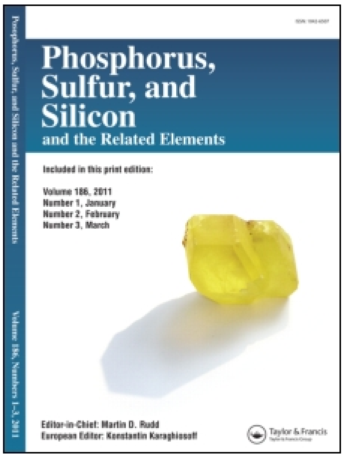

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SYNTHESIS OF NEW 4-ALKYLTHIAZOLO[5,4.D] PYRIMIDINE-1-OXIDES

Shaker Youssif[a]; Hiroshi Yamamoto[b]
[a] Chemisty Department, Faculty of Science, Zagazig University, Zagazig, Egypt [b] Chemistry Department, Faculty of Science Okayama University, Tsushima, Okayama, Japan

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SYNTHESIS OF NEW 4-ALKYLTHIAZOLO[5,4.D] PYRIMIDINE-1-OXIDES

Communication

SHAKER YOUSSIF[a]* and HIROSHI YAMAMOTO[b]

[a]*Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt. and* [b]*Chemistry Department, Faculty of Science Okayama University, Tsushima, Okayama 700 Japan*

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6-Chloro-1-methyluracil **1** was treated with various butyl and benzyl mercaptans to give 6-substituted-1-methyluracils **2a-d** which were nitrated to yield the corresponding 5-nitro derivatives **3a-d**. These were cyclized to 2-substituted-4-methylthiazolo[5,4-d] pyrimidine-5,7(**4H**)-dione-1-oxides **4a-c**. On the other hand. the reaction of 6-chloro-5-nitro-1-propyluracil **6** with the above mentioned reagents afforded 6-substituted-5-nitro-l-propyuracils **7a-d** which were cyclized similarly to give the corresponding 2-substituted-4-propylthiazolo[5,4-d]pyrimidine-5,7 (**4H**)-dione-1-oxide derivatives **8a-d**. The structures of these compounds were elucidated by ^{1}H nmr, uv, mass spectra and elemental analysis.

The N-oxides of guanine and xanthine were found to be potent carcinogenic agents[1]. In connection with a program for preparing new purine analogue derivatives, thiazolo[5,4-d] pyrimidine-N-oxides have been reported[2–4] as potential purine antagonists.

The present paper reports the synthesis of some new 4-alkylihiazolo[5,4-d] pyrimidine 1-oxides. The synthetic strategy toward the desired thiazolopyrimidine depends on either formation of an alkylthiopyrimidine, followed by nitration and subsequent base induced cyclization or reacting 6-chloro-5-nitrouracils with alkylmercaptans and subsequent ring closure. The treatment of 6-chloro-1-methyluracil[5,6] **1** with ethyl and methyl thioglycolate, butyl and benzyl mercaptane in the presence of triethylamine at room temperature afforded the corresponding 6-ethoxycarbonyl-methylenethio-, 6-methoxycarbonylmethylenethio-, 6-butylthio-, and 6-ben-

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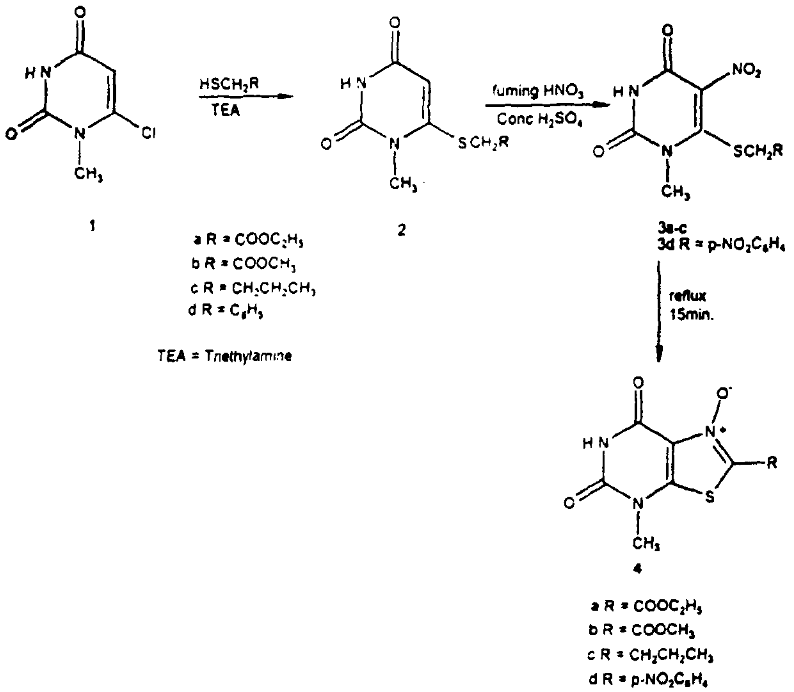
* Corresponding Author.

