Synthesis of 7,7′-Azoimidazo[2,1-*b*]thiazolium Salts

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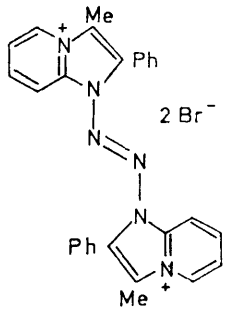
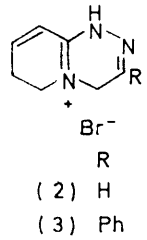
The preparation of 4*H*-thiazolo[2,3-*c*]-*as*-triazines from acetophenone thiazol-2-ylhydrazone and α-halogeno-ketones is described. Boiling concentrated hydrobromic acid failed to effect ring contraction of the 4*H*-thiazolotriazines to the corresponding 7-aminoimidazo[2,1-*b*]thiazolium salts. These last compounds were, however, prepared in high yield by treating the appropriate imidazo[2,1-*b*]thiazole bases with *O*-mesitylsulphonylhydroxylamine; oxidation of the 7-aminoimidazothiazolium salts with saturated aqueous bromine gave the title compounds.

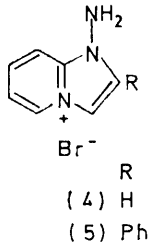
1,1′-AZOIMIDAZO[1,2-*a*]PYRIDINIUM salts of the type (1) exhibit useful neuromuscular blocking activity of the non-depolarizing type,[1,2] the effect being rapid in onset and of short duration. In a programme of work designed to determine the structural features of such compounds essential for their potency, the synthesis of the analogous title compounds (15) and (16) was undertaken. The method we proposed was the oxidation of the respective 7-aminoimidazothiazolium salts (11) and (12), which we hoped to obtain from acetophenone thiazol-2-ylhydrazone (6).[3]



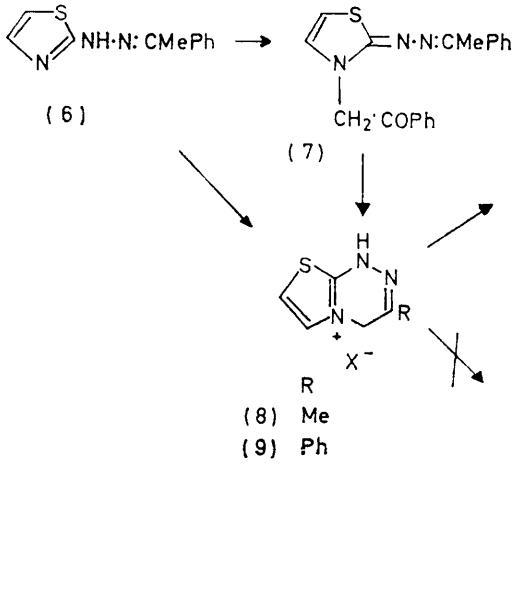
(1)



