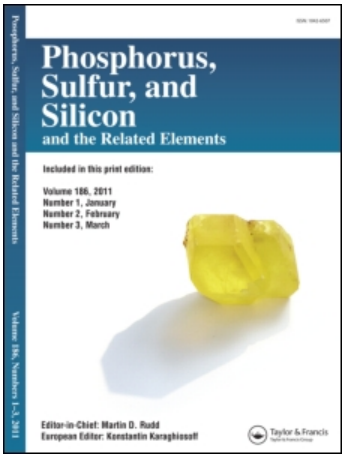

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS CONTAINING PYRIDOPY RIMIDINE

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To cite this Article El-Dean, A. M. Kamal(1990) 'SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS CONTAINING PYRIDOPY RIMIDINE', Phosphorus, Sulfur, and Silicon and the Related Elements, 48: 1, 211 — 215
To link to this Article: DOI: 10.1080/10426509008045899
URL: http://dx.doi.org/10.1080/10426509008045899

Phosphorus, Sulfur, and Silicon, 1990, Vol. 48, pp. 211–215
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Printed in the United Kingdom

SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS CONTAINING PYRIDOPYRIMIDINE

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(Received September 11, 1989; in final form October 2, 1989)

5,6,7,8-Tetrahydro-3-amino-2-methyl-1[2H]-thioxoisoquinoline-4-carbonitrile (**2**) reacted with carbon disulphide in alcoholic KOH followed by acidification with HCl to produce pyrimidotetrahydroisoquinoline dithiole (**3**), which when allowed to react with halocompounds, gave the compounds (**5–9**). It also reacted with acrylonitrile to produce compound (**10**). When compound (**2**) was allowed to react with ethylorthoformate in the presence of Ac_2O, the corresponding ethoxy azomethene derivative (**11**) was obtained, which when allowed to react with amines or hydrazine, in order to obtain pyrimidoisoquinoline (**12**), produced mainly the starting material (**2**).

Key words: Synthesis, tetrahydroisoquinolinthione, pyrimidotetrahydroisoquinolinthione.

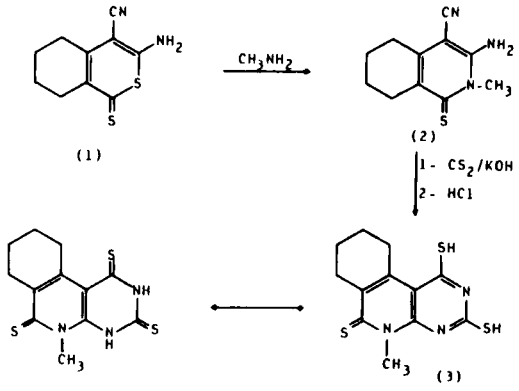
INTRODUCTION

G. H. Hitchings and co-workers have made a comprehensive study[1,2] of antifolic acid activity in 2,4-diaminopyridopyrimidines. They have demonstrated that very many such compounds, both simple and fused, show such activity. In this course of this work some pyrido[3,2-d]pyrimidines and a large number of pyrido[2,3-d]-pyrimidines were shown to be highly active against a variety of pathogenic bacteria.[3–6] It was also reported that some octahydropyrido[4,3-d]pyrimidine have an analgesic and antiarthritic activity,[7,8] and some tetrahydropyrido[4,3-d]pyrimidine show antipyretic, diuretic, bacteriostatic, sedative, and coronar-dilating activities.[9–12]

From these points and in continuation to our work in the synthesis of pyridines fused with different heterocyclic compounds,[13–15] herein we synthesise some heterocyclic compounds containing the pyridopyrimidine structure with the hope that they may be biologically active compounds.

