Synthesis and Quaternization of Some Heterocyclic Mono- and Di-sulphides

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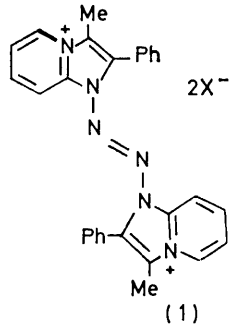
The synthesis of bis-(1-phenylimidazo[1,5-*a*]pyridin-3-yl) disulphide, its 3-phenyl 1,1'-linked analogue, bis-(2-phenylimidazo[1,2-*a*]pyridin-3-yl) disulphide, bis-(3-methyl-2-phenylindolizin-1-yl) disulphide, and bis-(α-2-pyridylbenzyl) disulphide is described, and also the synthesis of the corresponding 1- and 3-phenylimidazo[1,5-*a*]-pyridine monosulphides. The action of methyl iodide and methyl fluorosulphonate on these mono- and di-sulphides is described, as is the action of alkali on the derived disulphide diquaternary salts.

DIQUATERNARY salts of the type (1) containing imidazopyridine ring systems linked by an azo-group have recently been reported [1,2] as potent short-acting neuromuscular blocking agents of the non-depolarising type.



(1)

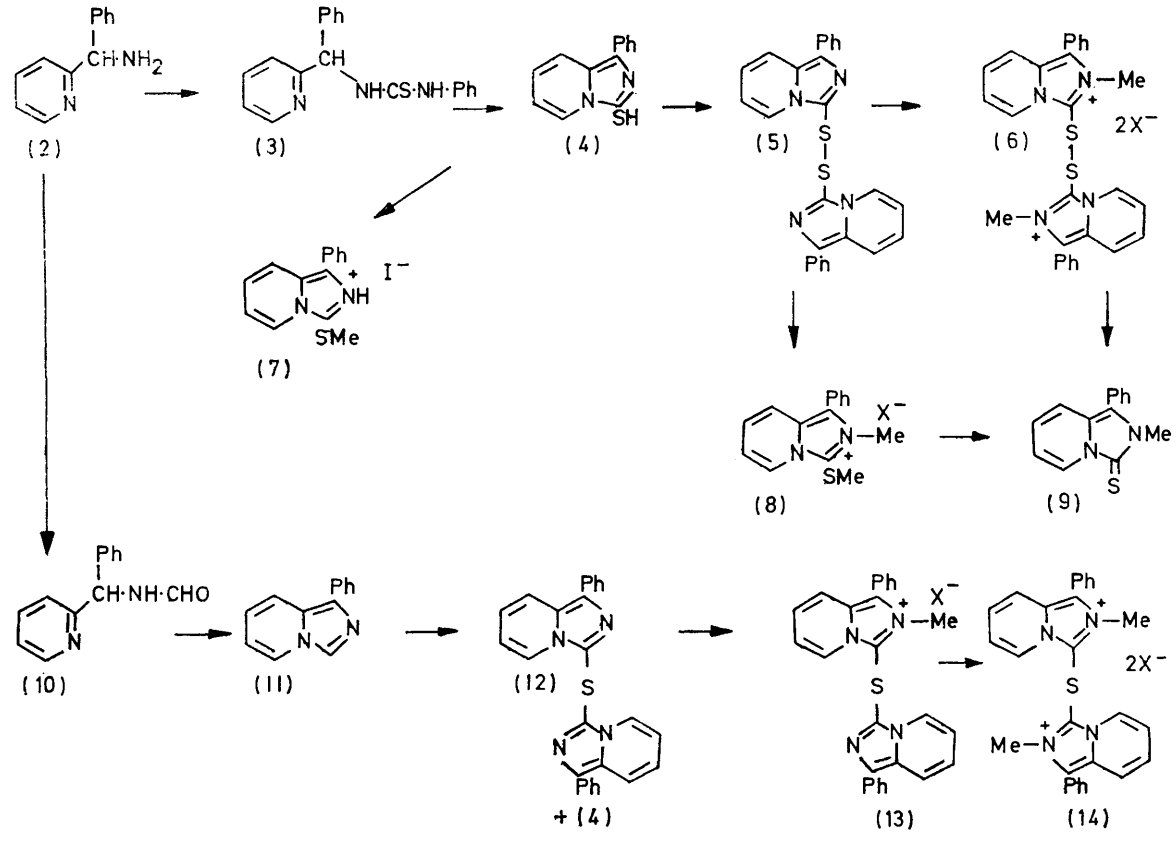
In a programme of work to establish the structural features of such systems (particularly with respect to changes in the nature of a labile group joining the quaternary heterocycles) which significantly affect their potency and duration of action, the synthesis of the diquaternary mono- and di-sulphides (6), (14), (17), (19), (24), (29), and (32) was undertaken.

