Action of Acids and Alkylating Agents on 1,4-Di-(2-pyridyl)tetraz-2-enes

By **Stephen Anderson, Edward E. Glover,* and Kenneth D. Vaughan,** Department of Chemistry, Teesside Polytechnic, Middlesbrough, Cleveland TS1 3BA

The synthesis of the title compounds and their conversion by acids or alkylating agents into 1-substituted tetrazolo-[1,5-*a*]pyridinium salts is reported.

In view of the current interest in diquaternary tetrazenes as short-acting non-depolarizing neuromuscular blocking agents,[1,2] the synthesis of the diquaternary derivatives (11) and (12) of the 1,4-di-(2-pyridyl)tetraz-2-enes (3) and (4) was undertaken. The tetrazenes (3) and (4) were obtained during the oxidation of (1). Treatment of the tetrazene (3) or (4) with methyl iodide or methyl fluorosulphate, however, did not yield the diquaternary tetrazene [(11) or (12)] but gave instead the respective 1-methyl- and 1-phenyl-tetrazolo[1,5-*a*]pyridinium salts

TABLE 1

Pyridine bases

Reactants	Product	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	Found (%) H	Found (%) N	Rqd. (%) C	Rqd. (%) H	Rqd. (%) N
Phenyl-2-pyridyl-nitrosamine [a] (4·0 g) in MeOH (60 ml) and HOAc (10 g) + Zn powder (18 g) in H_2O (20 ml) [a]	(2) [b]	25·5	*c*		70·9	6·2	22·4	71·3	6·0	22·7
(2) (0·8 g) in Et_2O (10 ml) + Ac_2O (0·45 g) in Et_2O (5 ml) [d]	(9)	77	153 [e]	$MeNO_2$	68·3	5·9	18·65	68·7	5·8	18·5
(2) (0·85 g) in MeOH (5 ml) + Br_2 (0·8 g) in MeOH (5 ml) [f]	*N*-(*p*-Bromophenyl)-2-pyridylamine hydrobromide	41	220—222	EtOH–Et_2O	40·0	3·2	8·3	40·0	3·05	8·5
	N-(*p*-Bromophenyl)-2-pyridylamine [g]		128—130	MeOH–H_2O	52·5	3·9	11·2	53·0	3·6	11·25
	N-(*p*-Bromophenyl)-2-pyridylamine picrate		234—238	$MeNO_2$	42·6	2·8	14·75	42·7	2·5	14·6

[a] The solution of the nitroso-compound was added dropwise to the ice-cold aqueous suspension of zinc powder and the mixture stirred for a further hour. The solution was then filtered and the residue washed with methanol (10 ml). Water (50 ml) was then added to the combined filtrate and washings and the solution extracted with ether, each extract being washed with a little water. The combined aqueous layer was then basified to pH 11 with 25% sodium hydroxide and re-extracted with ether (2 × 200 ml), each extract being in turn washed with water (15 ml). The combined ether extracts were evaporated and the residue was again extracted with ether. The dried extract was then evaporated and the residual hydrazine purified by disillation. [b] Lit.,[5] b.p. 140° at 0·2 mmHg. [c] B.p. 123° at 0·6 mmHg. [d] The acetyl derivative which separated was filtered off and recrystallized. [e] The melt re-solidified to form needles which remelted at 166°. [f] The solution was stirred and the bromine solution added dropwise. Ether was then added and the precipitated hydrobromide filtered off. [g] The position of the bromine atom followed from the ^1H n.m.r. spectrum in deuteriochloroform containing 0·3 mol. equiv. of the shift reagent tris-(2,2,6,6-tetramethylheptane-3,5-dionato)europium-(III). The signals due to the heteroaromatic and benzene ring protons were well separated and the signal of the latter showed the characteristic AA'XX' pattern.

TABLE 2

Oxidations with bromine

Reactants	Product	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	Found (%) H	Found (%) N	Rqd. (%) C	Rqd. (%) H	Rqd. (%) N
(1) [a] (2·0 g) in MeOH (3 ml) + sat. aq. Br_2 (30 ml) [a]	(3) [b]	22	137—138 [c]	MeOH	59·2	5·9	34·4	59·5	5·8	34·7
(2) (1·3 g) in MeOH (3 ml) + sat. aq. Br_2 (30 ml) [a]	(4)	19	145 [c]	MeCN	71·8	5·0	23·0	72·1	4·95	22·9
(10) (0·3 g) (sat. aq. soln.) + sat. aq. Br_2 (36 ml) [d]	(15) [e]	19	293—294	EtOH	42·1	4·0	7·95	41·9	3·5	8·1
	(15) picrate		163—166	MeCN	44·0	3·3	14·1	43·9	2·9	14·2