RESULTS AND DISCUSSION

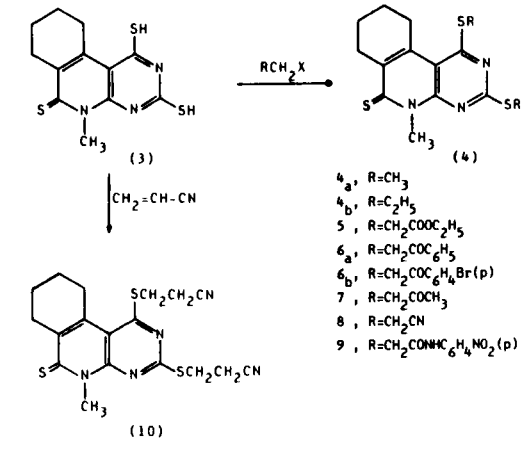
5,6,7,8-Tetrahydro-3-amino-2-methyl-1[2H]thioxoisoquinoline-4-carbonitrile (**2**)[16] which was prepared by the action of methyl amine on 3,4-tetramethylene-6-amino-5-cyano-thiopyran-2-thione (**1**),[17] was used as a starting material. When compound (**2**) was treated with carbon disulphide in refluxing ethanolic KOH (10%), followed by acidification with HCl 7,8,9,10-tetrahydro-5-methyl-7[6H]thioxopyrimido[4,5-c]isoquinoline-1,3-dithiole (**3**) was produced.



The structure of compound (**3**) was supported by elemental and spectral analyses.

When dimercaptopyrimidotetrahydroisoquinoline (**3**) was allowed to react with halocompounds namely, alkyl halides, ethyl chloroacetate, phenacyl bromide and its derivatives, bromoacetone, chloroacetonitrile, chloroacetanilides in warm ethanol and in the presence of sodium acetate, dialkylated thio derivatives were produced (**4–9**). Attempts to separate monoalkylated products have failed. The use of one or two moles of alkylating agent always produced the dialkylated product.

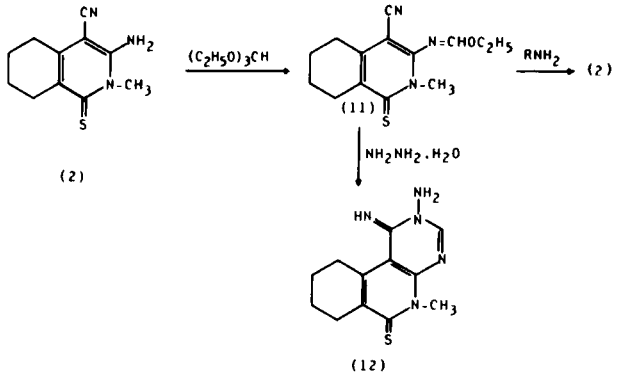
Also cyanoethylation of the two mercapto groups in compound (**3**) was achieved by refluxing compound (**3**) with acrylonitrile in ethanol and in the presence of drops of piperidine.



The structures of products (**4–10**) were confirmed by elemental and spectral data; IR of (**4a,b**) showed the disappearance of bands characteristic for (NH) groups; IR of (**5–7**) showed the disappearance of bands characteristic for (NH) group and absorption bands at 1470–1720 cm^{-1} (C=O) groups; IR of (**8,10**) showed absorption bands at 2240–2220 cm^{-1} (C=N) groups and IR of (**9**) showed bands at 3400–3300 cm^{-1} (NH) and 1710 cm^{-1} (C=O).

When compound (**2**) was refluxed with ethyl orthoformate in acetic anhydride,

the corresponding ethoxyazomethene derivative (**11**) was obtained which when treated with aliphatic or aromatic amine in ethanol effected the hydrolysis of azomethene group and produced compound (**2**), but when using hydrazine hydrate, the reaction mainly produced compound (**2**) and ten percent of pyrimidotetrahydroisoquinoline (**12**).



EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Pye–Unicam SP 3-100 spectrophotometer using KBr Wafer technique. The ^{1}H NMR spectra were obtained on a Varian EM-390 90 MHz NMR spectrometer. Elemental analysis were determined using Perkin–Elmer 240 C Microanalyser.

