VIC-IODOTHIOCYANATES AND IODOISOTHIOCYANATES. PART 7. THE SYNTHESIS OF 2-BENZYLAMINO-2-THIAZOLINES

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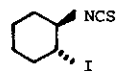
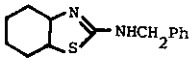
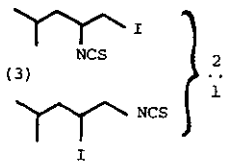
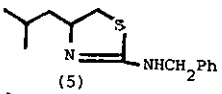
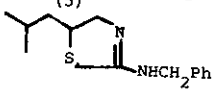
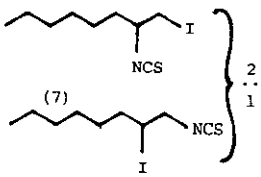
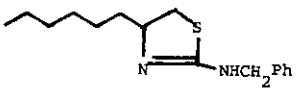
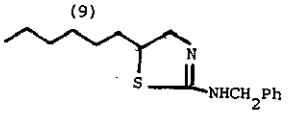
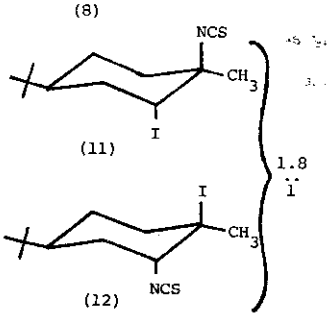
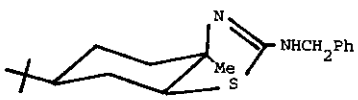
Abstract — Treatment of vic-iodoisothiocyanates with benzylamine gives 2-benzylamino-2-thiazolines. Inseparable mixtures of isomeric vic-iodoisothiocyanates are readily separated as these derivatives.

In Part 2 we reported[1] a new method for the preparation of 2-amino-2-thiazoline derivatives wherein a vic-iodoisothiocyanate was treated with aniline or an alkylamine. Our work assumes increased significance in view of the possible pharmacological potential of such derivatives as exemplified by the recent work of Campbell and Craig[2] who fused a 2-amino-2-thiazoline ring across C2 - C3 of a steroid by a route less direct than our own. Our method using the poor nucleophile aniline allowed separation of inseparable mixtures of steroidal vic-iodoisothiocyanates as the 2-phenylamino derivatives. Use of more basic amines such as 1-aminopentane gave analogous derivatives which were formed much faster but which were not always crystalline. We have now found that benzylamine not only provides a strong nucleophile for the reaction but also gives derivatives from inseparable mixtures of isomeric vic-iodoisothiocyanates which are readily separated by p.l.c. Some results are presented in Table 1. Unlike the case with other mixtures of vic-iodoisothiocyanates only one pure product, viz (13), was isolated from the mixture of (11) and (12). Each of the products was characterised from spectral data and elemental analyses. The i.r. spectrum of each compound showed an intense band due to imine absorption (ca. 1620 cm^{-1}) and NH stretching (ca. 3440 cm^{-1}). The ^1H n.m.r. spectra (cf. ref. 3) indicated that all products existed predominantly as the 2-thiazoline tautomers.[4]

Some diagnostic differences between the mass spectra of the 4-alkyl-substituted compounds (5) and (9) and their 5-alkyl-substituted isomers (6) and (10) (Table 2) were observed. In the spectra of compounds (6) and (10) the $M^{+\cdot} - H^{\cdot}$ ions and the ions at m/z 106 corresponding to $C_7H_8N^+$ are much more abundant than the corresponding ions from (5) and (9). The relative abundance of m/z 106 may depend in part on the stability of the radical which arises from ring cleavage (Scheme 1). The secondary radical formed by scission of the C5 - S bond in the

Table 1

Iodoisothiocyanates	Time[a]	Products	Yields (%)
 (1)	2 h	 (2)	49
 (3) : (4) = 2 : 1	4 h	 (5)	53
		 (6)	30
 (7) : (8) = 2 : 1	1 h	 (9)	52
		 (10)	27
 (11) : (12) = 1.8 : 1	1.5 h	 (13)	60