[a] The saturated aqueous bromine was added in bulk to the stirred solution. The mixture was then basified and triturated giving the tetrazene which was filtered off. [b] A small amount of methanol-insoluble material was obtained. Recrystallization from chloroform gave a compound, m.p. 243°, analytical data for which were consistent with structure (5) (Found: C, 36·0; H, 3·1; N, 21·5. $C_{12}H_{12}Br_2N_6$ requires C, 36·0; H, 3·0; N, 21·0%). [c] Decomp. [d] Added in bulk. The solution was then triturated giving a dark oil which was separated and boiled with acetone. Addition of ether to the acetone solution gave a yellow oil which was separated and triturated with ethanol, giving the bromide which was filtered off. [e] Also obtained in 78% yield by treating a methanolic solution of (14) with methanolic bromine and boiling the precipitated perbromide salt with acetone.

obtained in moderate yield by oxidation of the corresponding 2-pyridylhydrazines (1) [3] and (2) with bromine, a small amount of the brominated tetrazene (5) being (6) and (7); the methyl compound (6) was identical with a sample obtained by quaternization of tetrazolo[1,5-*a*]-pyridine (8) with methyl iodide. Cyclization of the tetrazenes (3) and (4) to the tetrazolopyridinium brom-

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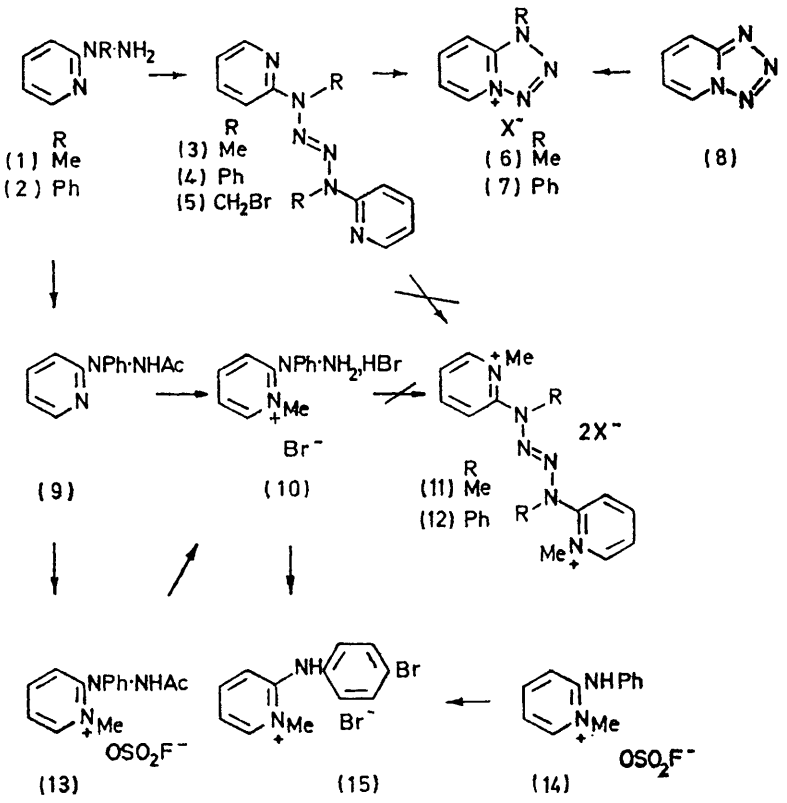
[5] G. Palazzo and L. Baiocchi, *Ann. Chim.* (*Italy*), 1965, **55**, 935.



