v-Triazolines. Part 7.[1] 3-Arylaminothiophens from Hexahydrothiopyrano[3,4-*d*]-*v*-triazoles

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By treating tetrahydrothiopyran-4-one with secondary amines and aryl azides, 1-aryl-7a-amino-1,3a,4,6,7,7a-hexahydrothiopyrano[3,4-*d*]-*v*-triazoles (2) were obtained. On heating with acids, compounds (2) afforded mixtures of the corresponding 3-arylamino-2-methylthiophen (3) and 1-aryl-1,4,6,7-tetrahydrothiopyrano[3,4-*d*]-*v*-triazole (4). The triazoles (4) were also obtained on heating compounds (2) with sodium hydroxide in methanol. 3,6-Dihydro-4-morpholino-2*H*-thiopyran (6) was treated with 4-nitrophenylsulphonyl azide yielding 4-morpholino-3-(4-nitrophenylsulphonylamino)-3,6-dihydro-2*H*-thiopyran (7). Reaction mechanisms are discussed.

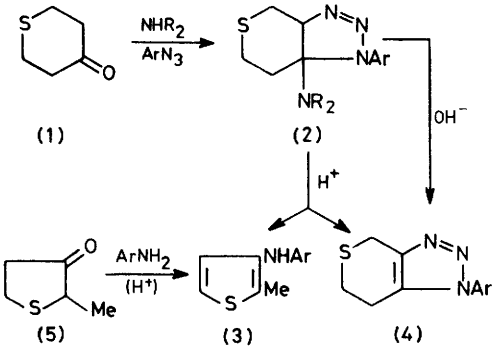
In a previous study of the degradation of 7a-amino-1-aryl-3a,4,5,6,7,7a-hexahydrobenzo-*v*-triazoles in acidic medium,[2] it was shown that one of the reaction paths involves cleavage of the triazoline ring followed by nitrogen loss and formation of a positive charge on the carbon atom formerly in position 4 of the triazoline.

Since several examples of the interaction of a positive carbon centre with a β-sulphur atom are known,[3] a study of the 5-thia-analogues of the hexahydrobenzo-*v*-triazoles was of interest.

RESULTS

The triazolines (2a—f) were easily obtained by treating tetrahydrothiopyran-4-one (1) with a secondary amine and the appropriate aryl azide in benzene solution (Scheme 1), according to a general method for the preparation of 5-aminotriazolines.[4] The structures of these compounds were demonstrated by analytical and ^{1}H n.m.r. data (Table 1).

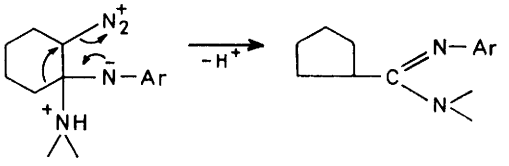
On heating the triazolines (2a—e) in ethanolic solution with acetic or hydrochloric acid, nitrogen was evolved and a mixture of a 3-arylamino-2-methylthiophen (3a—d) and a 1-aryl-1,4,6,7-tetrahydrothiopyrano[3,4-*d*]-*v*-triazole (4a—d) was obtained (Scheme 1). The mixtures were separated by column chromatography.



Scheme 1

The structures of the 3-arylamino-2-methylthiophens (3a—d) were inferred from their ^{1}H n.m.r. spectra (Table 2), in which the AB system associated with H-4 and H-5 was clearly evident.[5] Moreover, (3a and b) were synthesized independently through acid-catalysed condensation of 2-methyltetrahydrothiophen-3-one (5) with aniline and 4-methoxyaniline, respectively.† The intermediate enamine aromatizes spontaneously under the reaction conditions (Scheme 1).

The triazoles (4) were identified on the basis of analytical and ^{1}H n.m.r. data (Table 3). They could be better prepared by heating the corresponding *v*-triazolines (2) in ethanol with a catalytic amount of sodium hydroxide.‡ In this case they represent the sole product and were obtained in high yields. As far as we are aware, the triazoles (4) are the first examples of derivatives of the thiopyrano-[3,4-*d*]-*v*-triazole ring system.