zylthio-1-methyluracils respectively **2a-d** in good yields; their physical data are shown in Table I. The nitration of compounds **2a-c** using fuming nitric acid in concentrated sulfuric acid gave the 1-methyl-5-nitro-6-substituted thiouracils **3a-c**, whereas the nitration of compound **2d** occured also at the para position of the phenyl group as well, giving l-methyl-5-nitro-5-(4-nitrophenyl) methylenethiouracil **3d**. The physical data of compounds **3a-d** are shown in Table I. The cyclization of compounds **3a-d** was achieved by refluxing in ethanol in the presence of triethyl amine affording the desired 2-methoxycarbonyl-, 2-ethoxy-carbonyl-,2-(4-nitrophenyl)-, and 2-propyl-4-methyl-thiazolo [5,4-d]pyrimidine-5,7 **(4H)**-dione-1-oxides **4a-d** (Table I) and, (Scheme 1). The mass spectra of the N-oxides exhibited M^+-16 which is indicative for the N-oxygen atom.

TABLE I Physical data for compounds 2a-d, 3a-d and 4a-d

compd. no.	*m.p. °C*	*R_f (SG)*	*Yield %*	*Mol.Formula (mol.wt.)*	*Analysis calcd (found)*			*UV in methanol*	
					C	*H*	*N*	*γ max (nm)*	*logε max*
2a	166–67	0.51A	74	$C_9H_{12}N_2O_4S$	44.25	4.95	11.46	281.0	426
				(244.26)	(43.83)	(4.77)	(11.43)	220.0	4.33
b	168–69	0.54A	94	$C_8H_{10}N_2O_4S$	41.73	4.37	12.16	281.0	4.14
				(230.23)	(41.68)	(4.21)	(12.15)	220.0	4.16
c	164–65	0.47A	74	$C_9H_{14}N_2O_2S$	50.44	6.58	13.07	283.0	4.16
				(214.28)	(50.48)	(6.31)	(13.07)	222.0	4.09
d	248	0.60A	86	$C_{12}H_{12}N_2O_2S$	58.04	4.87	11.28	283.0	4.14
				(248.29)	(58.26)	(4.87)	(11.27)	220.0	423
3a	158.59	0.57A	57	$C_9H_{11}N_3O_6S$	37.36	3.83	14.52	294.0	3.99
				(289.26)	(37.16)	(3.72)	(14.61)	203.0	4.33
b	179.82	0.51B	42	$C_8H_9N_3O_6S$	34.90	3.29	15.26	292.0	4.06
				(275.23)	(34.90)	(3.17)	(15.22)	202.0	4.33
c	156	0.58A	16	$C_9H_{13}N_3O_4S$	41.69	5.05	16.20	288.0	4.04
				(259.27)	(41.22)	(4.90)	(16.38)	201.0	4.32
d	176.78	0.52A	47	$C_{12}H_{10}N_4O_6S$	42.60	2.97	16.56	275.0	4.18
				(338.29)	(42.83)	(2.85)	(16.94)	204.0	4.37
4a	165–72	0.19A	27	$C_9H_9N_3O_5S$	39.85	3.34	15.49	317,0; 277.0	4,37, 4.46
				(271.24)	(39.43)	(3.64)	(15.42)	255.0	4.35
b	190	0.11A	64	$C_8H_7N_3O_5S$	37.35	2.74	16.33	317.0, 277.0	4.16, 4.26
				(257.22)	(37.53)	(2.69)	(16.45)	255.0	4.16
c	264	0.20A	59	$C_9H_{11}N_3O_3S$	44.80	4.59	17.41	319.0, 265.0	3.45, 3.59
				(241.26)	(44.84)	(4.84)	(17.87)	238.0, 221.0	3.76, 3.84
d	>250	0.14A	36	$C_{12}H_8N_4O_5$	44.99	2.51	17.49	372.0, 285.0	4.43, 4.17
				(320.27)	(45.07)	(2.70)	(17.31)	255.0	4.14