The disulphides (18), (23), and (28) were obtained by the action of sulphur monochloride on the respective bases (15), (22), and (27). Treatment of the 1-phenylimidazopyridine base (11) with sulphur monochloride yielded, instead of the expected disulphide (5), a mixture of the monosulphide (12) and the thiol (4), which was subsequently more conveniently obtained by cyclization of the thiourea (3) in boiling xylene. Oxidation of the thiol (4) with methanolic hydrogen peroxide then gave the required disulphide (5). The disulphide (30) was obtained by the action of ammonia and hydrogen sulphide on 2-benzoylpyridine by a procedure similar to that described by Newman and Lutz [3] for the preparation of difluoren-9-yl disulphide from fluorenone.

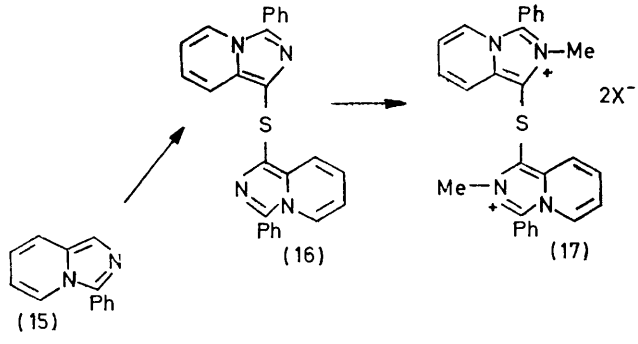
1-Phenylimidazo[1,5-*a*]pyridine (11) was obtained by formylation of α-2-pyridylbenzylamine and subsequent cyclization with phosphoryl chloride in boiling benzene; the 3-phenyl base (15) was obtained by the method described by Bower and Ramage.[4] 3-Methyl-2-phenylindolizine (27) was prepared from α-picoline and 2-bromopropiophenone *via* the intermediate carbinol (26), the uncyclized quaternary salt reported [5] not being isolated. The structure of (26) followed from its spectroscopic properties (strong ν_{OH} at 3200 cm^{-1}; no band attributable to ν_{CO}; for n.m.r. data see Table 1).

Attempts to prepare diquaternary salts of the disulphides (5) and (18) by treatment with methyl iodide in acetonitrile were unsuccessful, the products being the tri-iodides (8) and (20), respectively, derived by rupture of the disulphide link and subsequent *S*- as well as *N*-methylation. Treatment of the disulphides (5) and (18) with methyl fluorosulphonate did, however, afford the diquaternary salts (6) and (19), in high yield. The disulphide (5) was deep red in colour as was the derived diquaternary fluorosulphonate salt (6), which crystallized from ethereal ethanol or methanol with retention of the solvent alcohol; the derived perchlorate salt was, however, unsolvated. Similarly attempts to prepare

[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] M. S. Newman and W. B. Lutz, *J. Amer. Chem. Soc.*, 1956, **78**, 2469.
[4] J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 1955, 2835.
[5] M. Fraser, S. McKenzie, and D. H. Reid, *J. Chem. Soc.* (*B*), 1966, 44.



the diquaternary salt (32) by treating the disulphide (30) with methyl iodide in acetonitrile were unsuccessful, only the monoquaternary iodide (31) being obtained; treatment of the disulphide (30) with methyl fluorosulphonate, however, again yielded the required diquaternary salt (32).