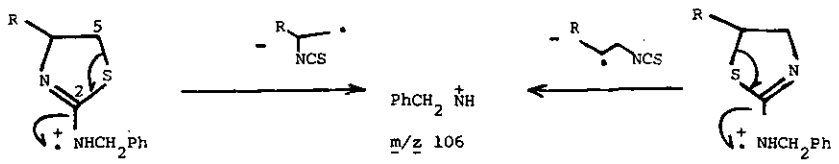
[a]Reactions were carried out in ether at room temperature using a 2:1 molar ratio of benzylamine to vic - iodoisothiocyanate(s).

Table 2

Mass spectral data for 2-thiazolines

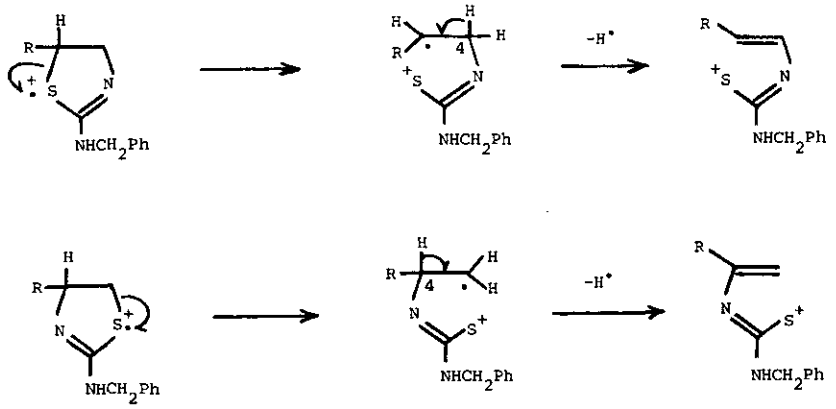
	$M^{+\cdot}$	$M^{+\cdot} - H^{\cdot}$	$C_7H_8N^+$	$C_7H_7^+$
(5)	248 (10%)	247 (<1%)	(7%)	(100%)
(9)	276 (12)	275 (<1)	(8)	(100)
(6)	248 (30)	247 (22)	(38)	(100)
(10)	276 (27)	275 (22)	(38)	(100)

Scheme 1

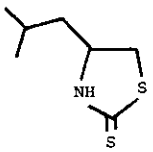


5-substituted 2-thiazolines is more stable than the primary radical formed by fragmentation of the corresponding 4-substituted isomers. The relative ease with which a hydrogen atom is lost from the molecular ion is determined partly by the stability of the cation which is formed. Clearly, the hydrogen atom most readily expelled from an intact ring will be that attached to C5.[5] Loss of a benzylic hydrogen atom would also be expected to occur readily but this process cannot account for the observed differences since this unit is common to all four compounds. However, loss of a hydrogen atom from the secondary C5 carbon atom of (5) and (9) will be less favourable than expulsion of H$^{\cdot}$ from the tertiary C5 carbon atoms of (6) and (10). An alternative route (Scheme 2) involves initial C-S bond cleavage followed by loss of an allylic hydrogen atom from C4; again this pathway will be more favourable for (6) and (9).

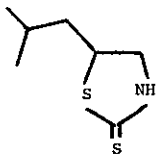
Scheme 2



1,3-Thiazolidine-2-thiones (14) and (15) were also prepared from a mixture of the iodoisothiocyanates (3) and (4) by treatment with sodium sulphide nonahydrate in the presence of Adogen 464 as a phase-transfer catalyst.[6] Spectral examination (i.r.,[7] ^{1}H n.m.r.,[8] and ^{13}C n.m.r.[9]) indicated that the derivatives existed exclusively as the thiazolidine-thione tautomers.



(14)



(15)

EXPERIMENTAL

General experimental details are given in ref. 10.