5,6,7,8-Tetrahydro-3-amino-2-methyl-2[1H]thioxoisoquinoline-4-carbonitrile (**2**)[17] was obtained by action of methyl amine on 3,4-tetramethylene-6-amino-5-cyano-2(1H)thione (**1**). The product was recrystallized from ethanol, m.p. 243–5°C.

1,2,3,4,7,8,9,10-Octahydro-5-methyl-6(5H)pyrimido-1,3,6-trithione (**3**). To a solution of compound (**2**) (0.01 mole) in ethanolic KOH (20 ml 10%), carbon disulphide (2 ml) was added. The mixture was refluxed for 3 hrs, then excess CS_2 was evaporated, and the mixture was acidified with HCl. The solid product was collected and recrystallized from ethanol as orange crystals in 70% yield, m.p. >300°C.

The IR spectrum of (**3**) showed absorption bands at 3250–3100 cm^{-1} for (NH) groups and also showed the disappearance of bands characteristic for (NH_2 and (C≡N) groups. ^{1}H NMR of (**3**) in CF_3COOH showed signals at δ1.9 (m, 4H, $2CH_2$), δ2.7 (m, 4H, $2CH_2$) of cyclohexane ring and at δ3.9 (s, 3H, N—CH_3).

Anal. Calcd. For $C_{12}H_{13}N_3S_3$: C, 48.81; H, 4.40; N, 14.23; S, 32.54%. Found: C, 49.10; H, 4.68; N, 13.95; S, 32.50%.

Reaction of compound (**3**) *with halocompounds.* General procedure: A mixture of compound (**3**) (0.01 mole), sodium acetate (1 gm) and halocompound (0.02 mole) in ethanol (30 ml) was heated on a water bath for $\frac{1}{2}$ hr. The solid product was collected and recrystallized from suitable solvent. The physical constants of compounds (4–9) are listed in Table I. ^{1}H NMR of (**4b**) (in $CDCl_3$) δ 1.3 (m, 6H, $2CH_3$), δ 3.7 (m, 4H, $2CH_2$) of ethyl groups, δ 1.9 (m, 4H, $2CH_2$) and δ 2.7 (m, 4H, $2CH_2$) of cyclohexane ring and at δ 1.9 (m, 4H, $2CH_2$) and δ 2.7 (m, 4H, $2CH_2$) of cyclohexane ring and at δ 4.00 (s, 3H, N—CH_3); ^{1}H NMR of (5) in $CDCl_3$, δ 1.4 (m, 6 h, $2CH_3$), and δ 4.4 (m, 4H, 2CH2) of ester group δ1.9 (m, 4H, $2CH_2$), δ 2.9 (m, 4H, $2CH_2$) of cyclohexane ring, δ 4.0 (s, 3H, N—CH_3) and δ 4.8 (s, 4H, S—CH_2), ^{1}H NMR of (**6a**) in DMSO-d_6, δ 1.9 (m, 4H, $2CH_2$), δ 2.8 (m, 4H, $2CH_2$) of cyclohexane ring, δ 4.0 (s, 3H, N—CH_3), δ 4.5 (s, 4H, 2 S—CH_2) and δ 7.3 (m, 5H, Ar—H).

Cyanoethylation of compound (**3**). To a mixture of compound (**3**) (0.01 mole) and acrylonitrile (0.02 mole) in ethanol (30 ml), drops of piperidine were added. The mixture was refluxed on water bath for one hour, allowed to cool, the solid product was collected and recrystallized from ethanol to give (**10**) as yellow needles (Table I).