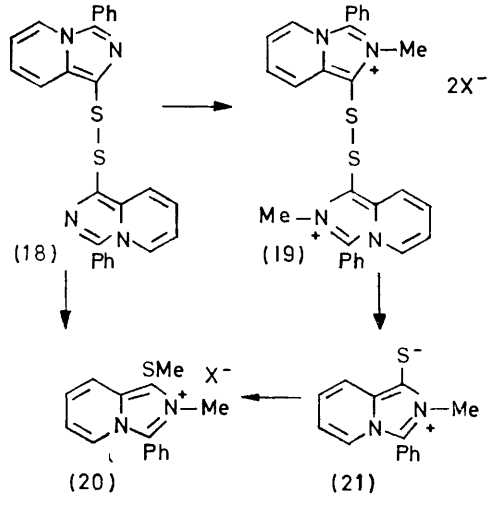


TABLE 1

^{1}H N.m.r. spectra (δ values; Me_4Si external standard)

Compound	Solvent	Assignments *
(7)	$(CD_3)_2SO$	8·5—6·6(aromatic), 2·47(SMe)
(8)	$(CD_3)_2SO$	8·8—7·0(heteroaromatic), 7·54(Ph), 3·94($\overset{+}{N}$Me), 2·45(SMe)
(9)	CCl_4	8·4—6·2(heteroaromatic), 7·36(Ph), 3·75($\overset{+}{N}$Me)
(20) I_3	$(CD_3)_2SO$	8·3—6·8 (heteroaromatic), 7·74(Ph), 3·93($\overset{+}{N}$Me), 2·45(SMe)
(21)	$CDCl_3$	8·5—6·4(aromatic), 3·97($\overset{+}{N}$Me)
(25)	$CDCl_3$	9·5—7·1(aromatic), 3·91($\overset{+}{N}$Me)
(26)	$F_3C{\cdot}CO_2H$	8·9—6·9(aromatic), 5·05(q, CH), 3·75(s, CH_2), 1·48 (d, Me)