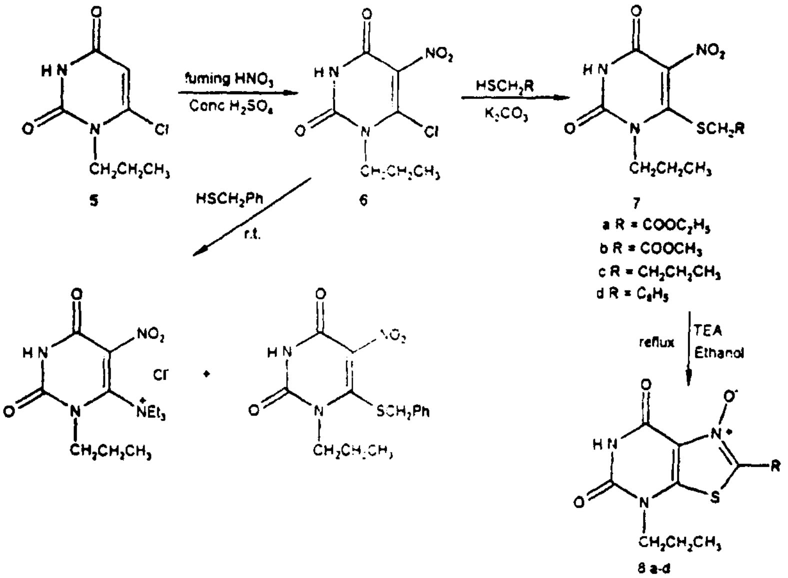


SCHEME 1

The corresponding 4-propylthiazolo[5,4-d]pyrimidine-N-oxides **8a-d** were similarly synthesized through the treatment of 6-chloro-5-nitro-1-propyluracil[7] **6** with an appropriate thiol and potassium carbonate as a base instead of triethyl amine, to give the desired intermediates 6-ethoxycarbonyl-methylenethio-, 6-methoxycarbonyl-methylenethio-, 6-butyl-thio-, and 6-benzyl-thio-5-nitro-1-propyluracil **7a-d** (Table II), and (Scheme 2). The cyclization of compounds **7a,b** was achieved easily in ethanol in the presence of triethyl amine at −10 °C giving 2-ethoxycarbonyl-, and 2-methoxycarbonyl-4-propylthiazolo [5,4-d]pyrimidine-5,7 (**4H**)-dione-1-oxide **8a,b** (Scheme 2) while compounds **7c,d**were cyclized under reflux in excess of triethyl amine in ethanol to give 2-propyl- and 2-phenyl-4-propyl thiazolo [5,4-d]pyrimidine-5,7 (**4H**)-dione-1-oxide **8c,d** (Scheme 2). The physical data of compounds **8a-d** are shown in Table II and. It was noted that the treatment of compound **6** with benzyl mercaptan in ethanol in the presence of one equivalent of triethyl amine at room temperature for 1h, led to the formation of 5-nitro-1-propyluracil-6-triethylammonium chloride **9** in 53% yield and compound **7d** in 14% yield.

TABLE II Physical data for compounds 7a-d and 8a-d

compd. no.	*m.p. °C*	*R_f (SG)*	*Yield %*	*Mol. Formula (mol. wt.)*	*Analysis calcd (found)*			*UV in methanol*	
					C	*H*	*N*	*λ max (nm)*	*logε max*
7a	83–85	0.60A	36	$C_{11}H_{15}N_3O_6S$	41.63	4.76	13.24	279.0	3.91
				(317.31)	(41.76)	(4.73)	(13.58)	202.0	4.10
b	66	0.52A	51	$C_{10}H_{13}N_3O_6S$	39.59	4.32	13.85	278.0	4.22
				(303.28)	(39.57)	(4.22)	(14.25)	202.0	4.55
c	111	0.58A	47	$C_{11}H_{17}N_3O_4S$	45.98	5.96	14.62	286.0	4.06
				(287.32)	(45.47)	(5.77)	(14.50)	202.0	4.29
d	193	0.68A	46	$C_{14}H_{15}N_3O_4S$	52.32	4.70	13.07	290.0	4.11
				(321.34)	(52.18)	(4.40)	(13.15)	202.0	4.55
8a	149–51	0.13A	43	$C_{11}H_{13}N_3O_5S$	44.14	4.37	14.03	314.0, 278.0	4.26, 4.38
				(299.29)	(44.21)	(4.76)	(14.78)	257.0	4.22
b	176–80	0.13A	52	$C_{10}H_{11}N_3O_5S$	42.10	3.88	14.72	318.0, 278.0	4.01, 4.12
				(285.27)	(42.20)	(3.62)	(14.72)	256.0, 204.0	3.99, 3.98
c	>270	0.14A	73	$C_{11}H_{15}N_3O_3S$	49.05	5.61	15.60	316.0, 243.0	4.01, 3.87
				(269.31)	(48.71)	(5.49)	(14.88)	221.0	4.31
d	193–5	0.16A	67	$C_{14}H_{13}N_3O_3S$	55.43	4.32	13.85	316.0, 242.0	4.29, 4.08
				(303.32)	(55.43)	(4.19)	(13.46)	220.0	4.49