Reactions of vic-Iodoisothiocyanates with Benzylamine. —

A solution of benzylamine (2 mol equiv.) in ether was added to a solution of the vic-iodoisothiocyanate (0.54 - 0.71 g) in ether (30 - 40 ml) under dry nitrogen and the mixture was stirred in the dark for 1 - 4 h. In each case a transient yellow colour was observed immediately upon mixing of the two solutions, followed by formation of a colourless precipitate. The mixture was extracted with ether, filtered, and solvent was removed from the filtrate to give an oil which was purified by multiple p.l.c. on alumina (hexane - chloroform, 3:1).

2-Benzylamino-cis-3a,4,5,6,7,7a-hexahydrobenzothiazole. —

trans-1-iodo-2-isothiocyanatocyclohexane (1) (0.53 g) gave *2-benzylamino*-cis-3a,4,5,6,7,7a-*hexahydrobenzothioazole* (2) (0.24 g, 49%) which crystallized from hexane as needles, m.p. 119-121°C [Found: C, 68.3; H, 7.6; N, 11.4. $C_{14}H_{18}N_2S$ requires C, 68.2; H, 7.5; N, 11.4%]; ν_{max} 3440 (NH), and 1615 cm^{-1} (C=N); ^1H n.m.r. δ 1.08 - 2.08 (m, CH_2), 3.55 - 4.10 (m, CHN and CHS), 4.33 (s, exchanged with D_2O, NH), 4.43 (s, $ArCH_2N$), and 7.30 (s, ArH); m/z 246 ($M^{+\cdot}$), 245 ($M^{+\cdot}$ - H$^\cdot$), 106 ($C_7H_8N^+$), and 91 ($C_7H_7^+$).

2-Benzylamino-4-(2-methylpropyl)-4,5-dihydrothiazole and 2-Benzylamino-5-(2-methylpropyl)-4,5-dihydrothiazole. —

A mixture (2:1) of 1-iodo-2-isothiocyanato-4-methylpentane (3) and 2-iodo-1-isothiocyanato-4-methylpentane (4) (0.71 g) gave an oil (0.69 g). P.l.c. of a portion (0.59 g) afforded (i) *2-benzylamino-4-(2-methylpropyl)-4,5-dihydrothioazole* (5) (0.30 g, 53%) which crystallized from hexane as needles, m.p. 88-89 °C [Found: C, 67.5; H, 8.4; N, 11.3; S, 12.9%; $M^{+\cdot}$ 248.1365. $C_{14}H_{20}N_2S$ requires C, 67.7; H, 8.1; N, 11.3; S, 12.9%; M, 248.1347]; $\nu_{max.}$ 3440, 3170 (NH), and 1620 cm^{-1} (C=N); ^1H n.m.r. δ 0.91 (d, J 5 Hz, 2'-gem Me_2), 1.18 - 1.95 (m, 2'-H, 1'-H_2), 2.91, 3.33 (2 dd, $J_{5Ha-5Hb}$ 10.5 Hz, J_{5Ha-4H} 7.5 Hz, J_{5H-4H} 7 Hz, 5-Ha, 5-Hb) 4.27 (m, 4-H), 4.43 (s, $ArCH_2N$), 5.20 (s, exchanged with D_2O, NH), and 7.30 (s, ArH); ^{13}C n.m.r. δ 22.6, 23.0 (2'-CH_3 and C-3'), 25.7 (C-2'), 39.4 (C-5), 44.8 (C-1'), 49.6 ($ArCH_2N$), 69.4 (C-4), 127.1 (p-C), 127.5, 128.4 (o-C and m-C), 138.8 (ipso-C), and 160.4 (C-2); m/z 248 ($M^{+\cdot}$, 10%), 247 ($M^{+\cdot}$ -H$^\cdot$, <1), 192 ($M^{+\cdot}$-C_4H_8, 32), 191 ($M^{+\cdot}$-$C_4H_9^\cdot$, 67), 106 ($C_7H_8N^+$, 7), and 91 ($C_7H_7^+$, 100), and (ii) *2-benzylamino-5-(2-methylpropyl)-4,5-dihydrothiazole* (6) (0.17 g, 30%) which crystallized from hexane as flakes, m.p. 87-88 °C [Found: C, 67.6; H, 7.9; N, 11.3; S, 12.9. $C_{14}H_{20}N_2S$ requires C, 67.7; H, 8.1; N, 11.3; S, 12.9%]; $\nu_{max.}$ 3450, 3180 (NH), and 1625 cm^{-1}