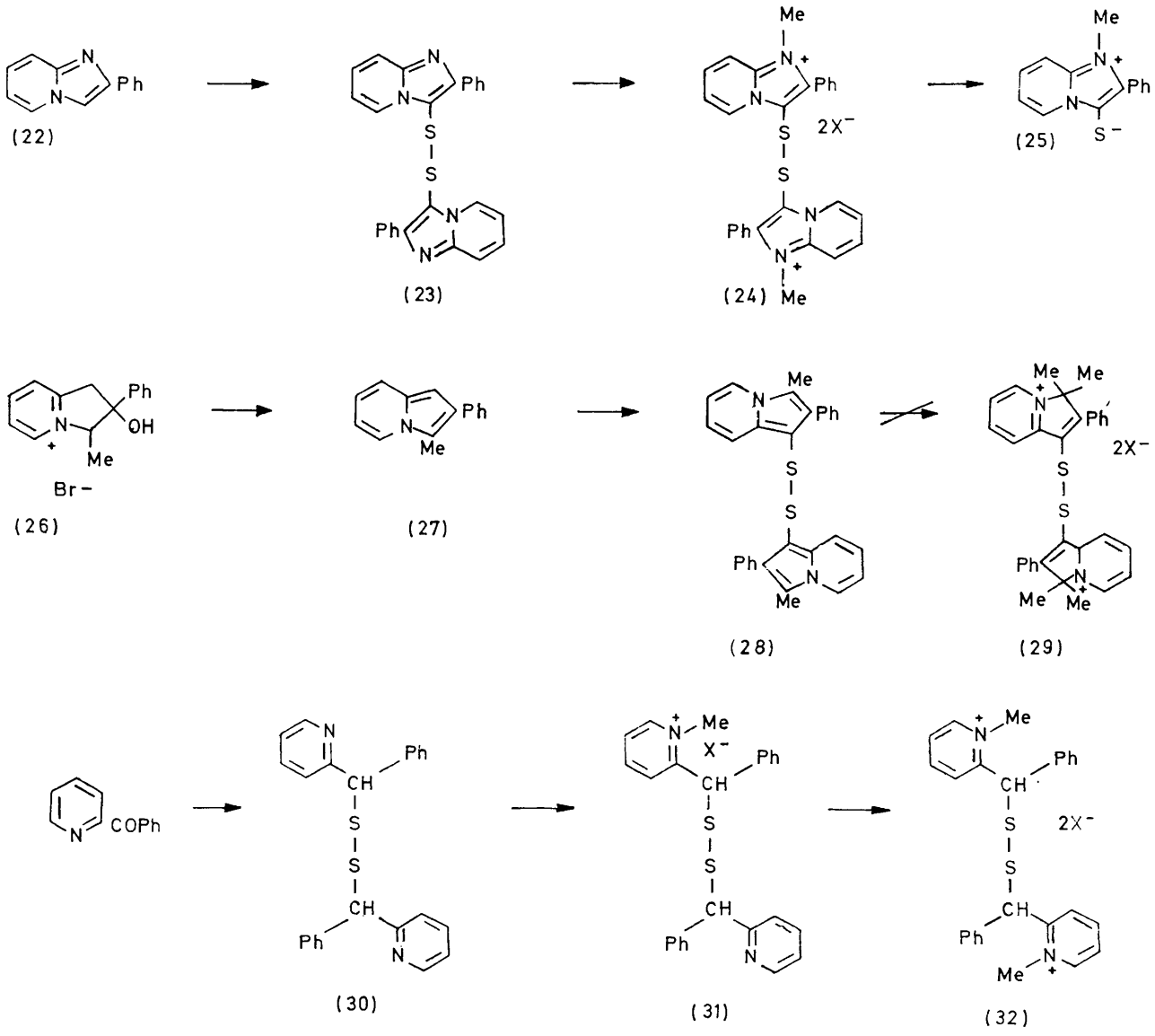
* Methyl signals are singlets except where otherwise indicated.

No products were identified from the reaction between the indolizine disulphide (28) and methyl iodide, and treatment of (28) with methyl fluorosulphonate gave a deep blue solid which could not be recrystallized.

The monosulphide (16) was obtained by treating 3-phenylimidazo[1,5-*a*]pyridine (15) with sulphur di-

chloride; treatment of the product (16) with methyl fluorosulphonate gave the diquaternary salt (17). The analogous monosulphide (12) was similarly converted into the diquaternary fluorosulphonate salt (14).

Treatment of aqueous solutions of the diquaternary disulphides (6), (19), and (24) with aqueous alkali resulted in cleavage of the disulphide link and precipitation of the cyclic thiourea (9) and the thiolate betaines (21) and (25), respectively. Methylation of the sulphides (9) and (21) with methyl fluorosulphonate, with action of methyl iodide on the corresponding disulphides (5) and (18).



EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were determined with a Perkin-Elmer R12A spectrometer.

N-Phenyl-N'-(α-2-pyridylbenzyl)thiourea (3).—A solution of α-2-pyridylbenzylamine [7] (2) (3·24 g) and phenyl isothiocyanate (2·38 g) in benzene (45 ml) was boiled under reflux for 20 min. The white solid (5·3 g, 94%) which separated gave the *thiourea* as prisms, m.p. 191—193° (from acetonitrile) (Found: C, 71·3; H, 5·4; N, 13·1. $C_{19}H_{17}N_3S$ requires C, 71·5; H, 5·4; N, 13·2%).