Scheme 2

DISCUSSION

Several examples of the behaviour of 5-aminotriazolines towards acids have been studied previously, particularly the case of non-sulphur-containing analogues of the triazolines (2), *i.e.* 1-aryl-7a-aminohexahydrobenzotriazoles. Two competitive reaction paths have been generally observed: (i) deamination to the corresponding *v*-triazole derivatives; and (ii) cleavage of the triazoline ring followed by nitrogen elimination and rearrangement to an amidine derivative according to Scheme 2.[2,7,8] In the case of the triazolines (2) the rearrangement of the zwitterionic intermediate to a thiophen derivative (3) is preferred over path (ii). This is clearly related to the ability of the sulphur atom to assist the acid-induced cleavage of the triazoline ring through an episulphonium ion. This intermediate can

† This reaction failed to give (3c) or (3d) with 4- or 3-nitroaniline under similar conditions, probably owing to the lower nucleophilicity of these nitroanilines.

‡ This base-catalysed deamination has been widely applied to 5-aminotriazolines obtained through cycloaddition of aryl azides to enamines derived from aldehydes, and is thought to involve a C-4 carbanionic intermediate.[6]

[1] Part 6, P. Dalla Croce and R. Stradi, *Tetrahedron*, 1977, **33**, 865.

[2] G. Bianchetti, D. Pocar, and P. Dalla Croce, *Rend. Ist. Lombardo*, 1965, **A99**, 316.

[3] See *e.g.* L. Brandsma and J. F. Arens in ' The Chemistry of the Ether Linkage,' ed. S. Patai, Wiley, London, 1967, p. 591.

[4] R. Stradi and D. Pocar, *Gazzetta*, 1969, **99**, 1131, and references therein.

[5] T. J. Batterham, ' NMR Spectra of Simple Heterocycles,' Wiley, New York, 1973, pp. 429—440.

[6] N. E. Munk and Y. K. Kim, *J. Amer. Chem. Soc.*, 1964, **86**, 2213.

[7] R. Fusco, G. Bianchetti, and D. Pocar, *Gazzetta*, 1961, **91**, 849.

[8] R. Fusco, G. Bianchetti, and D. Pocar, *Gazzetta*, 1961, **91**, 933.

TABLE 1

1-Aryl-7a-amino-1,3a,4,6,7,7a-hexahydrothiopyrano[3,4-*d*]-*v*-triazoles (2)

Compound	Ar	NR_2	M.p. (°C)	Reflux time (h)	Cryst. from	Yield (%)	Found (%) [Calc. (%)]	^{1}H N.m.r. (δ) in $CDCl_3$ (*J* in Hz)
(2a)	Ph	Morpholino	160—162	6	EtOH	70	C, 59.1; H, 6.4; N, 18.35 [C, 59.2; H, 6.6; N, 18.4]	2.20—2.70 (4 H, m, SCH_2CH_2), 3.02 (2 H, m, SCH_2), 4.88 (1 H, t, *J* 3.5, CH)
(2b)	4-$MeOC_6H_4$	Morpholino	136—138	5	Pr^i_2O	25	C, 56.9; H, 6.6; N, 16.6 [C, 57.45; H, 6.65; N, 16.75]	2.23—2.62 (4 H, m, SCH_2CH_2), 2.94—3.09 and 4.83 (3 H, ABX, J_{AB} *ca.* 13.5, J_{AX} *ca.* 4, J_{BX} *ca.* 4, SCH_2CH)
(2c)	4-$NO_2C_6H_4$	Morpholino	172	10	EtOH	85	C, 51.3; H, 5.65; N, 20.15 [C, 51.55; H, 5.5; N, 20.05]	2.05—2.90 (4 H, m, SCH_2CH_2), 3.11 (2 H, m, SCH_2), 5.09 (1 H, t, *J* 3.5, CH)
(2d)	4-$NO_2C_6H_4$	NMe_2	141	1	Pr^i_2O	40	C, 50.15; H, 5.35; N, 22.75 [C, 50.8; H, 5.55; N, 22.8]	2.0—2.9 (4 H, m, SCH_2CH_2), 3.12 (2 H, m, SCH_2), 4.98 (1 H, t, *J* 3.3, CH)
(2e)	3-$NO_2C_6H_4$	Morpholino	180—182	16	Pr^i_2O	80	C, 51.5; H, 5.5; N, 19.85 [C, 51.55; H, 5.5; N, 20.05]	2.1—2.67 (4 H, m, SCH_2CH_2), 3.05—3.16 and 5.07 (3 H, ABX, J_{AB} *ca.* 14, J_{AX} *ca.* 4, J_{BX} *ca.* 3, SCH_2CH)
(2f)	2-$NO_2C_6H_4$	Morpholino	133—135	8 (50 °C)	Pr^i_2O	25	C, 51.3; H, 5.6; N, 19.7 [C, 51.55; H, 5.5; N, 20.05]	2.3—2.7 (4 H, m, SCH_2CH_2), 2.72—3.14 and 4.86 (3 H, ABX, J_{AB} *ca.* 14.5, J_{AX} *ca.* 6.5, J_{BX} *ca.* 5.5, SCH_2CH)

