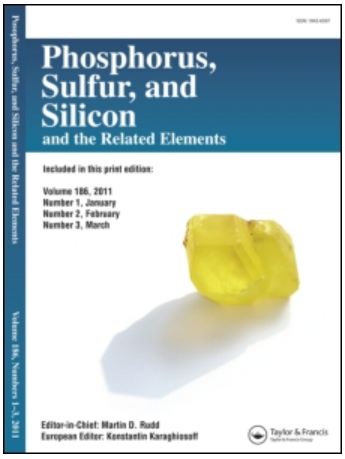

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Synthesis of Arsenical Adduct: Synthesis and Transformation of Dimercapto Compound to Arsenical Adduct

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SYNTHESIS OF ARSENICAL ADDUCT: SYNTHESIS AND TRANSFORMATION OF DIMERCAPTO COMPOUND TO ARSENICAL ADDUCT

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Reaction of isothiocyanates with thioamide in presence of pyridine afforded 1,3-dimercapto substrates in good yield. Adipoin reacts with phenylarsine oxide and triphenylarsine to give the bicyclic 1,3,2-dioxarsole derivatives. A variety of 1,3,2-arsadithiolane derivatives were obtained by reaction of 1,3-dimercapto substrate with arsenic trioxide, phenylarsine oxide, triphenylarsine triphenylarsine oxide in ethanol or better in chloroform.

Keywords: 1,3,2-arsadithiolane derivatives; 1,3-dithiol compounds; 1,3,2-dioxarsole derivatives; arsenic compounds; isothiocyanates; thioamide

Epidemiological evidence indicates that ingestion of arsenic compounds via drinking water can result in skin cancer and cancer of internal organs,[1] whereas occupational arsenic exposure seems to cause lung cancer and possibly other cancers.[2] Skin disorders such as hyperkeratosis, hyperpigmentation, and depigmentation have been described in relation to arsenic containing water and there are dermatologic manifestations in children.[3] Noncirrhotic portal fibrosis is another disorder reported after consumption of water containing arsenic.[4] Peripheral vascular disease and cardiovascular disease have been associated with environmental exposure to inorganic arsenic in drinking water[5–12] as well as occupational exposures.[13–16] Diabetes Mellitus has also been reported a risk factor for peoples exposed to arsenic through drinking water.[17,18]

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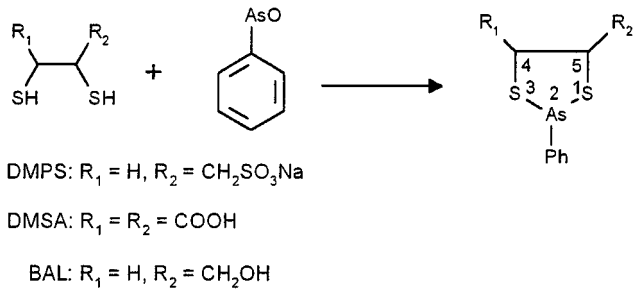
Ground water pollution by arsenic compounds has drawn considerable attention and raised serious concern in Bangladesh and other locations.[19] According to available information, millions of people are "at risk," endangered by arsenic in Bangladesh.[19] Arsenic poisoning is known to interfere with the cell's sulfhydryl groups. In humans, the toxicity of trivalent arsenic is mainly due to its binding to the sulfhydryl groups of lipoic acid.[20–22] Therefore, arsenic intoxication can be ameliorated by the administration of dithiol compounds. In mammals, fungi, and algae, detoxification of arsenic usually involves methylation and other biotransformations such as incorporation of arsenic into organic molecules by the formation of arsenocholine, arsenobetaine, or arsenosugars, for example.[23–25]

Three chelating agents sodium 2,3-dimercapto-1-propane sulfonate (DMPS, Dimaval), meso-2,3-dimercaptosuccinic acid (DMSA, succimer) and 2,3-dimercapto-1-propanol (BAL, British Antilewisite) are being used therapeutically at the present time.[26–32] DMPS, DMSA, and BAL all have a vicinal dithiol groups as the arsenic binding site.[26–32] As is true with three therapeutic agents, each of these chelating agents has advantages and disadvantages. It is generally accepted that all of them form stable 1,3,2-arsadithiolane derivatives with bifunctional arsenicals (Scheme 1).



DMPS: $R_1 = H$, $R_2 = CH_2SO_3Na$

DMSA: $R_1 = R_2 = COOH$

BAL: $R_1 = H$, $R_2 = CH_2OH$

SCHEME 1

Because of high affinity of thiols for arsenic compounds, in this paper follows that line of research by reporting on a new series of dimercapto substrate **4a–c**, **7a**,**b** which are more useful chelating agents for arsenic compounds. Here, we report on the synthesis of five chelating agents, dimercapto substrate **4a–c**, **7a**,**b** from isothiocyanates and their reaction with arsenic trioxide, phenylarsine oxide, triphenylarsine, or triphenylarsine oxide in solvent chloroform or ethanol afforded six membered heterocyclic ring.