1-Phenylimidazo[1,5-a]*pyridine-3-thiol* (4).—A solution of the thiourea (3) (5·0 g) in xylene (100 ml) was boiled under reflux for 12 h, then cooled; the solid which separated

subsequent conversion into the tri-iodide salts, gave the respective dimethyl compounds (8) and (20); these products were identical with those obtained by the

[6] A. O. Fitton and R. K. Smalley, 'Practical Heterocyclic Chemistry,' Academic Press, 1968, p. 132.
[7] S. O. Winthrop and G. Gavin, *J. Org. Chem.*, 1959, **24**, 1936.

(2·61 g, 74%) gave the *base* as orange needles, m.p. 221—223° (from methanol) (Found: C, 68·9; H, 4·3; N, 12·4. $C_{13}H_{10}N_2S$ requires C, 69·0; H, 4·5; N, 12·4%).

2-*Methyl*-1-*phenylimidazo*[1,5-a]*pyridine*-3(2H)-*thione* (9).—An aqueous solution of the difluorosulphonate salt (6) (0·154 g) was basified and the liberated base (0·08 g, 73%) was filtered off. Recrystallization from methanol gave the *thione* as yellow needles, m.p. 116—117° (Found: C, 69·8; H, 5·1; N, 11·8. $C_{14}H_{12}N_2S$ requires C, 70·0; H, 5·0; N, 11·7%).

3-*Methylthio*-1-*phenylimidazo*[1,5-a]*pyridine Hydroiodide* (7).—A solution of the thiol (4) (0·1 g) in methyl iodide (1 ml) and acetonitrile (3 ml) was boiled under reflux for 0·75 h. Ether was then added and the *hydroiodide* was filtered off; yield 0·062 g (22·5%), m.p. 126—128° (from ethanol–ether) (Found: C, 45·5; H, 3·9; N, 7·4. $C_{14}H_{12}N_2S,HI$ requires C, 45·7; H, 3·6; N, 7·6%).

N-(α-2-*Pyridylbenzyl*)*formamide* (10).—A solution of α-2-pyridylbenzylamine dihydrochloride [7] (26·7 g) in formic acid (79·4 g) was boiled under reflux for 9·5 h. The solution was then evaporated under reduced pressure and the residue was basified with aqueous 10% sodium hydroxide. The liberated base was extracted into ether (3 × 250 ml); the extract was dried and evaporated. Recrystallization of the residue from ethanol–ether, and then ether, gave the *base* as yellow prisms, m.p. 75—76° (12·4 g, 56%) (Found: C, 73·4; H, 5·6; N, 13·0. $C_{13}H_{12}N_2O$ requires C, 73·6; H, 5·7; N, 13·2%).

1-*Phenylimidazo*[1,5-a]*pyridine* (11).—A solution of the substituted formamide (10) (12·4 g) and phosphoryl chloride (25 ml) in benzene (50 ml) was boiled under reflux for 33 h. Water was then added to the cooled mixture; basification, extraction with ether, evaporation of the dried extract, and recrystallization of the residue from ether gave the *base* as orange prisms (9·8 g, 86%), m.p. 101—102° (Found: C, 80·4; H, 5·1; N, 14·2. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·2; N, 14·4%). The picrate crystallized from nitromethane as yellow needles, m.p. 210—215° (lit.,[8] 209—212°) (Found: C, 54·1; H, 3·0; N, 16·4. Calc. for $C_{13}H_{10}N_2,C_6H_3N_3O_7$: C, 53·9; H, 3·1; N, 16·5%). The 3-*bromo-derivative*, obtained by treating a solution of the base (11) in chloroform with bromine in chloroform followed by basification of the resulting hydrobromide, gave pale yellow prisms, m.p. 101—102° [from petroleum (b.p. 40—60°)] (Found: C, 57·5; H, 3·3; N, 10·1. $C_{13}H_9BrN_2$ requires C, 57·2; H, 3·3; N, 10·3%).