TABLE 2

3-Arylamino-2-methylthiophens (3)

Compound	Ar	M.p. (°C) [B.p. (°C/Torr)]	Cryst. solvent	Found (%) [Calc. (%)]	^{1}H N.m.r. (δ) in $CDCl_3$ (*J* in Hz)	*m/e* (%)	$\nu_{max.}$/cm^{-1} (NH)
(3a)	Ph	[140/0.2]		C, 69.5; H, 5.95; N, 7.1 [C, 69.8; H, 5.85; N, 7.4]	2.20 (3 H, s, Me), 5.00 (1 H, NH, exch.), 6.50—7.25 (7 H, m, aromatic)	189 (100) ($M^{+\cdot}$), 188 (48), 186 (10), 173 (8), 156 (16), 155 (14), 154 (14), 144 (9), 112 (26), 97 (9), 77 (18)	3 390
(3b)	4-$MeOC_6H_4$	[135—145/0.5]		C, 65.35; H, 6.15; N, 6.55 [C, 65.7; H, 5.95; N, 6.4]	2.20 (3 H, s, Me), 4.70 (1 H, NH, exch.), 6.75 (1 H, d, *J ca.* 5.5, H-4), 6.93 (1 H, d, *J ca.* 5.5, H-5)	219 (87) ($M^{+\cdot}$), 218 (5), 216 (2), 204 (100), 189 (7), 186 (10), 111 (15), 108 (10), 97 (9)	3 380
(3c)	4-$NO_2C_6H_4$	134	PhH	C, 56.15; H, 4.1; N, 11.8 [C, 56.4; H, 4.3; N, 11.95]	2.32 (3 H, s, Me), 5.94 (1 H, NH, exch.), 6.92 (1 H, d, *J ca.* 5.5, H-4), 7.19 (1 H, d, *J ca.* 5.5, H-5)	234 (100) ($M^{+\cdot}$), 233 (11), 204 (12), 201 (3), 188 (23), 173 (35), 155 (11), 154 (11), 112 (6), 97 (3)	3 600 3 480
(3d)	3-$NO_2C_6H_4$	101—103	Pr^i_2O	C, 56.1; H, 4.45; N, 11.9 [C, 56.4; H, 4.3; N, 11.95]	2.32 (3 H, s, Me), 5.54 (1 H, NH, exch.), 7.07 (1 H, d, *J ca.* 5.5, H-4), 7.16 (1 H, d, *J ca.* 5.5, H-5)	234 (100) ($M^{+\cdot}$), 233 (7), 201 (3), 188 (24), 173 (51), 155 (15), 154 (12), 112 (6), 97 (5)	3 370

TABLE 3

1-Aryl-1,4,6,7-tetrahydrothiopyrano[3,4-*d*]-*v*-triazoles (4)