TABLE I

Physical constants and analytical data of compounds (4–10)

Compound no.	RR	M.P. 0°	Solvent of crystallization	Yield %	Molecular formula	Analytical data calcd/found C	H	N	S
4a	CH_3	150	Ethanol	85	$C_{14}H_{17}N_3S_3$	52.01	5.26	13.00	29.72
						51.85	5.60	13.32	29.55
4b	C_2H_5	97–9	Ethanol	90	$C_{16}H_{21}N_3S_3$	54.70	5.98	11.96	27.35
						55.04	6.12	11.80	27.50
5	$CH_2COOC_2H_5$	128–30	Ethanol	90	$C_{20}H_{25}N_3O_4S_3$	51.39	5.35	8.99	20.55
						51.50	5.60	9.18	20.32
6a	$CH_2COC_6H_5$	195	Acetic acid	87	$C_{28}H_{25}N_3O_2S_3$	63.27	4.70	7.90	18.07
						63.00	4.98	8.12	17.92
6b*	$CH_2COC_6H_5Br(p)$	215	Acetic acid	83	$C_{28}H_{23}Br_2N_3O_2S_3$	48.76	3.33	6.09	13.93
						48.92	3.02	5.82	14.16
7	CH_2COCH_3	176	Ethanol	80	$C_{18}H_{21}N_3O_2S_3$	53.07	5.15	10.31	23.58
						53.26	4.87	10.08	23.79
8	CH_2CN	200	Ethanol	88	$C_{16}H_{15}N_5S_3$	51.47	4.02	18.76	25.73
						51.72	3.76	18.51	25.98
9	$CH_2CONHC_6H_4NO_2(p)$	238	Acetic acid	80	$C_{28}H_{25}N_7O_6S_3$	51.61	3.84	15.05	14.74
						51.86	4.08	14.77	15.00
10	CH_2CH_2CN	197	Ethanol	75	$C_{18}H_{19}N_5S_3$	53.96	4.73	17.45	23.94
						54.08	5.09	17.12	24.22

* Calcd. Br = 23.22, found = 22.95.

Reaction of compound (**3**) *with ethyl orthoformate.* A mixture of compound (**3**) (0.01 mole) and ethyl orthoformate (0.01 mole) was refluxed for 3 hrs, then allowed to cool. The solid product was collected and recrystallized from ethanol to give (**11**) as yellow needles, in 75% yield, m.p. 150°C.

The IR spectrum of compound (**11**) showed an absorption band at 2230 cm^{-1} (C≡N) and also showed the disappearance of the band characteristic for (NH_2) group.

Anal. Calcd. For $C_{14}H_{17}N_3OS$: C, 61.09; H, 6.18; N, 15.27; S, 11.63%. Found: C, 61.35; H, 5.92; N, 15.53; S, 11.50%.

Reaction of compound (**11**) *with amines and/or hydrazine hydrate.* A mixture of compound (**11**) (0.01 mole) and aliphatic amine solution (methyl-or ethyl amine) and/or hydrazine hydrate (0.01 mole) was refluxed in ethanol for 2 hrs then allowed to cool. The solid product was identified as a compound (**2**) by m.p., m.m.p. TLC, and IR spectra and in the case of using hydrazine hydrate, the product when recrystallized from ethanol, the dissolved portion was identified as compound (**2**) by m.p., m.m.p., TLC and IR spectra, and the undissolved portion was identified as pyrimidotetrahydroisoquinoline (**12**). The IR spectrum of (**12**) showed absorption band at 3400–3200 cm^{-1} for (NH_2 and NH) groups and also showed the disappearance of a band characteristic for (C≡N) group. ^1H NMR of (**11**) in $CDCl_3$ showed signals at δ 1.3 (t, 3H, CH_3) and δ 4.5 (q, 2H, CH_2) of ethyl group, δ 1.9 (m, 4 H, $2CH_2$) and δ 2.7 (m, 4H, $2CH_2$) of cyclohexane ring, δ 3.9 (s, 3H, N—CH_3) and δ 7.9 (s, 1H, CH=N—).

Anal. Calcd. For $C_{12}H_{14}N_5S$: C, 55.38; H, 5.38; N, 26.92; S, 12.30%; Found: C, 55.60; H, 5.52; N, 27.08; S, 12.00%.

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