2-*Methyl*-3-*phenylimidazo*[1,5-a]*pyridinium*-1-*thiolate* (21).—A suspension of the difluorosulphonate salt (19) (1·08 g) in aqueous 25% sodium hydroxide was warmed on a water-bath and triturated. The resulting yellow solid was filtered off, washed with water, and recrystallized from ethanol giving the *betaine* as yellow prisms (0·57 g, 75%), m.p. 212° (Found: C, 69·9; H, 5·0; N, 11·7; S, 13·6. $C_{14}H_{12}N_2S$ requires C, 70·0; H, 5·0; N, 11·7; S, 13·3%).

1-*Methyl*-2-*phenylimidazo*[1,2-a]*pyridinium*-3-*thiolate* (25).—The difluorosulphonate salt (24) (1·38 g) was treated as

[8] J. H. Boyer and L. T. Wolford, *J. Org. Chem.*, 1958, **23**, 1053.

TABLE 2

Mono- and di-sulphides

Starting base	Reagent	Product	Cryst. solvent	Yield (%)	M.p. (°C)	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(4) (1·13 g) in boiling MeOH (50 ml)	10% H_2O_2 in methanol (20 ml) [a]	(5) [b]	MeOH	81	156—158	69·75	3·9	12·2	69·3	4·0	12·4
(11) (1 g) stirred in MeCN (10 ml)	S_2Cl_2 (0·37 g) in MeCN (10 ml) [a]	(12) [c]	C_5H_4N–Et_2O	32·5	247—248	74·4	4·2	13·6	74·6	4·3	13·4
(15) (1 g) stirred in Et_2O (30 ml)	SCl_2 (0·26 g) in Et_2O (10 ml) [a]	(16) [d]	$MeNO_2$	36	212—214	74·55	4·3	13·4	74·6	4·3	13·4
(15) [4] (0·97 g) stirred in MeCN (10 ml)	S_2Cl_2 (0·37 g) in in MeCN (5 ml) [a]	(18) [e]	EtOH	39	152—156	69·2	4·1	12·4	69·3	4·0	12·4
(22) [6] (3·88 g) stirred in Et_2O (300 ml)	S_2Cl_2 (1·36 g) in Et_2O (20 ml) [a]	(23) [f]	MeOH	24	244—245	69·3	3·9	12·3	69·2	4·0	12·4
(27) [5] (4·14 g) stirred in Et_2O (100 ml)	S_2Cl_2 (1·35 g) in Et_2O (30 ml) [a]	(28) [g]	MeOH	46	195—196	75·9	5·1	5·7	75·6	5·1	5·9
2-Benzoylpyridine (6·0 g)in EtOH (80 ml)	H_2S, NH_3, and S [h]	(30)	EtOH	55	148	72·0	5·0	7·0	72·4	5·2	6·8
		(30), $(HClO_4)_2$	$MeNO_2$		203—207	48·2	3·6	5·0	47·9	3·7	4·7

[a] Added dropwise. [b] Obtained by evaporating the reaction mixture to 50 ml and cooling. [c] The solid product (12) was filtered off and the filtrate stirred overnight with Amberlite IRA 400(OH) resin; the resin was filtered off and the filtrate evaporated under reduced pressure. The residual *thiol* (4) crystallized from methanol as orange needles, m.p. 221—223° (0·16 g, 14%), identical with the sample described previously. [d] The mixture was basified and cooled and the product filtered off. [e] The yellow solid was filtered off, washed with ether, dissolved in methanol, and stirred with Amberlite IRA 400(OH) resin. The resin was filtered off and the filtrate evaporated. [f] The precipitated solid was filtered off, washed with ether, and recrystallized. [g] The precipitated solid was filtered off, washed with ether, and dissolved in methanol. The solution was then concentrated and the product allowed to crystallize. [h] Procedure described in ref. 3 for the preparation of difluoren-9-yl disulphide.