(C=N); ^{1}H n.m.r. δ 0.90 (d, J 5 Hz, 2'-CH_3, 3'-H), 1.57 (m, $W_{\frac{1}{2}}$ 13 Hz, 1'-H_2, 2'-H), 3.30 - 4.20 (overlapping m, $W_{\frac{1}{2}}$ 4 Hz, 5-H), 4.44 (s, ArCH_2N), 6.00 (br s, exchanged by D_2O, NH), and 7.32 (s, ArH); ^{13}C n.m.r.δ 21.8 (2'-CH_3), 22.9 (C-3'), 27.5 (C-2'), 44.4 (C-1'), 49.1 (ArCH_2N), 51.7 (C-5), 64.9 (C-4), 127.3 (p-C), 127.6, 128.5 (o-C and m-C), 138.6 (ipso-C), and 161.5 (C-2); m/z 248 ($M^{+\cdot}$, 30%), 247 ($M^{+\cdot}$-H, 22), 192 ($M^{+\cdot}$-C_4H_8, 48), 191 ($M^{+\cdot}$-$C_4H_9^{\cdot}$, 32), 106 ($C_7H_8N^+$, 38), and 91 ($C_7H_7^+$, 100).

2-Benzylamino-4-hexyl-4,5-dihydrothiazole and 2-Benzylamino-5-hexyl-4,5-dihydrothiazole. —

A mixture (2:1) of 1-iodo-2-isothiocyanato-octane (7) and 2-iodo-1-isothiocyanato-octane (8) (0.69 g) gave an oil (0.78 g). P.l.c. of a portion (0.77 g) afforded (i) *2-benzylamino-4-hexyl-4,5-dihydrothiazole* (9) (0.32 g, 52%) which crystallized from hexane as plates, m.p. 58-59 °C [Found: C, 69.8; H, 8.8; N, 10.4; S, 11.8%; $M^{+\cdot}$ 276.1668. $C_{16}H_{24}N_2S$ requires C, 69.5; H, 8.8; N, 10.1; S, 11.6%; M, 276.1660]; ν_{max} 3450, 3170 (NH), and 1620 cm^{-1} (C=N); ^{1}H n.m.r. δ 0.90 (t, 6'-H_3), 1.10 - 2.00 (overlapping m, 1'-H_2, 2'-H_2, 3'H_2, 4'-H_2, and 5'-H_2), 2.97, 3.36 (2dd, $J_{5Ha-5Hb}$ 10.4 Hz, J_{5Ha-4H} 7.5 Hz, J_{5Hb-4H} 7 Hz, 5-Ha, 5-Hb), 4.18 (m, 4-H), 4.47 (s, ArCH_2N), 4.50 (s, exchanged with D_2O, NH), and 7.34 (s, ArH), ^{13}C n.m.r. 14.1 (C-6'), 22.6 (C-5'), 26.6 (C-4'), 29.3 (C-3'), 31.8 (C-2'), 35.8 (C-1'), 39.0 (C-5), 49.7 (ArCH_2N), 71.2 (C-4), 127.1 (p-C), 127.5, 128.3 (o-C and m-C), 138.9 (ipso-C), and 160.7 (C-2); m/z 276 ($M^{+\cdot}$, 12%), 191 ($M^{+\cdot}$-$C_6H_{13}^{\cdot}$, 58), 106 ($C_7H_8N^+$, 8), and 91 ($C_7H_7^+$, 100); and (ii) *2-benzylamino-5-hexyl-4,5-dihydrothiazole* (10) (0.17 g, 27%) which crystallized from hexane as needles, m.p. 53-54 °C [Found: C, 69.6; H, 9.1; N, 10.4%, $M^{+\cdot}$ 276.1667. $C_{16}H_{24}N_2S$ requires C, 69.5; H, 8.8; N, 10.1%; M, 276.1660]; $\nu_{max.}$ 3450, 3200 (NH), and 1625 cm^{-1} (C=N); ^{1}H n.m.r. δ 0.88 (t, 6'-H_3), 1.07 - 1.90 (overlapping m, 1'-H_2, 2'-H_2, 3'-H_2, 4'-H_2, and 5'-H_2), 3.76 (overlapping m, $W_{\frac{1}{2}}$ 4 Hz, 4-H_2, 5-H), 4.40 (s, ArCH_2N), 5.30 (s, exchanged with D_2O, NH), and 7.30 (s, ArH); ^{13}C n.m.r. δ 14.1 (C-6'), 22.6 (C-5'), 28.4 (C-4'), 29.0 (C-3'), 31.7 (C-2'), 35.7 (C-1'), 49.2 (ArCH_2N), 53.5 (C-5), 64.6 (C-4), 127.23 (p-C), 127.6, 128.5 (o-C and m-C), 138.7 (ipso-C), and 161.4 (C-2); m/z 276 ($M^{+\cdot}$, 27%), 275 ($M^{+\cdot}$-H', 22), 191 ($M^{+\cdot}$-$C_6H_{13}^{\cdot}$, 44), 106 ($C_7H_8N^+$, 38), and 91 ($C_7H_7^+$, 100).