(2) R = H
(3) R = Ph



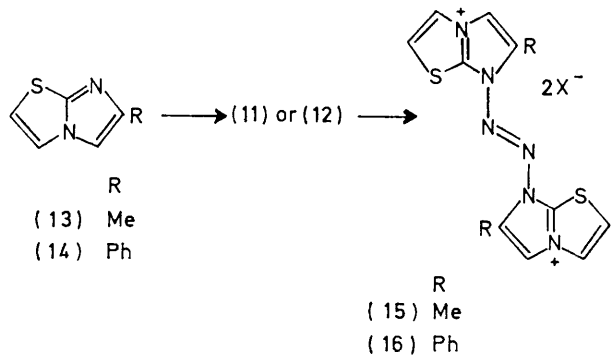
(4) R = H
(5) R = Ph



(6) → (7) → (8) R = Me; (9) R = Ph → (10); (11) R = Me; (12) R = Ph

Treatment of acetophenone thiazol-2-ylhydrazone (6) with phenacyl bromide in the presence of base gave the azine (7), which was cyclized to the thiazolotriazine hydrobromide (9) by boiling hydrobromic acid. Alternatively both (8) and (9) were obtained by heating a solution of the hydrazone (6) in acetonitrile with the appropriate α-halogeno-ketone and subsequently adding hydrobromic acid. The structure of the hydrobromides (8) and (9) followed from their elemental analyses and n.m.r. spectra (Table, footnotes *p* and *t*). Further, basification of (9) gave 3-phenyl-4*H*-thiazolo[2,3-*c*]-*as*-triazine (10).

The analogous pyridotriazine hydrobromides (2) and (3) undergo ring contraction in boiling hydrobromic acid to give the corresponding 1-aminoimidazopyridinium salts (4) [1] and (5),[4] respectively. Treatment of the thiazolotriazine hydrobromides (8) and (9) with boiling 48% hydrobromic acid, however, failed to effect ring contraction to the respective 7-aminoimidazolthiazolium salts (11) and (12). These last compounds were subsequently obtained in high yield from the corresponding imidazothiazoles (13) [5] and (14) [6] by treatment with the



(13) R = Me
(14) R = Ph

(15) R = Me
(16) R = Ph

[1] E. E. Glover and M. Yorke, *J. Chem. Soc.* (*C*), 1971, 3280.
[2] L. Bolger, R. J. Brittain, D. Jack, M. R. Jackson, L. E. Martin, J. Mills, D. Poynter, and M. B. Tyers, *Nature*, 1972, **238**, 354.
[3] H. Beyer, H. Höhn, and W. Lässig, *Chem. Ber.*, 1952, **85**, 1122.
[4] C. K. Bradsher, R. D. Brandon, J. E. Boliek, and T. L. Hough, *J. Org. Chem.*, 1969, **34**, 2129.
[5] I. Iwai and T. Hiraoka, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 813.
[6] P. M. Kochergin and M. N. Shchukina, *J. Gen. Chem.* (*U.S.S.R.*), 1956, **26**, 3233.

Reactants	Heating time (temp.)	Product	X	Yield (%)	Cryst. solvent	M.p. (°C)	Found (%) C	H	N	Required (%) C	H	N
(6) [a] (5·4 g) + $BzCH_2Br$ (5·0 g) + $NaHCO_3$ (5·4 g) in MeCN (100 ml)	25 min (Reflux) [b]	(7)		58	MeCN	179—180	67·8	5·1	12·65	68·0	5·1	12·5
(6) [a] (0·5 g) + $BzCH_2Br$ (0·5 g) in MeCN (5 ml)	0·5 h (Reflux) [b]	(9)	Br	56	MeOH–Et_2O	252	44·3	3·5	14·0	44·6	3·4	14·2
(7) (4·8 g) in 48% HBr (48 ml)	0·25 h (Reflux) [c]	(9)	Br	66	MeOH–Et_2O	252						
		(9)	$C_6H_2N_3O_7$ †		$MeNO_2$	184—186	46·0	2·8	19·1	45·9	2·7	18·9
(9) [d] (0·5 g) in H_2O (5 ml) + aq. 50% NaOH (1 ml) [e]	(Ambient) [f]	(10)		80	H_2O–MeOH	153—154	61·1	4·0	19·65	61·4	4·2	19·5
(6) [a] (2·17 g) + $AcCH_2Br$ (1·37 g) in MeCN (20 ml)	2 h (Reflux) [g]	(8)	Br	36	MeOH–Et_2O	242	30·9	3·5	17·7	30·8	3·4	18·0
		(8)	$C_6H_2N_3O_7$ †		$MeNO_2$	217—219	37·2	2·75	21·8	37·7	2·6	22·0
(13) [h] (0·57 g) in CH_2Cl_2 (5 ml) + MSH [h] (0·89 g) in CH_2Cl_2 (10 ml) [i]	(Ambient) [i]	(11)	$C_9H_{11}SO_3$ [j]	79	EtOH	239—240	51·1	5·5	11·75	51·0	5·4	11·9
		(11)	$C_6H_2N_3O_7$ †		MeOH	130—131	37·8	2·8	21·8	37·7	2·6	22·0
(14) [k] (0·093 g) in CH_2Cl_2 (1 ml) + MSH [h] (0·1 g) in CH_2Cl_2 (1 ml) [l]	5 min (Ambient) [l]	(12)	$C_9H_{11}SO_3$ [j]	74	$MeNO_2$	181—182	54·5	5·5	9·1	54·3	5·5	9·5 [k]
		(12)	$C_6H_2N_3O_7$ †		MeOH	187	45·7	3·1	18·8	45·9	2·7	18·9
(11) [e] (0·6 g) in H_2O [m] + sat. aq. Br_2 (72 ml) [n]	(Ambient) [o]	(15) [p]	Br	63	MeOH	294—295 [q]	28·45	3·5	16·3	28·8	3·2	16·8 [r]
		(15)	$C_6H_2N_3O_7$ †		$MeNO_2$	>320 [s]	37·8	2·4	22·1	37·9	2·1	22·1
(12) [t] (0·2 g) in MeOH [m] + sat. aq. Br_2 (24 ml) [n]	(Ambient) [o]	(16) [t]	Br	46	MeOH	272 [q]	44·6	3·1	14·2	44·9	2·7	14·3
		(16)	$C_6H_2N_3O_7$ †		$MeNO_2$	238—239	46·2	2·7	18·9	46·2	2·3	19·0