Compound	Ar	M.p. (° C)	Cryst. solvent	Yield * (%)	Found (%) [Calc. (%)]	^{1}H N.m.r. (δ) in $CDCl_3$ †
(4a)	Ph		EtOH	95	C, 60.8; H, 5.1; N, 19.05 [C, 60.8; H, 5.1; N, 19.35]	2.83 (4 H, m, CH_2CH_2), 3.90 (2 H, s, CH_2)
(4b)	4-$MeOC_6H_4$	118—119	Pr^i_2O	75	C, 58.0; H, 5.3; N, 16.6 [C, 58.3; H, 5.3; N, 17.0]	2.93 (4 H, s, CH_2CH_2), 3.86 (3 H, s, OMe), 3.92 (2 H, s, CH_2)
(4c)	4-$NO_2C_6H_4$	238—239	MeOH	90	C, 49.5; H, 3.95; N, 20.7 [C, 50.35; H, 3.85; N, 21.35]	2.90—3.30 (4 H, m, CH_2CH_2), 4.05 (2 H, m, CH_2)
(4d)	3-$NO_2C_6H_4$	150—151	Pr^i_2O	75	C, 50.05; H, 3.65; N, 21.5 [C, 50.35; H, 3.85; N, 21.35]	2.80—3.25 (4 H, m, CH_2CH_2), 3.92 (2 H, m, CH_2)
(4e)	2-$NO_2C_6H_4$	148—150	Pr^i_2O	50	C, 50.15; H, 3.6; N, 21.0 [C, 50.35; H, 3.85; N, 21.35]	2.87 (4 H, s, CH_2CH_2), 3.90 (2 H, m, CH_2)

* From base-catalysed deamination of the corresponding triazoline (2). † C_5D_5N for (4c).

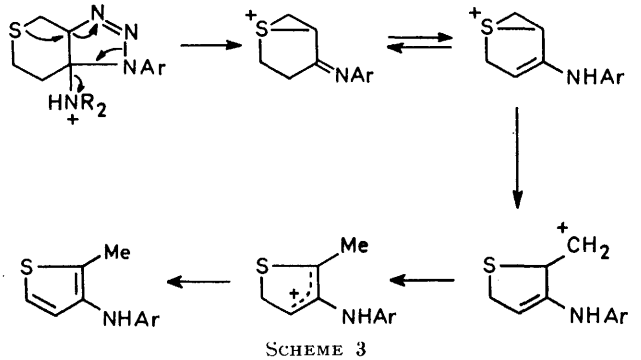
rearrange to thiophen through opening of the three-membered ring and deprotonation of the resultant cation (Scheme 3).*

In Table 4 are reported the overall yields of thiophens (3) plus triazoles (4), together with their molecular ratios, as obtained from the acidic degradation of the

* Several ring-contraction reactions proceeding by various mechanisms in the thioketone, thioketone enamine, and thiocycloalcanol series [9] have been described.

[9] N. J. Leonard and J. Figueras, *J. Amer. Chem. Soc.*, 1952, **74**, 917, and references therein; F. H. M. Deckers, W. N. Speckamp, and H. O. Huisman, *Chem. Comm.*, 1970, 1521, and references therein; Ae. de Groot, J. A. Boerma, and H. Wynberg, *Tetrahedron Letters*, 1968, 2365; H. Hofmann and G. Salbeck, *Angew. Chem.*, 1969, **81**, 424.

triazolines (2). The relative amount of thiophen derivative increases with the electron-withdrawing power of the substituent on the phenyl group, both in hydrochloric acid and in acetic acid. This is in good agreement with the general trend of 5-amino-*v*-triazolines to



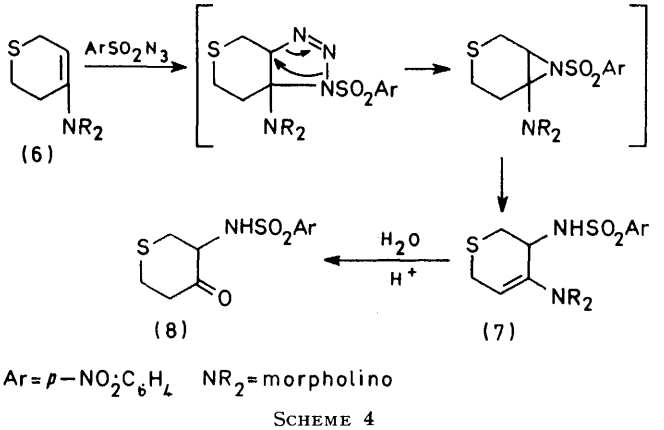
SCHEME 3

TABLE 4

Overall yields and ratios of products (3) and (4)

Starting compound	Acid	Reaction time (h)	Overall yield (%) [(3) + (4)]	Ratio (3) : (4)
(2a)	AcOH	10	70	5 : 5
(2a)	HCl	0.5	75	2 : 8
(2b)	AcOH	15	85	2 : 8
(2b)	HCl	0.5	80	8 : 2
(2c)	AcOH	16	80	8 : 2
(2c)	HCl	0.5	45	2 : 8 *
(2d)	AcOH	10	75	8 : 2
(2e)	AcOH	16	75	7 : 3
(2e)	HCl	0.5	75	7 : 3

* Besides products (3) and (4), *p*-nitroaniline (*ca.* 50%) was isolated.