2-Benzylamino-r-6-t-butyl-t-3a-methyl-4,5,6,7,7a-pentahydrobenzothiazole. —

A mixture (1:8:1) of r-1-iodo-t-2-isothiocyanato-2-methyl-t-5-t-butylcyclohexane (11) and r-1-iodo-t-2-isothiocyanato-1-methyl-c-4-t-butylcyclohexane (12) (0.54 g) gave (i) *2-benzylamino-r-6-t-butyl-t-3a-methyl-4,5,6,7,7a-pentahydrobenzothiazole* (13) (0.29 g, 60%), m.p. 123-126 °C (from hexane) [Found: C, 72.1; H, 9.4; N, 8.8. $C_{19}H_{28}N_2S$ requires C, 72.1; N, 8.9; N, 8.85%]; ν_{max} 3420 (NH), and 1609 cm^{-1} (C=N); ^{1}H n.m.r. δ 0.87 (s, CMe_3), 0.93 - 2.43 (overlapping m, CH_2, CH), 1.22 (s, CH_3), 3.25 (dd, J_{7eq-7a} 5.8 Hz, J_{7ax-7a} 11.2 Hz, 7a-H), 4.28 (br s, NH), 4.41 (s, CH_2N), and 7.28, (s, ArH), ^{13}C n.m.r. δ 22.9 (C-5), 27.4 (CMe_3), 27.6 (Me), 32.4 (CMe_3), 25.9, 37.6 (C-4, C-7), 46.8 (C-6), 50.1 (ArCH_2N), 57.2 (C-7a), 71.0 (C-3a), 126.9 (p-C), 127.3, 128.3 (o-C and m-C), 139.3 (ipso-C), and 160.9 (C-2), m/z 316 ($M^{+\cdot}$), 301 ($M^{+\cdot}$-Me$^{\cdot}$), 217, (301 -C_6H_{12}), and 91 ($C_7H_7^+$).