SYNTHESIS OF 1,3-DIMERCAPTO SUBSTRATE

Recently we have been reported[33–35] the synthesis of mono mercapto heterocycles from ethyl isothiocyanatoacetate. In this article we report on dimercapto substrate by the reaction of various isothiocyanate with thioamido moiety. For better result and smooth reaction firstly we used very sensitive isothiocyanates: phenyl isothiocyanate (**3a**), methyl isothiocyanate (**3b**), and ethyl isothiocyanatoacetate (**3c**) with thioacetamide and thiobenzamide at reflux temperature in presence of pyridine.

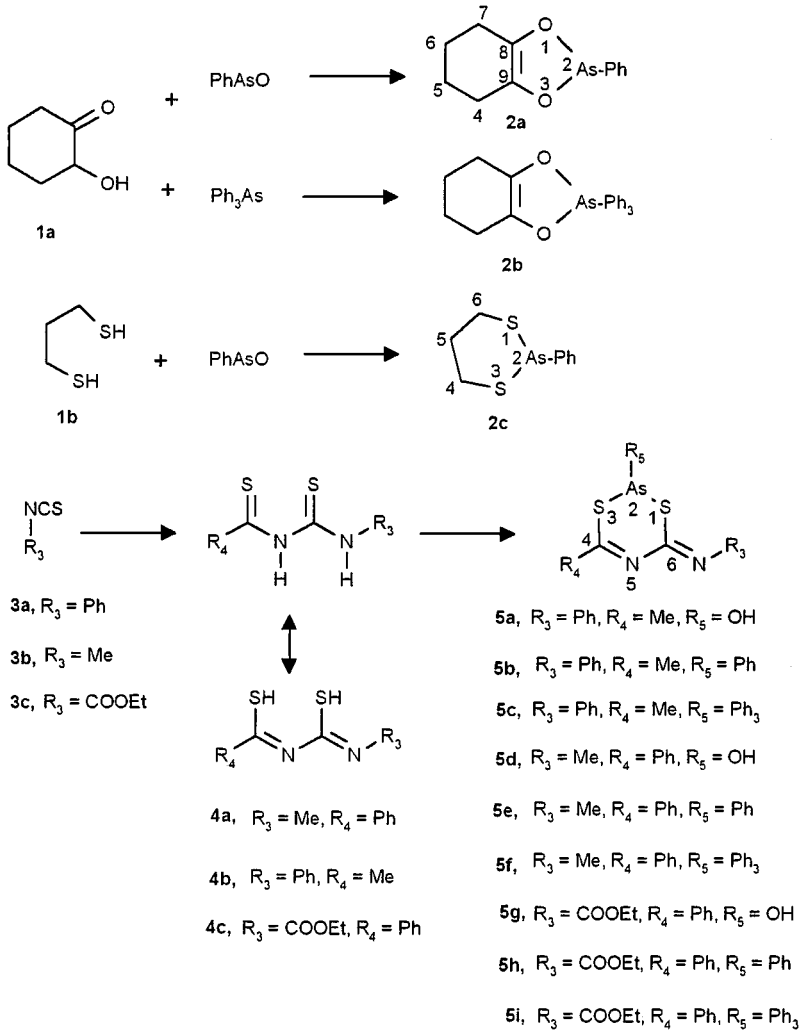
Thus, the desired and conceivable product, 1-thioacetyl-3-phenyl-2-thiourea (**4a**) was synthesized from thioacetamide and phenyl isothiocyanate (**3a**) at reflux for 4 h in pyridine medium. After usual work up precipitated materials were collected by filtration and obtained in 59% yield and mp 165–167°C as white needles after recrystallization from ethanol. Similarly, 1-thiobenzoyl-3-methyl-2-thiourea (**4b**) was prepared in 63% yield, m.p. 156–158°C as yellow needles by a direct condensation of thiobenzamide with methyl isothiocyanate (**3b**). In a similar manner, 1-thiobenzoyl-3-ethoxycarbonyl-2-thiourea (**4c**) was also obtained as brown needles frequently from thiobenzamide and ethyl isothiocyanatoformate (**3c**) (Scheme 2).

The reaction of thiobenzamide and ethyl isothiocyanatoacetate[33] (**6**) refluxing for 2 h in pyridine to afford open chain product 1-thiobenzoyl-3-ethoxycarbonylmethyl-2-thiourea (**7a**) as yellow needles in 62% and m.p. 122–124°C. By a similar method treatment of thioacetamide and ethyl isothiocyanatoacetate (**6**) in pyridine for 2 h furnished 1-thioacetyl-3-ethoxycarbonylmethyl-2-thiourea (**7b**) as yellow needles in 57% as shown in Table I.