[b] The solution was filtered and cooled and the product filtered off. [c] 48% Hydrobromic acid (2·5 ml) was then added and the solution boiled for a further 10 min. The mixture was then evaporated under reduced pressure and the residue triturated with ether, yielding the bromide. [d] The solution was cooled and the product filtered off. [e] Bromide salt. [f] Added dropwise with stirring. [g] The precipitated base was filtered off and recrystallised. [h] 48% Hydrobromic acid (10 ml) was then added and the mixture boiled under reflux for a further 15 min. The mixture was then evaporated under reduced pressure and the residue recrystallised. [i] *O*-Mesitylsulphonylhydroxylamine.[7] [j] The mixture was triturated with ether and the product filtered off. [k] Mesitylenesulphonate. [l] For $1·5H_2O$. [m] Mesitylenesulphonate salt. [n] Saturated solution. [o] Added in bulk. [p] The precipitated perbromide was triturated until solid and then filtered off and boiled with acetone. The resulting dibromide was then filtered off and recrystallised. [q] $\lambda_{max.}(H_2O)$ 195, 225, and 378nm (log ε 4·58, 4·14, and 4·27), δ ($F_3C{\cdot}CO_2H$) (Me_4Si ext. standard) 1·8 (s,Me) 4·58 (s,CH_2), and 6·7—7·0 (ArH). [r] Decomp. [s] For $2H_2O$. [t] Decomposed without melting below the temp shown. [u] $\lambda_{max.}(H_2O)$ 200, 228, and 380 nm (log ε 4·84, 4·52, and 4·14), δ ($F_3C{\cdot}CO_2H$) (Me_4Si ext. standard) 4·95 (s,CH_2) and 6·6—7·5 (ArH).

† Picrate.

recently described powerful *N*-aminating agent *O*-mesitylsulphonylhydroxylamine.[7]

The 7-aminoimidazothiazolium salts (11) and (12) were smoothly oxidized by saturated aqueous bromine yielding the title compounds (15) and (16), respectively, which showed characteristic u.v. absorption bands in the 380 nm region.

[7] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, 4133.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. spectra were determined with a Perkin-Elmer 137 spectrophotometer and n.m.r. spectra with a Perkin-Elmer R12A spectrometer.

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