-dicyano-1-methylvinyl)thiophene (2) with phenylhydrazine

Method (A)

A mixture of 2, (0.01 mol) and phenylhydrazine (0.01 mol) in ethanol (50 ml) was refluxed for 2 hr, the product obtained was crystallized from ethanol to give the hydrazone derivative (4, Table I).

* The radiation dose was supplied by ^{137}Cs γ-rays (6.5 Gy) at the National Center for Radiation Research and Technology.

Method (B)

To a solution of 1, (0.01 mol) in ethanol (50 ml) was added phenylhydrazine (0.01 mol). The reaction mixture was refluxed for 2 hr to give 2-(1-phenylhydrazonoethyl)thiophene (4) (mixture m.p. was not depressed).

Reaction of (2) with amines

The amine (0.01 mol) dissolved in ethanol (50 ml), was added in portions to a solution of the dicyano derivative 2, (0.01 mol) in ethanol, then heated at reflux for 3 hr. After cooling the precipitate was filtered off, dried and crystallized from ethanol to give 2-(2,2-dicyano-1-ethylamino or benzylamio-1-methylethyl)thiophene 5a,b (Table I).

Reaction of (2) with sulfur

Equimolar amounts (0.01 mol) of (2) and elemental sulfur in ethanol (50 ml) were treated with a few drops of piperidine. The reaction mixture was refluxed for 3 hr and the precipitate was collected by filtration and crystallized from ethanol to give 2-(5-amino-4-cyano-3-thienyl)thiophene 6, (Table I).

Reaction of (2) with carbon disulfide

To a solution of 1, (0.1 mol) in pyridine (10 ml), carbon disulfide was added and the resulting solution was heated at reflux for 10 hr. After cooling, methanol (30 ml) was added and the precipitated solid was collected, filtered and crystallized from ethanol to give pyridine-1,3-dithione derivative 7, (Table I).

General procedures for formation of 6-amino-4-(2-thienyl)-1,2-dihydro-2-oxo-1-phenylpyridine-5-carbonitrile (9) and 5-(2-thienyl)-2,7-dithioxo-3,8-N-phenyl-1,2,3,7,8-pentahydropyrido [2,3-d] pyrimidine-4-imine (11)

A mixture of 2, (0.01 mol), finely divided sodium metal (0.01 mol) and phenyl isocyanate or phenyl isothiocyanate were refluxed for 7 hr in dry

dioxan (50 ml), then allowed to cool, poured onto cold water and neutralized with dilute HCl. The pricipitate was filtered off and crystallized from dioxan to give (9) and (11), respectively (Table I).

Reaction of (2) with cinnamonitrile derivatives

A suspension of 2; (0.01 mol) in ethanol (30 ml) was treated with an equimolar amount of 12a-h; (0.01 mol) and a catalytic amount of piperidine (0.1 ml). The reaction mixture was refluxed for 2 hr. The precipitate was filtered off and crystallized from ethanol to give (15a-d; Table I).

Formation of 4-imino-2-oxo-1,2,3-trihydro-3-phenyl-5-(4-chlorophenyl)-7-(2-thienyl)quinazoline-8-carbonitrile (17) and 4-imino-2-thioxo-1,2,3-trihydro-3-phenyl-5-(4-chlorophenyl)-7-(2-thienyl)quinazoline-8-carbonitrile (18)

A mixture of 15b; (0.01 mol), finely divided sodium metal (0.01 mol) and phenyl isocyanate or phenyl isothiocyanate were refluxed for 7 hr in dry dioxan (50 ml) then allowed to cool, poured onto cold water and neutralized with dilute HCl. The precipitate was filtered off and crystallized from ethanol to give (17) and (18), respectively (Table I).

Acknowledgements

The authors are grateful to Dr. Mona A. El-Gawish, Biology Department, National Center for Radiation Research and Technology, for the antiradiation screening.

References

[1] M.S. Manhas and S.G. Amin; J. Heterocyclic Chem., 14, 161 (1977).
[2] K. Hirota, M. Shirahashi and S. Senda; J. Heterocyclic Chem., 27, 717 (1990).
[3] J.B. Press and R.K. Russell, US. Patent 4, 670, 560 (1987); Chem. Abstr., 107, 115604 v (1987).
[4] F. Ishikawa, A. Kosasayama, H. Yamaguchi, Y. Watanabe, J. Saegusa, S. Shibamura, K. Sakuma, S. Ashida and Y. Abiko; J. Med. Chem., 24, 376 (1981).
[5] V.D. Patil, D.S. Wise and L.B. Townsend; J.Chem. Soc., Perkin Trans. 1, 1853 (1980).
[6] M.M. Ghorab; S.G. Abdel-Hamide; G.M. Ali and El-Sayed H. Shaurub; Pestic. Sci; 48, 13, (1996).
[7] M.M. Ghorab; S.G. Abdel-Hamide and M.M. Abo Zeid,; Phosphorus, Sulfur, and Silicon; 112, 7, (1996).
[8] M.M. Ghorab, Y.A. Mohamid; S.A. Mohamed and Y.A. Ammar; Phosphorus, Sulfur, and Silicon, 108, 249, (1996).

[9] M.M. Ghorab; S.G. Abdel-Hamide and A.E. El-Hakim; Indian Journal of Heterocyclic Chemistry, 5, 115, (1995).
[10] M.M. Ghorab and S.G. Abdel-Hamide; Phosphorus, Sulfur, and Silicon, 106, 9, (1995).
[11] M.M. Ghorab, H.I. Heiba and Mona A. El-Gawish; Phosphorus, Sulfur, and Silicon, 106, 85, (1995).
[12] R.D. Westland and J.L. Holmes; J. Med. Chem., 15, 976, (1972).
[13] R.D. Westland, M.L. Mouk, J.L. Holmes, R.A. Cooley, J.S. Hong and M.M. Grenan; J. Med. Chem., Vol. 15, No. 9, 968–975 (1972).
[14] R.D. Westland, J.L. Holmes, M.L. Mouk, D.D. Marsh, R.A. Cooley, Jr. and J.R. Dice; J. Med. Chem., 11, 1190 (1968).
[15] W. Shapiro, M.F. Tansy and S. Elkin; J. Pharm, Sci., 57, 1725 (1968).
[16] A.A. Elagamey, F.M.A. El-Taweel and M.N.M. Khodeir, Pharmazie, 47, (1992), H.6.
[17] S. Abdou, S.M. Fahmy, M.M. Khader and M.H. Elnagdi; Monatsh. Chem., 113, 985 (1982).
[18] K. Gewald; Chem. Ber., 98, 357 (1965).
[19] K. Gewald, J. Laebschet and M.J. Keydel, J. Prakt. Chem., 312, 533 (1970).
[20] D.L. Klayman; M.M. Grenan and D.P. Jacobus; J. Med. Chem., 12, 723 (1969).
[21] N.C. Young, D.C. Thompson, H.S. Heine and J.H. Chung; J. Pharma, 21 (1), 1, (1985).