The common type of prototropic tautomerism in heterocyclic compounds involved the movement of a proton between a ring nitrogen atom and substituent sulfur atom connected to the ring.[33–35] In case of compounds **4a–c**, **7a**,**b** the tautomeric equilibrium between thioamide and imine-thiol form have been indicated by ^{1}H and ^{13}C NMR spectra (Table II).

HETEROCYCLIC RING FROM ADIPOIN

When a solution of one equivalent of 2-hydroxycyclohexanone (adipoin[40] **1a**) in dry dioxane was added to that of phenylarsine oxide, the reaction was completed at reflux temperature for 24 h (Scheme 2). The product was isolated in 63% yield and formulated as 2-phenyl-4, 5,6,7-tetrahydro-1,3,2-benzodioxarsole (**2a**). In the same way, **1a** reacts



SCHEME 2

with triphenylarsine in dry dioxane at reflux temperature for 12 h to give the 2,2,2-triphenyl-4,5,6,7-tetrahydro-1,3,2-benzodioxarsole (**2b**). This adduct is a colorless crystalline substance with a sharp melting point and is remarkably stable. Reaction of triphenylarsine with *ortho*-quinones in a manner rather different from the already known.[36]

TABLE I

No.	IR (KBr): ν_{max} cm^{-1}	Yd %	m.p.°C	Molecular formula	Anal. Calcd./Found C%	H%	N%
4c		54	99–101	$C_{11}H_{12}N_2O_2S_2$	49.23	4.51	10.43
					49.06	4.62	10.58
7a		62	122–124	$C_{12}H_{14}N_2O_2S_2$	51.04	4.99	9.92
					51.13	5.06	9.78
7b		57	146–148	$C_7H_{12}N_2O_2S_2$	38.15	5.49	12.78
					38.27	5.41	12.67
2a	2933, 2370, 1542, 1508, 1438, 1195, 1095, 775, 740, 692	63	158–160	$C_{12}H_{13}O_2As$	54.56	4.95	
					54.31	5.19	
2b	2931, 2368, 2345, 1560, 1542, 1508, 1438, 1195, 1095, 775, 692	51	120–122	$C_{24}H_{23}O_2As$	68.90	5.54	
					68.59	5.67	
2c	2904, 2366, 2345, 2202, 1637, 1560, 1508, 1419, 1240, 1095, 852, 574	56	232–235	$C_9H_{11}S_2As$	41.86	4.29	
					42.07	5.61	
5a	3197, 2366, 2345, 1724, 1639, 1607, 1508, 1465, 1419, 1240, 1211, 1174, 1027, 721, 640	45	149–151	$C_9H_9N_2OS_2As$	36.00	3.02	9.32
					36.75	3.41	9.63
5b	3180, 2994, 2367, 2345, 1642, 1615, 1540, 1479, 1430, 1240, 1376, 1334, 1301, 1226, 1176, 1074, 1022, 998, 692	52	188–189	$C_{15}H_{13}N_2S_2As$	50.00	3.63	7.77
					50.32	3.84	7.59
5c	3184, 2983, 2365, 2340, 1640, 1613, 1547, 1480, 1443, 1241, 1372, 1335, 1305, 1230, 1180, 1075, 1020, 680	54 35	130–132	$C_{27}H_{23}N_2S_2As$	63.02	4.50	5.44
					63.26	4.74	5.17
5d	3191, 2357, 2342, 1729, 1640, 1607, 1508, 1465, 1420, 1240, 1211, 1180, 1027, 724, 645	42	165–167	$C_9H_9N_2OS_2As$	38.03	3.19	9.85
					37.76	3.40	9.61
5e		46	185–187	$C_{15}H_{13}N_2S_2As$	50.00	3.63	7.77
					50.31	3.39	7.98

(Continued on next page)

TABLE I (*Continued*)