SCHEME 1

TABLE 3

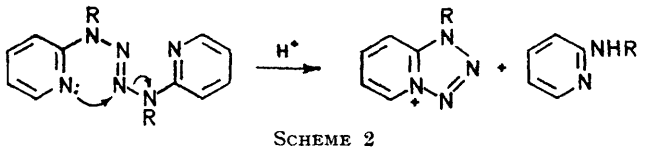
Quaternary salts

Reactants	Product	X	Yield (%)	M.p. (°C)	Cryst. solvent	Found (%) C	H	N	Rqd. (%) C	H	N
(9) (0·2 g) + $MeOSO_2F$ [a]	(13)		80	143	MeOH–Et_2O	49·5	4·8	12·2	49·3	4·7	12·3
(13) (0·4 g) + 48% HBr (5 ml) [b]	(10)		28	172—174	EtOH–Et_2O	40·1	4·3	11·8	39·9	4·2	11·6
(9) (0·5 g) + MeI (3 ml) and MeOH (3 ml) [c]	(10)		26	172—174	EtOH–Et_2O						
2-Anilinopyridine (0·85 g) in $CHCl_3$ (10 ml) + $MeOSO_2F$ (0·57 g) [d]	(14)		82	155—156	EtOH	50·9	4·95	9·8	50·7	4·6	9·9
(4) (0·24 g) + MeI (3 ml) and MeCN (3 ml) [e]	(7)	I	38	216—217	$MeNO_2$	40·8	2·5	17·4	40·8	2·8	17·3
(4) (0·08 g) in EtOH (20 ml) and 48% HBr (0·2 ml) [f]	(7)	ClO_4 [g]	31	243—244	$MeNO_2$–Et_2O	44·0	3·3	18·7	44·5	3·1	18·9
	(7)	Br		234	$MeNO_2$–Et_2O	46·2	3·5	19·6	46·5	3·8	19·7 [h]
(3) (0·3 g) + MeI (3 ml) and MeOH (3 ml) [i]	(6)	I [j]	39 [k]	199	$MeNO_2$–Et_2O	27·6	2·95	21·2	27·5	2·7	21·4
(8) [l] (0·2 g) + MeI (2 ml) [i]	(6)	I [j]	60	200	MeOH–Et_2O	27·6	2·7	21·4	27·5	2·7	21·4
(3) (0·1 g) in EtOH (20 ml) and 48% HBr (0·07 ml) [m]	(6)	Br	84	234	MeOH–Et_2O	33·5	3·3	26·05	33·3	3·1	25·8

[a] The reaction mixture was maintained at 0 °C until all the solid had dissolved. Trituration then gave the fluorosulphate which was filtered off. [b] The solution was boiled under reflux for 1 h and evaporated to dryness under reduced pressure. The residue was then recrystallized. [c] The solution was boiled under reflux overnight and evaporated to dryness under reduced pressure. The residue was then boiled with 16% HBr (5 ml) for 5 min and again evaporated to dryness. The residue was then recrystallized. [d] Added dropwise to the stirred solution. The product separated and was filtered off. [e] The solution was boiled under reflux overnight and then cooled, and the product was filtered off. [f] The solution was boiled under reflux for 2·5 h and then evaporated to dryness under reduced pressure. Attempts to recrystallize the residue from nitromethane–ether gave a gum which was dissolved in chloroform (15 ml) and treated with 70% perchloric acid (3 drops). The chloroform was then evaporated off and the residue recrystallized first from ethanol–ether and then from nitromethane–ether. [g] Also obtained from the iodide by treatment with 70% perchloric acid. [h] For the hemihydrate. [i] The solution was boiled under reflux for 17 h and then cooled. Addition of ether precipitated the crude product which was filtered off. Evaporation of the filtrate and recrystallization of the residue from aqueous methanol gave the starting tetrazene (0·16 g). [j] The two samples were identical (i.r. spectra and mixed m.p.). [k] Before recrystallization and based on starting material consumed. [l] The reaction mixture was heated in a sealed tube at 100 °C for 20 h. The solution was then evaporated and the residue recrystallized. [m] The reaction mixture was boiled under reflux for 2 h. The solution was then cooled and ether added to incipient precipitation. The bromide which separated on cooling was filtered off and the filtrate evaporated to dryness. The residue was basified and extracted with ether. Evaporation of the dried extract and treatment of the residue with alcoholic picric acid gave 2-methylaminopyridine picrate, m.p. 189—190°, identical with an authentic sample.

[1] R. G. Fargher and R. Furness, *J. Chem. Soc.*, 1915, 688.

ides (6) and (7) respectively was also effected by boiling ethanolic hydrobromic acid, and the isolation of 2-methylaminopyridine from such a cyclization of the dimethyltetrazene (3) confirmed the mechanism to be as shown in Scheme 2. In addition to establishing the



SCHEME 2

position of alkylation of tetrazolo[1,5-*a*]pyridine the reaction also provides a route to the otherwise inaccessible 1-aryltetrazolo[1,5-*a*]pyridinium salts.

We also considered an alternative route to the diquaternary tetrazene (12) *via* oxidation of the quaternized pyridylhydrazine (10) with bromine. However, this gave instead the quaternary bromo-compound (15), identical with samples prepared by direct bromination of the anilinopyridinium salt (14) and by quaternization of *N*-(4-bromophenyl)-2-pyridylamine with methyl fluorosulphate followed by exchange with bromide ion on Amberlite IRA 400 (Br^-) resin.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and n.m.r. spectra on a Perkin-Elmer model R12A spectrometer.

We thank Allen and Hanburys for a maintenance grant (to K. D. Vaughan).

[4/2365 *Received*, 12*th November*, 1974]