SCHEME 2

EXPERIMENTAL

Melting points were taken on a YANACO micro-stage melting point apparatus and are uncorrected. All reactions were followed by tlc (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(A) 1:9 methanol-chloroform; (B) 1:4 methanol-chloroform].

6-Ethoxycarbonylmethylenethio-, and 6-Methoxycarbonyl Methyl-Enethio-1-Methyluracil (2a,b)

Ethyl- or methylthioglycolate (3.1 mmol) and triethyl amine (0.3 ml, 1 eq) were added to a suspension of 6-chloro-1-methyluracil (0.5 g, 3.1 mmol) in ethanol (10 ml) at room temperature followed by stirring for 30 min. The resulting precipitates were collected by filtration, washed with ethanol and recrystallized from ethanol to give 2a,b. ^{1}H NMR (DMSO-d$_6$) of compound **2a** showed, d 1.13 (t, CH$_3$, 3H), d 3.27 (s, NCH$_3$, 3H), d 3.58 (s, SCH$_2$, 2H), d 4.11 (q, CH$_2$, 2H), d 5.26 (s, 5CH, 1H), and d 10.15 (bs, NH, 1H).

6-Butylthio- and 6-Benzylthio-1-Methyluracil (2c,d)

To a suspension of 6-chloro-1-methyluracil (0.5 g, 3, 1 mmol) in ethanol (10 ml), butyl mercaptane or benzyl mercaptane (3.1 mmol) and triethyl amine (3.1 mmol) were added at room temperature and stirred for 2h. The resulting precipitates were filtered off, washed with ethanol, dried at 80 °C and recrystallised from ethanol to give **2c**, **2d**. ^{1}H NMR (DMSO-d_6) of compound **2d** showed, d 3.17 (s, NCH_3, 3H), d 3.91 (s, SCH_2, 2H), d 5.28 (s, 5CH, 1H), d 7.14 (s, aromatic, 5H), and d 10.18 (bs, NH, 1H).

6-Alkoxycarbonylmethylenethio-, 6-Butylthio-, and 6-(4-Nitrophenyl)-1-Methyl-5-Nitrouracil (3a-d)

To an ice cooled compound **2a-d** in concentrated sulphuric acid (1.12 ml), fuming nitric acid (0.38 ml) was added dropwise with stirring, the temperature being kept below 5 °C. The reaction mixture was stirred for 15 min at this temperature and then poured on ice with vigorous shaking. The resulting precipitate was filtered off, washed with ether, dried at 50 °C and recrystallized from ethanol. ^{1}H NMR (DMSO-d_6) of compound **3b** showed, d 3.64 (s, NCH_3, 3H), d 3.77 (s, SCH_2, 2H), d 3.78 (s, 3H, OCH_3) d 11.55 (bs, NH, 1H), and 3c showed, d ().88 (t, CH_3, 3H), d 1.5 (m, CH_2, 4H), d 2.89 (t, SCH_2, 2H), d 3.55 (s, NCH_3, 3H), d 11.48 (bs, NH, 1H).