No.	IR (KBr): ν_{max} cm^{-1}	Yd %	m.p.°C	Molecular formula	Anal. Calcd./Found C%	H%	N%
5f	3191, 2988, 2345, 1722, 1637, 1605, 1473, 1421, 1323, 1210, 1180, 1024, 701	52 33	125–127	$C_{27}H_{23}N_2S_2As$	63.02 63.28	4.50 4.68	5.44 5.23
5g	3189, 2366, 2342, 1720, 1641, 1630, 1508, 1465, 1415, 1235, 1211, 1170, 1045, 728, 640	40	145–147	$C_{11}H_{11}N_2O_3S_2As$	36.87 36.52	3.09 3.44	7.81 8.43
5h		51	170–172	$C_{17}H_{15}N_2O_2S_2As$	48.80 48.53	3.61 3.76	6.69 6.81
5i	3190, 2985, 2345, 1720, 1635, 1600, 1470, 1416, 1330, 1211, 1170, 1021, 695	53 35	132–134	$C_{29}H_{25}N_2O_2S_2As$	60.83 60.38	4.40 4.89	4.89 5.23
8a	3188, 2360, 2348, 1720, 1645, 1632, 1505, 1465, 1421, 1245, 1210, 1178, 1025, 720, 630	46	230–232	$C_{12}H_{13}N_2O_3S_2As$	38.71 38.97	3.51 3.74	7.52 7.19
8b	3180, 2998, 2365, 2345, 1720, 1640, 1626, 1509, 1479, 1430, 1241, 1376, 1330, 1335, 1228, 1171, 1070, 1021, 998, 690	51	172–174	$C_{18}H_{17}N_2O_2S_2As$	50.01 50.37	3.96 3.85	6.47 6.64
8c	3182, 2989, 2340, 1721, 1635, 1609, 1508, 1465, 1418, 1332, 1210, 1174, 1021, 685	53 39	154–156	$C_{30}H_{27}N_2O_2S_2As$	61.05 61.65	4.98 4.78	4.77 4.98
8d	3197, 2366, 2345, 1720, 1640, 1615, 1501, 1465, 1419, 1240, 1210, 1178, 1025, 640	39	238–240	$C_7H_{11}N_2O_3S_2As$	27.10 26.53	3.57 3.75	9.02 8.61
8e		44	175–177	$C_{13}H_{15}N_2O_2S_2As$	42.16 42.34	4.08 4.27	7.56 7.72
8f	3180, 2994, 2367, 2345, 1739, 1640, 1624, 1588, 1479, 1430, 1240, 1376, 1334, 1301, 1226, 1176, 1074, 1022, 998, 734, 692	46 31	147–149	$C_{25}H_{25}N_2O_2S_2As$	57.24 56.63	4.80 4.99	5.34 5.01

TABLE II

No.	^{1}H NMR ($CDCl_3$): δ_H ppm	^{13}C NMR ($CDCl_3$): δ_C ppm
4a	2.50 (s, 3H, Me), 7.20–7.50 (m, 5H, Ar—H), 8.22 (s, 1H, NH), 10.80 (s, 1H, NH)	34.96 (s, Me), 126.79 (d, C-4′), 127.22 (d, C-3′ and C-5′), 129.59 (d, C-2′ and C-6′), 137.19 (s, C-1′), 179.70 (s, C═S), 175.51 (s, C═S)
4b	3.67 (s, 3H, Me), 7.25–7.40 (m, 5H, Ar—H), 8.36 (s, 1H, NH), 9.82 (s 1H, NH)	50.14 (q, Me), 127.65 (d, C-4′), 128.92 (d, C-3′ and C-5′), 129.20 (d, C-2′ and C-6′), 137.59 (s, C-1′), 173.07 (s, C═S), 177.15 (s, C═S)
4c	1.40 (t, $J = 7.20$ Hz, 3H, Me), 4.20 (q, $J = 7.2$ Hz, 2H, OCH_2), 7.25–7.40 (m, 5H, Ar—H), 8.02 (s, 1H, NH), 9.10 (s, 1H, NH)	14.01 (q, Me), 127.28 (d, C-4′), 128.76 (d, C-3′ and C-5′), 129.53 (d, C-2′ and C-6′), 137.28 (s, C-1′), 167.24 (s, C═O), 171.04 (s, C═S), 200.53 (s, C═S)