TABLE 3

Quaternary salts

Starting sulphide	Reagent	Product	X	Cryst. solvent	Yield (%)	M.p. (°C)	Found (%) C	H	N	Required (%) C	H	N
(5) (0·7 g)	MeI (7 ml) in MeCN (21 ml) [a]	(8)	I_3	MeOH	77	154	28·65	2·3	4·2	28·3	2·4	4·4
(9) (0·3 g) in $CHCl_3$ (3 ml)	$MeOSO_2F$ [b]	(8)	SO_3F [c]	EtOH	41	145—146	50·5	4·35	7·9	50·8	4·3	7·9
(5) (0·3 g)	$MeOSO_2F$ (1·5 ml) [d]	(6)	ClO_4 [e]	$MeNO_2$–Et_2O	87	220—221	49·2	3·7	8·1	49·5	3·6	8·25
		(6)	Br [f]	MeOH–Et_2O		135—136	49·7	4·1	8·1	49·7	4·2	8·3 [g]
(12) (0·1 g) in $CHCl_3$ (5 ml)	$MeOSO_2F$ (0·1 g) in $CHCl_3$ (1 ml) [h]	(13)	SO_3F	MeOH–Et_2O	77	175—178	61·4	4·0	10·1	60·9	4·0	10·5
		(13)	Br [f]	EtOH–Pr^i_2O		200—202	63·6	4·2	10·5	63·15	4·1	10·9
(12) (0·4 g)	$MeOSO_2F$ (4 ml) [d]	(14)	ClO_4 [e]	$MeNO_2$–Et_2O	88	314	51·7	4·0	8·4	51·9	3·7	8·65
		(14)	Br [f]	EtOH–Pr^i_2O		182—183	51·0	4·3	8·0	50·8	4·6	8·5 [i]
(16) (0·2 g) in $CHCl_3$ (2 ml)	$MeOSO_2F$ (0·5 ml) [j]	(17)	SO_3F	$MeNO_2$–EtO_2	57	273—275	52·2	3·7	8·6	52·0	3·7	8·7
		(17)	Br [f]	$MeNO_2$–Et_2O		197—198	52·4	4·3	8·6	52·2	4·4	8·7 [g]
(18) (0·5 g)	MeI (3 ml) in MeCN (9 ml) [a]	(20)	I_3	MeOH	80	163—164	28·3	2·5	4·45	28·3	2·4	4·4
(21) (0·1 g) in $CHCl_3$ (min. vol)	$MeOSO_2F$ [b]	(20)	SO_3F [c]	EtOH	88	191—193	50·9	4·3	7·9	50·8	4·3	7·9
(18) (0·473 g) in $CHCl_3$ (2 ml)	$MeOSO_2F$ (0·23 g) in $CHCl_3$ (2 ml) [k]	(19)	SO_3F	MeCN	93	216	49·3	3·9	8·45	49·5	3·6	8·3
		(19)	Br [f]	MeOH–Et_2O		205	52·3	4·0	8·6	52·5	3·8	8·7
(23) (0·21 g) in $CHCl_3$ (5 ml)	$MeOSO_2F$ (0·21 g) in $CHCl_3$ (2 ml) [l]	(24)	SO_3F	MeCN–Et_2O	92	258—260	48·6	3·45	8·0	48·3	3·8	8·0 [m]
		(24)	Br [f]	$MeNO_2$		199—200	50·9	3·9	8·35	51·1	4·0	8·5 [m]
(30) (2·4 g)	MeI (40 ml) in MeCN (40 ml) [n]	(31)	I	MeCN [o]	68	104—106	55·3	4·4	5·1	55·3	4·3	5·2
(30) (0·5 g) in $CHCl_3$ (1 ml)	$MeOSO_2F$ (0·3 g) in $CHCl_3$ (1 ml) [p]	(32)	SO_3F	MeOH–Et_2O [q]	69	123—125 [r]	50·1	4·5	4·0	49·7	4·2	4·5
		(32)	ClO_4 [s]	H_2O		118—121	50·0	4·3	4·4	49·6	4·2	4·45
		(32)	Br [f]	MeOH–Et_2O [f]		158—160	50·7	4·6	4·2	50·6	4·7	4·5 [t]