2-Ethoxycarbonyl-, 2-Methoxycarbonyl-, and 2-(4-Nitrophenyl)-4-Methylthiazolo[5,4.d]Pyrimidine-5,7 (4H)-Dione-1-Oxide (4a,b,d)

Triethyl amine (1 mol eq) was added to a suspension of compound **3a** or **3b** or **3d** (0.83 mmol) in ethanol (15 ml) with stirring under reflux during 30 min. The reaction mixture was evaporated in vacuo. The residue was washed with ether several times, and then with methanol. The precipitate was filtered off, dried in vacuo and recrystallized from ethanol/DMF. ^{1}H NMR (DMSO-d_6) of compound **4a** showed. d 1.3 (t, CH_3, 3H), d 3.36 (s, NCH_3, 3H), d 4.33 (q, OCH_2, 2H), d 11.48 (bs, NH, 1H). and compound **4d** showed, d 3.49 (s, NCH_3, 3H), d 8.3–8.65 (dd, aromatic, 4H), d 11.58 (bs, NH, 1H). -MS (70eV); m/z (%) of compound **4a** = 272 (100) [M^+ + H]. 256 (29) [M^+-O], 210 (11) [M^+-OCO_2H], 185 (49)

[M + -OCO_2Et-H_2], compound **4b** showed m/z (%) = 258 (23) [M^+ + H], 242 (10) [M^+-O]. 210 (5) [M + -OCH_3OH], 185 (100) [M^+-OCO_2CH].

2-Propyl-4-Methylthiazolo[5,4-d]Pyrimidine-5,7 (4H)-Dione 1-Oxide (4c)

Triethylamine (1 mol eq) was added to a suspension of 6-butylthio-1-methyl-5-nitrouracil **3c** (0.06 g, 0.2 mmol) in ethanol with stirring under reflux and the reflux was continued for 6h. After cooling, the resulting precipitate was collected by filtration, washed with ethanol, dried in an oven at 80 °C and recrystallised from ethanol/DMF.

6-Ethoxy-, and 6-Methoxycarbonylmethylenethio-5-Nitro-Propyl-Uracil (7a,b)

To a suspension of 6-chloro-5-nitro-1-propyluracil (0.20 g. 0.85 mmol) in ethanol and potassium carbonate (0.12 g. 0.85 mmol) ethyl, or methylglycolate (1 mol eq) were added at room temperature with stirring for 45 min. The reaction mixture was evaporated in vacuo. The residue was dissolved in chloroform and washed with water several times. The organic layer was dried and evaporated in vacuo, the residue was triturated with hexane. The resulting precipitate was filtered off, dried in vacuo and recrystallised from chloroform. ^1H NMR ($CDCl_3$) of compound **7a** showed, d 0.98 (t, CH_3, 3H), d 1.29 (t, CH_3, 3H), d 1.69 (m, CH_2, 2H), d 3.77 (s, SCH_2, 2H), d 4.11–4.35 (t, q, NCH_2, OCH_2, 4H), d 8.92 (bs, NH, 1H) and compound **7b** showed, d 0.98 (t, CH_3, 3H), d 1.68 (m, CH_2, 2H), d 3.76 (s, OCH_3, 3H), d 3.78 (s, SCH_2, 2H), d 4.1 (t, NCH_2, 2H), d 9.28 (bs, NH, 1H).

6-Butylthio-, and 6-Benzylthio-5-Nitro-1-Propyluracil (7c,d)

To a suspension of 6-chloro-5-nitro-1-propyluracil (0.20 g, 0.85 mmol) in ethanol and potassium carbonate (0.12 g. 0.85 mmol) butyl-, or benzyl mercaptane (1 mol eq) were added at room temperature with stirring for 8h. The mixture was evaporated in vacuo, the residue was dissolved in chloroform and washed with water. The chloroformic layer was evaporated in vacuo, the resulting precipitate was filtered off, dried in vacuo and recrystallised from chloroform. ^1H NMR ($CDCl_3$) of compound **7c** showed, d 0.9–1.6 (tt, $2CH_3$, 6H), d 1.54–1.69 (m, $3CH_2$, 6H), d 2.99 (t,

NCH_2, 2H), d 4.1 (t, SCH_2, 2H), d 8.68 (bs, NH, 1H) and compound **7d** showed, d 0.97 (t, CH_3, 3H), d 1.55 (m, CH_2, 2H), d 3.86 (t, NCH_2, 2H), d 4.21 (s, SCH_2, 2H), d 7.33 (s, aromatic, 5H), d 8.68 (bs, NH, 1H). -MS (70eV); m/z (%) of compound **7d** = 321 (6) [M^+], 277 (5) [M^+-CO,], 185 (57) [M + -CH_2O_2ph], 171 (23) [M + -NO_2CH_2ph], 157 (43), 93 (100).