7a	1.25 (t, $J = 7.1$ Hz, 3H, Me), 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2), 4.51 (s, 2H, CH_2), 7.82 (m, 2H, 2′-H and 6′-H), 7.38 (m, 3H, 3′-H, 4′-H and 5′-H) 8.09 (s, 1H, NH), 8.70 (s, 1H, NH)	13.99 (q, Me), 48.76 (t, CH_2), 62.02 (t, OCH_2), 126.88 (d, C-4′), 128.38 (d, C-3′ and C-5′), 131.93 (d, C-2′ and C-6′), 139.05 (s, C-1′), 166.92 (s, C═O), 171.10 (s, C═S), 183.94 (s, C═S)
7b	1.24 (t, $J = 7.2$ Hz, 3H, Me), 2.49 (s, 3H, Me), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2), 4.50 (s, 2H, CH_2), 7.97 (s, 1H, NH), 9.85 (s, 1H, NH)	13.95 (q, Me), 32.80 (q, Me), 48.76 (t, CH_2), 62.03 (t, OCH_2), 166.99 (s, C═O), 171.99 (s, C═S), 183.81 (s, C═S)
2a	1.17–1.83 (m, 4H, $2CH_2$), 2.05–2.50 (m, 4H, $2CH_2$), 7.36–7.47 (m, 3H, 3′-H, 4′-H and 5′-H), 7.69–7.76 (m, 2H, 2′-H and 6′-H)	25.24 (t, CH_2), 27.56 (t, CH_2), 37.72 (t, CH_2), 39.48 (t, CH_2), 128.55 (d, C-3′ and C-5′), 129.36 (s, C-1′), 130.52 (d, C-4′), 132.88 (d, C-2′ and C-6′), 144.21 (s, 2C—O—As)
2b	1.40–1.70 (m, 4H, $2CH_2$), 2.00–2.50 (m, 4H, $2CH_2$), 7.64 (m, 6H, 2′-H and 6′-H), 7.50 (m, 9H, 3′-H, 4′-H and 5′-H)	25.91 (t, CH_2), 27.57 (t, CH_2), 37.86 (t, CH_2), 39.34 (t, CH_2), 129.33 (d, C-3′ and C-5′), 131.51 (s, C-1′), 132.16 (d, C-4′), 132.53 (d, C-2′ and C-6′), 142.63 (s, 2C—O—As)
2c	2.09–2.17 (m, 2H, CH_2), 2.78–2.92 (t, 4H, CH_2), 7.75–7.87 (m, 1H, 2′-H and 6′-H), 7.37–7.47 (m, 3H, 3′-H, 4′-H and 5′-H)	25.92 (t, CH_2), 28.28 (t, CH_2), 36.90 (t, CH_2), 128.58 (d, C-4′), 129.14 (d, C-3′ and C-5′), 129.68 (d, C-2′ and C-6′) 132.35 (s, C-1′)
5a	2.46 (s, 3H, Me), 7.18–7.35 (m, 5H, Ar—H), 8.10 (bs, 1H, As—OH)	26.45 (q, Me), 127.37 (d, C-4′), 128.92 (d, C-3′ and C-5′), 129.69 (d, C-2′ and C-6′), 137.25 (s, C-1′), 167.06 (s, C—S), 175.51 (s, C—S)
5b	2.87 (s, 3H, Me), 7.10–7.45 (m, 10H, Ar—H)	26.58 (s, Me), 127.31 (d, C-4′), 128.78 (d, C-3′ and C-5′), 129.75 (d, C-2′ and C-6′), 137.68 (s, C-1′), 167.84 (s, C—S), 176.08 (s, C—S)
5c	2.90 (s, 3H, Me), 7.40–7.80 (m, 20H, Ar—H)	26.78 (s, Me), 127.62 (d, C-4′), 129.05 (d, C-3′ and C-5′), 129.85 (d, C-2′ and C-6′), 137.63 (s, C-1′), 167.72 (s, C—S), 175.41 (s, C—S)
5d	3.61 (t, 3H, Me), 7.10–7.35 (m, 5H, Ar—H), 7.68 (bs, 1H, As—OH)	45.97 (q, Me), 127.53 (d, C-4′), 128.90 (d, C-3′ and C-5′), 129.64 (d, C-2′ and C-6′), 137.21 (s, C-1′), 146.43 (s, C-8a), 167.13 (s, C—S), 175.50 (s, C—S)