SCHEME 4

undergo an easier acid-catalysed ring cleavage when the substituent in position 1 is electron-withdrawing.[8] Indeed this would enhance thiophen formation.*

On the other hand the reaction between 3,6-dihydro-4-morpholino-2*H*-thiopyran (6) and nitrophenylsulphonyl-azide did not yield a thiophen derivative, but only the sulphonylamino-enamine (7) [which was readily hydrolysed to the corresponding sulphonylamino-ketone (8)].

The formation of (7) can be rationalized as indicated in Scheme 4. Arylsulphonyl azides are known to react with enamines affording only unstable adducts,[10] which rearrange even at room temperature.[11]

The above results show that in the present case ring closure to aziridine is preferred over the formation of an episulphonium intermediate.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Varian A60 instrument with Me_4Si as internal standard. I.r. spectra were obtained with a Beckman Acculab 4 spectrophotometer (Nujol mulls). Low resolution mass spectra were obtained with a Perkin-Elmer 270 gas chromatograph–mass spectrometer [OV 101 (3%) (2 m) glass column, temp. 150—250 °C (8 °C min^{-1})], at 70 eV, ion source temperature 150 °C [for (3a) and (3b)] and with a Hitachi RMU-6L mass spectrometer at 70 eV, ion source temperature 120 °C, by direct insertion (120 °C) [for (3c) and (3d)].

General Method for the Preparation of the Triazolines (2).—Tetrahydrothiopyran-4-one [12] (10 mmol) was dissolved in anhydrous benzene (10 ml). The azide (10 mmol) in benzene (10—50 ml) was added, followed by the secondary amine [10 mmol (15 mmol for dimethylamine)]. The mixture was refluxed for the time indicated and the product precipitated with n-pentane. Alternatively, the crude mixture was evaporated and the residue crystallized.

Base-catalysed Deamination of the Triazolines (2) *to the Triazoles* (4).—The triazoline (5 mmol) was dissolved in methanolic 1% sodium hydroxide (20 ml) and refluxed for 1—5 h (until reaction was shown by t.l.c. to be complete). The mixture was evaporated, and the residue taken up in water and neutralized with conc. hydrochloric acid. The product was filtered off and recrystallized. Alternatively the residue was extracted with ether, and the ethereal layer washed with water, dried (Na_2SO_4), and evaporated. The product was then recrystallized as indicated.

Acid-catalysed Reaction of the Triazolines (2) *to give the Thiophens* (3) *and the Triazoles* (4).—The triazoline (5 mmol) was suspended in ethanol (40 ml), and acetic acid (0.5 ml) or 37% hydrochloric acid (0.25 ml) was added. The mixture was refluxed until reaction was complete (t.l.c.). After evaporation the oily residue was taken up in chloroform and the solution washed with water and aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica column (20—60 g; benzene–ethyl acetate, 4 : 1). The fraction containing the thiophen (3) was evaporated and the product distilled at reduced pressure in a bulb tube or recrystallized. The products were identified by analytical and spectroscopic data and, for (3a) and (3b), also by comparison with an authentic sample.

The fraction containing the triazole (4) was evaporated and the product recrystallized. A product identical with

* In the case of the degradation of (2c) in hydrochloric acid the ratio is apparently reversed. However in this case a substantial amount (yield *ca.* 50%) of 4-nitroaniline was obtained probably owing to hydrolysis of the cationic intermediate. This markedly lowers the yield of the thiophen derivative but confirms that in this case too ring cleavage is the preferred process.

[10] D. Pocar and P. Trimarco, *J.C.S. Perkin I*, 1976, 622, and references therein.