2-Ethoxycarbonyl-, and 2-Methoxycarbonyl- 4- Propylthiazolo [5,4.d]Pyrimidine 5,7(4H) Dione-1-Oxide (8a,b)

Triethyl amine (1mol eq) was added to compound **7a** or **7b** (0.15 mmol) in abs. ethanol with stirring and the stirring was continued for 15 min. at room temperature. The formed precipitate was filtered off, washed with ether and dried in vacuo. ^{1}H NMR ($CDCl_3$) of compound **8a** showed, d 0.80 (t, CH_3, 3H), d 1.28 (t, CH_3, 3H), d 1.66 (m, CH_2, 2H), d 3.73 (t, NCH_2, 2H), d 4.32 (q, OCH_2, 2H), and d 11.56 (bs, NH, 1H) and compound **8b** showed, d 1.01 (t, CH_3, 3H), d 1.68 (m, CH_2, 2H), d 3.79 (s, OCH_3, 3H), d 4.16 (t, NCH_2, 2H), d 9.17 (bs, NH, 1H). -MS (70eV): m/z (%) of compound 8a = 300 (92) [M^+ + H], 284 (100) [M^+-O], 238 (27) [M + -OCO_2H], 185 (14) [M + -$NCOCO_2$Et], 93 (34)

2,4-Dipropyl-, and 2-Phenyl-4-Propylthiazolo[5,4-d]Pyrimidine-5,7 (4H)-dione-1-Oxide (8c,d)

A mixture of triethyl amine (4 mol eq) and compound **7c** or **7d** (0.17 mmol) in abs. ethanol were refluxed for 12h. The formed precipitate was collected by filtration, washed with ethanol, dried in vacuo at 40 °C and recystallized from chloroform. ^{1}H NMR ($CDCl_3$) of compound **8c** showed, d 0.80 (t, CH_3, 6H), d 1.5 (m, CH_2, 4H), d 3.52 (t, CH_2,4H), d 9.98 (bs, NH, 1H) and compound **8d** showed, d 0.98 (t, CH_3, 3H), d 1.63 (m, CH_2, 2H), d 3.71 (t, CH_2, 2H), d 6.72–7.13 (m, 5H, aromatic H), d 9.34 (bs, NH, 1H).

5-Nitro-1-Propyluracil-6-Triethylammonium Chloride (9) and (7d)

Triethyl amine (2.0 mol eq). compound **6** (0.30 g, 1.28 mmol) in ethanol and benzyl mercaptane (0.16 g, 1.28 mmol) were mixed with stirring at room temperature for 20h. The reaction mixture was evaporated in vacuo and triturated with ether several times. The resulting precipitate was filtered off, dried in vacuo giving **9** (0.23 g, 53%), m.p. 95 °C. ^{1}H NMR showed, d 0.84 (t, CH_3, 3H), d 1.34 (1, CH_3, 9H), d 1.73 (m, CH_2, 2H), d 3.10–3.17 (q, CH_2, 6H), d 3.82 (1, CH_2, 2H), d 10.67 (bs, NH, 1H).

UV (methanol)	λ_{max}	316.0, 244.0, 221.0
	$\log\varepsilon_{max}$	4.16, 3.72, 4.37

The mother liquor was allowed to stand at room temperature for 1 day. The resulting precipitate was filtered off, washed with ether, dried in vacuo and recrystallised from ethanol giving (60 mg) of compound **7d.**

References

[1] F.M. Jr. Schabel. J.A. Montgomery, H.E. Skipper. W.R. Laster and J.R. Thomson. *Cancer Research,* **21**, 691 (1961).

[2] K. Senga, M. Ichiba. H. Kanazawa and S. Nishgaki, *J. Heterocyclic Chem.*, **19**, 77 (1982).

[3] G.B. Brown. G. Levin, S. Murphy, A. Sele, H.C. Reilly, G.S. Tarnowski, F.A. Schmid, M.N. Teller and C.C. Stock, *J. Med. Chem.*, **8**, 190–5 (1965).

[4] K. Senga, M. Ichiba and S. Nishigaki, *J. Org. Chem.*, **44**, 3830 (1979).

[5] T. Itoh, R.G. Melik-Obanjanian, I. Ishikawa, N. Kawabara, Y. Mizuno, Y. Honma. M. Hozumi and H. Ogura, *Chem. Pharm. Bull.*, **37**, 3184 (1989).

[6]] Z. Kazimieiczuk and D. Shugar, *Acta Biochim Polon.*, **17**, 325 (1970).

[7] Sh. Youssif. *Ph.D. Thesis, Chem. Department, Fac. of Sci.*, Zagazig Uni., Zagazig Egypt (1993).