TABLE II (*Continued*)

No.	^{1}H NMR ($CDCl_3$): δ_H ppm	^{13}C NMR ($CDCl_3$): δ_C ppm
5e	3.54 (s, 3H, Me), 7.10–7.45 (m, 10H, Ar—H)	45.75 (s, Me), 127.21 (d, C-4′), 128.49 (d, C-3′ and C-5′), 129.81 (d, C-2′ and C-6′), 137.43 (s, C-1′), 167.25 (s, C—S), 174.59 (s, C—S)
5f	3.54 (s, 3H, Me), 7.10–7.65 (m, 20H, Ar—H)	45.26 (s, Me), 127.09 (d,C-4′), 128.18 (d, C-3′ and C-5′), 129.32 (d, C-2′ and C-6′), 136.56 (s, C-1′), 167.84 (s, C—S), 175.43 (s, C—S)
5g	1.35 (t, J = 7.00 Hz, 3H, Me), 4.25 (q, J= 7.00 Hz, 2H, OCH_2), 7.15–7.35 (m, 5H, Ar—H), 7.98 (bs, 1H, As—OH)	13.82 (q, Me), 60.58 (t, OCH_2), 127.90 (d, C-4′), 128.81 (d, C-3′ and C-5′), 129.64 (d, C-2′ and C-6′), 137.04 (s, C-1′, 152.21 (s, C═O), 167.94 (s, C—S), 176.05 (s, C—S)
5h	1.35 (t, J = 7.00 Hz, 3H, Me), 4.30 (q, J = 7.00 Hz, 2H, OCH_2), 7.10–7.50 (m, 10H, Ar—H)	13.19 (q, Me), 60.45 (t, OCH_2), 127.98 (d, C-4′), 128.72 (d, C-3′ and C-5′), 129.46 (d, C-2′ and C-6′), 137.05 (s, C-1′), 152.21 (s, C═O), 166.97 (s, C—S), 176.26 (s, C—S)
5i	1.35 (t, J = 7.00 Hz, 3H, Me), 4.25 (q, J = 7.00 Hz, 2H, OCH_2), 7.10–7.55 (m, 20H, Ar—H)	13.89 (q, Me), 60.71 (t, OCH_2), 128.31 (d, C-4′), 128.91 (d, C-3′ and C-5′), 129.78 (d, C-2′ and C-6′), 137.20 (s, C-1′), 152.80 (s, C═O), 167.32 (s, C—S), 175.97 (s, C—S)
8a	1.30 (t, J = 7.00 Hz, 3H, Me), 4.25 (t, J = 7.00 Hz, 2H, OCH_2), 5.20 (s, 2H, CH_2), 7.20–7.40 (m, 5H, Ar—H), 7.79 (bs, 1H, As—OH)	13.49 (q, Me), 46.31 (t, CH_2), 60.71 (t, OCH_2), 127.73 (d, C-4′), 128.46 (d, C-3′ and C-5′), 129.72 (d, C-2′ and C-6′), 137.25 (s, C-1′), 156.84 (s, C═O), 167.96 (s, C—S), 176.15 (s, C—S)
8b	1.30 (t, J = 7.00 Hz, 3H, Me), 4.25 (t, J = 7.00 Hz, 2H, OCH_2), 5.20 (t, 2H, CH_2), 7.18–7.50 (m, 10H, Ar—H)	13.76 (q, Me), 46.54 (s, CH_2), 60.45 (t, OCH_2), 127.69 (d, C-4′), 128.35 (d, C-3′ and C-5′), 129.66 (d, C-2′ and C-6′), 137.24 (s, C-1′), 156.87 (s, C═O), 167.50 (s, C—S), 175.51 (s, C—S)
8c	1.25 (t, J = 7.00 Hz, 3H, Me), 4.20 (q, J = 7.00 Hz, 2H, OCH_2), 5.25 (s, 2H, CH_2) 7.50–7.80 (m, 20H, Ar—H)	13.42 (q, Me), 46.65 (t, CH_2), 60.39 (t, OCH_2), 127.17 (d, C-4′), 128.75 (d, C-3′ and C-5′), 131.98 (d, C-2′ and C-6′), 132.67 (s, C-1′), 156.65 (s, C═O), 167.96 (s, C—S), 175.43 (s, C—S)
8d	1.30 (t, J = 7.00 Hz, 3H, Me), 2.50 (s, 3H, Me), 4.20 (q, 2H, J = 7.00 Hz, OCH_2), 5.20 (s, 2H, CH_2), 7.15–7.35 (m, 5H, Ar—H), 7.95 (bs, 1H, As—OH)	δ_c 13.71 (q, Me), 27.92 (q, Me), 46.31 (t, CH_2), 60.72 (t, OCH_2), 127.85 (d, C-4′), 128.62 (d, C-3′ and C-5′), 129.28 (d, C-2′ and C-6′), 156.98 (s, C═O), 167.06 (s, C—S), 176.83 (s, C—S)
8e	1.35 (t, J = 7.00 Hz, 3H, Me), 2.58 (s, 3H, Me), 4.25 (q, J = 7.00 Hz, 2H, OCH_2), 5.20 (q, 2H, CH_2), 7.18–7.50 (m, 10H, Ar—H)	13.39 (q, Me), 27.42 (q, Me), 46.76 (t, CH_2), 60.35 (t, OCH_2), 127.86 (d,C-4′), 128.90 (d, C-3′ and C-5′), 129.43 (d, C-2′ and C-6′), 137.20 (s, C-1′), 157.09 (s, C═O), 167.76 (s, C—S), 176.31 (s, C—S)
8f	1.30 (t, J = 7.00 Hz, 3H, Me), 2.53 (s, 3H, Me), 4.20 (q, J = 7.00 Hz, 2H, OCH_2), 5.20 (s, 2H, CH_2), 7.10–7.55 (m, 15H, Ar—H)	14.04 (q, Me), 27.09 (q, Me), 46.85 (t, CH_2), 60.81 (t, OCH_2), 126.97 (d, C-4′), 128.69 (d, C-3′ and C-5′), 129.56 (d, C-2′ and C-6′), 137.04 (s, C-1′), 157.02 (s, C═O), 167.48 (s, C—S), 176.33 (s, C—S)