4- and 5-(2-Methylpropyl)thiazolidine-2-thiones (14) and (15). ——

A mixture of 1-iodo-2-isothiocyanato-4-methylpentane (3) and 2-iodo-1-isothiocyanato-4-methylpentane (4) (2:1) (0.24 g, 0.89 mmol), sodium sulphide nonahydrate (1.07 g, 4.4 mmol), and Adogen 464 (20 mg) in chloroform-water (1:2, 4 ml) was shaken vigorously in the dark at room temperature for 2h. The mixture was extracted with chloroform and the extract was worked up to give an oil (0.13 g) which was separated by multiple elution p.l.c. (hexane-chloroform, 1:1) into (i) 4-(2-methylpropyl)thiazolidine-2-thione (14) (16.5 mg, 11%) which crystallized from hexane as needles, m.p. 72-75°C; $\nu_{max.}$ 3400, 3150 (NH), 1495 (CSNH), and 1015 cm^{-1} (C=S); ^1H n.m.r. δ 0.96 (overlapping d, J 6 Hz, 2'-CH_3, 3'-H_3), 1.40 - 2.00 (m, 2'H, 1'-H_2), 3.19, 3.58 (2dd, $J_{5Ha-1Hb}$ 10.5 Hz, J_{5Ha-4H} 8 Hz, J_{5Hb-4H} 7.5 Hz, 5-Ha, 5-Hb), 4.34 (m, 4-H), and 8.50 (br s, exchanged with D_2O, NH), ^{13}C n.m.r. δ 22.3, 22.7 (C-3', 2'-CH_3), 25.2 (C-2'), 38.9 (C-5), 42.9 (C-1'), 62.7 (C-4), and 200.3 (C-2), m/z 175 ($M^{+\cdot}$, 100), and 118 ($M^{+\cdot}-C_4H_9\cdot$, 99); and (ii) 5-(2-methylpropyl)thiazolidine-2-thione (15) (7.5 mg, 5%) which crystallized from hexane as needles, m.p. 109-112°C, ν_{max} 3400, 3.50 (NH), 1490 (CSNH), and 1020 cm^{-1} (C=S); ^1H n.m.r. δ 0.93 (2d, 2'-CH_3, 3'-H_3), 1.28 - 1.92 (m, 2'-H, 1'-H_2), 3.55 - 4.68 (m, 4-H_2, 5-H), and 7.13 (br s, exchanged with D_2O, NH), m/z 175 ($M^{+\cdot}$, 100%), and 118 ($M^{+\cdot}-C_4H_9\cdot$, 41).

References

1. R.C.Cambie, H.H.Lee, P.S.Rutledge, and P.D.Woodgate, J.C.S. Perkin I, 1979, 765.
2. M.M.Campbell and R.C.Craig, J.C.S.Perkin I, 1980, 766.
3. J.Rabinowitz, Helv. Chim. Acta, 1969, *52*, 255.
4. J.Elguero, C.Marzin, A.R.Katritzky, and P.Linda, "The Tautomerism of Heterocycles", Academic Press, New York, 1976, pp 398, 427.
5. Q.N.Porter and J.Baldas, "Mass Spectrometry of Heterocyclic Compounds", Wiley-Interscience, 1971, p. 537.
6. R.C.Cambie, G.D.Mayer, P.S.Rutledge, and P.D.Woodgate, J.C.S. Perkin I, 1981, 52.
7. T.A.Foglia, L.M.Gregory, G.Maerker, and S.F.Osman, J.Org. Chem., 1971, *36*, 1068.
8. M.Chanon and J.Metzger, Bull. Soc. Chim. Fr., 1968, 2847, 2851, 2855.
9. F.Chanon, M.Rajmann, M.Chanon, J.Metzger, and G.Pouzard, Can. J. Chem., 1980, *58*, 599; F.Chanon, M.Rajmann, M.Chanon, J.Metzger, G.Pouzard, and T.Drakenberg, Can. J. Chem., 1980, *58*, 604.
10. R.C.Cambie, H.H.Lee, P.S.Rutledge, and P.D.Woodgate, J.C.S. Perkin I, 1979, 757.

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