[11] For a discussion on the possible mechanism of triazoline decompositions see P. Scheiner, in 'Selective Organic Transformations,' ed. B. S. Thyagarajan, vol. 1, Wiley, New York, 1970, p. 327.

[12] P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.*, 1970, **35**, 584.

that from the basic deamination of the corresponding triazoline was obtained.

Synthesis of Compounds (3a) *and* (3b) *from 2-Methyltetrahydrothiophen-3-one.*— 2-Methyltetrahydrothiophen-3-one [13] (10 mmol) and an aniline (11 mmol) were dissolved in anhydrous benzene (10 ml) and refluxed with a trace of toluene-*p*-sulphonic acid. The water formed was distilled off as a water–benzene azeotrope. The solution was then evaporated and the residue distilled under reduced pressure in a bulb tube.

3,6-Dihydro-4-morpholino-2H-thiopyran (6).—Tetrahydrothiopyran-4-one (8 mmol) and morpholine (50 mmol) were dissolved in anhydrous benzene (50 ml) and treated with titanium tetrachloride (4.5 mmol) at 0 °C under nitrogen.[14] After stirring for 4 h, more titanium chloride (2 mmole) was added and stirring was continued for 20 h at room temperature. The mixture was filtered and distilled, affording, after a small fore-run of starting ketone, the *enamine* (6), b.p. 135—145° at 1 Torr (55%) (Found: C, 57.9; H, 8.15; N, 7.35. $C_9H_{15}NOS$ requires C, 58.35; H, 8.15; N, 7.55%), δ ($CDCl_3$) 2.38 (2 H, m, SCH_2CH_2), 2.78 (6 H, m, SCH_2CH_2 and CH_2NCH_2), 3.24 (2 H, m, CH_2CH), 3.72 (4 H, m, CH_2OCH_2), and 4.87 (1 H, t, *J* 4 Hz, CH).

Reaction of Compound (6) *with 4-Nitrophenylsulphonyl Azide.*—The azide (5 mmol), dissolved in benzene (5 ml), was slowly dropped into a solution of the enamine (6) (5 mmol) in anhydrous benzene (25 ml). Nitrogen (*ca.* 120 ml) was immediately evolved and the *sulphonamide* (7) was obtained as a pale yellow precipitate (1.1 g, 57%), m.p. 147—150° (from benzene) (Found: C, 47.15; H, 5.05; N, 10.95. $C_{15}H_{19}N_3O_5S_2$ requires C, 46.75; H, 4.95; N, 10.9%), δ (C_5D_5N) 2.20—3.30 (8 H, m, CH_2SCH_2 and CH_2NCH_2), 3.45 (4 H, t, CH_2OCH_2), 4.55 (1 H, m, CH), 4.90 (1 H, 2d, =CH–), and 8.35 (4 H, s, C_6H_4), ν_{NH} 3 130, $\nu_{C=C}$ 1 650 cm^{-1} (Nujol).

3-(4-Nitrophenylsulphonylamino)tetrahydrothiopyran-4-one (8).—The enamine (7) (1 mmol) suspended in hydrochloric acid (10%; 5 ml) was refluxed for 15 min. The *precipitate* was collected and recrystallized from ethanol; m.p. 153—155° (0.25 g, 80%) (Found: C, 41.6; H, 3.9; N, 8.85. $C_{11}H_{12}N_2O_5S_2$ requires C, 41.75; H, 3.8; N, 8.8%), δ (C_5D_5N) 2.81 (4 H, s, CH_2CH_2), 3.02, 3.47, and 4.76 (3 H, ABX system, J_{AX} 11.5, J_{BX} 5.5, J_{AB} 13.5 Hz, CH_2CH), 4.85 (1 H, NH), and 8.18 (4 H, s, C_6H_4), ν_{NH} 3 220, ν_{CO} 1 720 cm^{-1} (Nujol).

We thank Drs. L. F. Zerilli and M. Landi, Lepetit, S.p.A., Milan, for the mass spectra.

[7/111 *Received*, 24*th January*, 1977]

[13] P. Karrer and H. Schmidt, *Helv. Chim. Acta*, 1944, **27**, 124.
[14] W. A. White and H. Weingarten, *J. Org. Chem.*, 1967, **32**, 213.