HETEROCYCLIC RING FROM DITHIOL

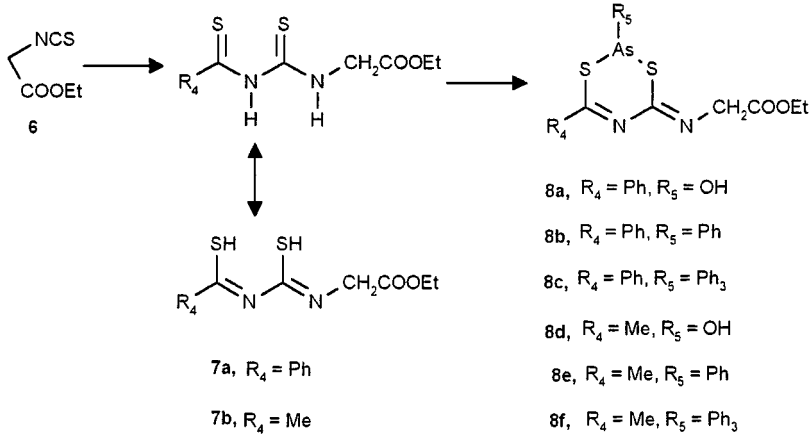
It was already reported[21] that $PhAsCl_2$ reacts with vicinal thiol groups on a molecule to form a stable five membered heteroatom ring and to the development of antidotes to arsenic poisoning. Based on, we synthesized five chelating agents, 1,3-dimercapto substrates **4a–c**, **7a**,**b** from isothiocyanates. Treatment of dimercapto substrate by arsenic trioxide, phenylarsine oxide, triphenylarsine or triphenylarsine oxide in solvent chloroform or ethanol afforded 1,3,2-arsadithiolane derivatives **5a–i**, **8a–f** as shown in Scheme 2. Here, this work is relevant to the development of antidotes to arsenic poisoning by using 1,3-dithiol compounds **4a–b**, **7a**,**b** instead of 1,2-dithiols (vicinal thiols). Dithiol compounds **1b**, **4a–c**, **7a**,**b** containing 1,3-dithiol groups and if a one-to-one adduct is formed between the arsenical and compounds **1b**, **4a–c**, **7a**,**b** a six membered heteroatom ring should be produced.

Thus, when 1,3-propanedithiol (**1b**) was allowed to react with phenylarsine oxide in dry dioxane for 5 h to afford 1,3,2-arsadithiolane derivative **2c**, as a similar frequently observed from methylarsine oxide (MeAs=O) with the johnsongrass malic enzyme (MenzSH) and dithiols described by Knowles.[37] He also proposed that reaction of arsenic compounds with dithiols yields cyclic compounds which are considerably more stable than the noncyclic compounds obtained with monothiols.[38]

1-Thioacetyl-3-phenyl-2-thiourea (**4a**) was treated with arsenic trioxide in chloroform to give arsenical adduct **5a** as pale yellow crystals in 45% yield. Cyclization of **4a** occurred through its tautomeric equilibrium structure. The IR spectrum of this compound **5a** showed sharp bands at 1639, 1607 cm^{-1} and other signals at 1508 and 721 cm^{-1} indicating the stretchings of C=N (two), C=C and As–OH bonds, respectively (Table I). The ^1H NMR spectrum of **5a** exhibited three-proton singlet at δ 2.46 for methyl group and another five-proton multiplet at δ 7.18–7.35 was indicated for phenyl group. Again ^{13}C NMR spectrum displayed singlets at δ 167.06 and 175.51 for two C–S was indicative of the formation of a new 1,3,2-arsadithiolane ring. The spectrum also showed the presence of nine carbons corresponding to $C_9H_9N_2OS_2As$ and this molecular formula was also supported by elemental analysis. Treatment of **4a** with phenyl arsenic oxide in refluxing chloroform gave the 1,3,2-arsadithiolane derivative **5b** in 52% of yellow crystals. A perusal of resulting 1,3,2-arsadithiolane derivative **5c** was similarly readily accessible from triphenylarsine or triphenylarsine oxide in 54% and 34% respectively as shown in Table I. Reduction of such type of trimethylarsine oxide to trimethylarsine by thiols and dithiols including cystine glutathione and lipoic acid was also established by Cullen et al.[39]

The reaction of 1-thiobenzoyl-3-methyl-2-thiourea (**4b**) with arsenic trioxide, phenylarsine oxide, triphenylarsine, or triphenylarsine oxide in boiling chloroform afforded 1,3,2-arsadithiolane derivative **5d–f**. Via this method, other 1,2,6-arsadithiolane derivatives **5g–i** were obtained from 1-thiobenzoyl-3-ethoxycarbonyl-2-thiourea (**4c**) with arsenic trioxide, phenylarsine oxide, triphenylarsine, or triphenylarsine oxide in resonable yield. The IR spectrum of the compound **5g** revealed a C=O absorption at 1720 cm^{-1} and completely disappearance of absorption at 872 cm^{-1} for As=O stretching indicate the formation of **5g**. Its ^1H NMR spectrum revealed three-proton triplet at δ 1.35 and two-proton quartet at δ 4.25 assignable ethyl ester peaks in the molecule. The rest of the spectrum including ^{13}C NMR spectrum and element analysis was in conformity with the structure accorded to **5g**.