[a] The solution was boiled under reflux for 0·75 h and cooled; ether was added and the product filtered off and recrystallized. [b] Added dropwise until the solution became colourless. Ether was then added and the product filtered off. [c] Treatment of a methanolic solution of the fluorosulphonate salt with an aqueous solution of potassium tri-iodide gave (8) as the tri-iodide salt, identical with the sample obtained by treating the disulphide (5) with methyl iodide. [d] The mixture was stirred and heated on a boiling water bath for 4—5 min, then cooled, and ether was added. The product was filtered off and recrystallized. [e] The hygroscopic fluorosulphonate salt was dissolved in methanol and 70% perchloric acid was added. The perchlorate salt which separated was filtered off and recrystallized. [f] Prepared by passing a methanolic solution of the fluorosulphonate salt down a column of Amberlite IRA 400(Br^-). [g] For $2H_2O$. [h] The mixture was warmed to effect dissolution and then set aside for 10 min. Ether was then added and the solid filtered off. Treatment of the solid with ethanol gave a gum which was triturated until solid; the solid was filtered off and recrystallized. [i] For $3H_2O$. [j] The solid product separated and was filtered off and recrystallized. [k] The mixture was set aside for 10 min; ether was added and the product filtered off. [l] The mixture was warmed on a boiling water bath for 1 min, then cooled, and the product was filtered off. [m] For $1H_2O$. [n] The solution was boiled under reflux for 0·75 h and then concentrated and cooled; the product separated. [o] Crystallization from acetone gave a solvated product, m.p. 109—119° (Found: C, 56·2; H, 4·8; N, 4·65. $C_{25}H_{23}IN_2S_2,Me_2CO$ requires C, 56·0; H, 4·9; N, 4·7%). [p] The mixture was set aside for 10 min; ether was then added, and the precipitated gum was triturated with more ether until solid. [q] The product was purified by allowing it to separate from warm methanol–ether and triturating the resulting gum with ether. [r] With previous softening at 100°. [s] Prepared by treating a methanolic solution of the fluorosulphonate with 70% perchloric acid. [t] For $1·5H_2O$.

described for the preparation of the betaine (21). The *betaine* (25) formed yellow prisms (0·63 g, 65%), m.p. 251—252° (from ethanol) (Found: C, 69·8; H, 5·0; N, 11·6; S, 13·2. $C_{14}H_{12}N_2S$ requires C, 70·0; H, 5·0; N, 11·7; S, 13·3%). The *hydroperchlorate* crystallized from acetonitrile–ether as prisms, m.p. 285—286° (Found: C, 49·4; H, 3·7; N, 8·2. $C_{14}H_{12}N_2S,HClO_4$ requires C, 49·3; H, 3·8; N, 8·2%).

*2,3-Dihydro-2-hydroxy-3-methyl-2-phenyl-*1H*-pyrrolo-*[1,2-a]*pyridinium Bromide* (26).—A mixture of 2-bromopropiophenone (10·0 g) and an excess of α-picoline (6·9 g) was heated in a boiling water bath for 35 min, cooled, and triturated with ether. The resulting solid (4·3 g, 30%) gave the *carbinol* as needles, m.p. 242° (from aqueous methanol) (Found: C, 59·0; H, 5·3; N, 4·8. $C_{15}H_{16}BrNO$ requires C, 58·8; H, 5·3; N, 4·6%).

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