Cyclization of 1-thiobenzoyl-3-ethoxycarbonylmethyl-2-thiourea (**7a**) into the 1,3,2-arsadithiolane derivative **8a** occurred in refluxing chloroform with arsenic trioxide. The IR spectrum of this compound exhibited the absorption band at 1720 cm^{-1} for C=O and at 1645, 1632, 1505 cm^{-1} for C=N (two), C=C groups respectively. The ^1H NMR spectrum of compound **8a** showed singlet two-proton at δ 5.20 for CH_2 peak and 1.30, 4.25 for $-OCH_2CH_3$ peaks respectively. The aromatic five-proton appeared as multiplet at δ 7.20–7.40 (Table II). The formation of the compound **8a** was also proved by its ^{13}C NMR spectrum and also supported by elemental analysis. The desired arsenical adducts **8b** was also obtained from **7a** with phenylarsine oxide in a similar manner. Same product **8c** was obtained when **7a** reacts with either triphenylarsine or triphenylarsine oxide in refluxing chloroform (Scheme 3) and gave 53% and 39% yield.



SCHEME 3

1-Thioacetyl-3-ethoxycarbonylmethyl-2-thiourea (**7b**) was treated with arsenic trioxide in chloroform at reflux temperature and gave compound **8d** in 39% yield. The IR spectrum of this compound **8d** showed absorption peaks at 1640, 1615 cm^{-1} for two C=N and 1501 for C=C. In its ^1H NMR spectra appeared a three-proton singlet at δ 2.50 for CH_3 and a two-proton singlet at δ 5.20 for CH_2 in the molecule. A two-proton quartet at δ 4.20 and a three-proton triplet at 1.30 δ also suggested the presence of ethyl group in the molecule. The compound **8d** was further proved by ^{13}C NMR spectra, with the resonances at δ 27.92 for CH_3, 46.31 for CH_2, 167.06 and 176.83 C–S carbons have been observed. The presence of one ethyl ester group in the molecule was confirmed resonances at δ 156.98 for C=O, 60.72 for OCH_2 and 13.71 for CH_3 respectively.

Compound **7b** with phenylarsine oxide, it gave the 1-phenyl-1,3,2-arsadithiolane derivative **8e** in 44% yield. On reaction with **7b**, triphenylarsine or triphenylarsine oxide afforded the 2,2,2-triphenyl-1,3,2-arsadithiolane derivative **8f** as brown crystals in 46% and 31% yield.

The products **5a**, **5b**, **5d**, **5g**, **5h**, **8a**, **8e** were purified by column chromatography (eluent chloroform-acetone, 9:2). The 2-hydroxy-1,3,2-arsadithiolane derivative **5a**, **5d**, **5g**, **8a**, **8d** are moderately stable, only for few days, toward atmospheric moisture and their spectral data are vary considerably according to their sample history.

Thus, the above dimercapto substrate **4a–c**, **7a**,**b** has the advantage of easy accessibility by simple method of available starting materials, mild reaction conditions, also overall in good yields and the cyclization step with high substitution in the 1,3,2-arsadithiolane six membered heterocyclic ring **5a–i**, **8a–f**.

EXPERIMENTAL

Melting points were determined on a Yanaco hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JNM–ALPHA 500 (500 MHz) spectrometer in $CDCl_3$ using TMS as internal standard and the chemical shifts are expressed in δ ppm. IR spectra were recorded on KBr disc with a JASCO FT-IR spectrophotometer and the data are given in cm^{-1}. Elemental analyses were performed on an EA 1108 (Fisons Instruments) Elemental Analyzer. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated plastic sheets (layer thickness 0.2 mM) and spots were detected by UV lamp (Model UVGL 58). Column chromatography was carried out at room temperature with silica gel G_{60}. All evaporations were conducted under reduced pressure at bath temperature below 40°C.

General Procedure for the Synthesis of Thiourea Derivatives 4a–c, 7a,b

A solution of thioacetamide or thiobezamide (20 mmol) and appropriate isothiocyanate (**3a–c**, **6**, 20 mmol) in pyridine (12 ml) was refluxed for 5 h (**4a–c**) or for 2 h (**7a**,**b**). The reaction mixture was diluted with ethanol and cooled. The resulting crystals were collected by filtration and recrystallized from ethanol to give **4a–c**, **7a**,**b** as needles.

General Procedure for the Cyclization Reaction: Synthesis of Compounds 2a–c, 5a–i, 8a–f

A mixture of 2-hydroxycyclohexanone[40] or dimercapto compound (4 mmol) and arsenic compound (4 mmol) in dry dioxane or chloroform (7 ml) was refluxed for 5 to 6 h (except **2a**, 24 h and **2b**, 12 h). The solvent was evaporated in vacuo. The obtained solid was choromatographed on silica gel in chloroform-acetone (9:2) or recrystallizated from ethanol. Alternatively, carrying out the above experiments, using the ethanol instead of chloroform led, also to the formation of **5a–i**, **8a–f** in poor yield.

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