Halogen-Substituted Acridizinium Derivatives

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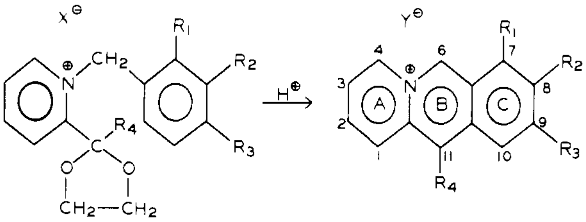
Through cyclization of suitable 1-benzyl-2-(1,3-dioxolan-2-yl)- and 1-benzyl-2-(2-methyl-1,3-dioxolan-2-yl) pyridinium salts, 19 acridizinium systems have been prepared, each substituted in ring C by one or more halogen atoms.

THE LITERATURE affords no example of a halogen-substituted acridizinium salt. As part of two unrelated projects, 19 such salts have been synthesized, all having halogen in ring *C*. Nine of these salts had an additional methyl group at position 11, having been formed by the cyclization of ketals, 1-benzyl-2-(2-methyl-1,3-dioxolan-2-yl)pyridinium salts (III), instead of the closely related acetals, 1-benzyl-2-(1,3-dioxolan-2-yl)pyridinium salts (I).

Although the acetals (I) and ketals (III) were not cyclized under conditions exactly comparable, cyclization of the ketals appears to be more difficult. The quaternary salt (I) derived from 2,4-dichlorobenzyl halide and the acetal of 2-pyridine carboxaldehyde could be cyclized in 48% yield whereas no conditions were found for cyclizing the comparable ketal (IIIs). A similar observation was made with the quaternary salt (IIIu) (formed by reaction of *p*-nitro-

Table I. Synthesis of Halogen-Substituted Acridizinium Salts



I. $R_4 = H$
III. $R_4 = CH_3$

II. $R_4 = H$
IV. $R_4 = CH_3$

	Substituents			I			II		
	R_1	R_2	R_3	X	Solvent[a]	Yield, %	H^-	Y	Yield, %
a	F	H	H	Cl	FA/DMF	..[b]	PPA	ClO_4	5
b	Cl	H	H	Cl	FA/DMF	..[b]	PPA	ClO_4	38
c	Br	H	H	Br	DMF	64	PPA	ClO_4	83
d	I	H	H	Br	DMF	97	PPA[c]	ClO_4	60
e	H	H	F	Br	DMF	85	PPA	ClO_4	76
f	H	H	Cl	Cl	FA	..[b]	PPA	ClO_4	28
g	H	H	Br	Br	DMF	75	HBr	Br	70
h	H	H	I	Br	DMF	88	HBr	Br	81
i	Cl	H	Cl	Cl	TMS	20	PPA[d]	ClO_4	48
j	H	Cl	Cl	Cl	TMS	31	PPA	ClO_4[e]	64
	$R_4 = CH_3$			III			IV		
k	F	H	H	I	TMS	91	PPA[f]	ClO_4	46[g]
l	Cl	H	H	Br	TMS	70	PPA	ClO_4	77
m	Br	H	H	Br	TMS	71	PPA	I	58[h]
n	I	H	H	Br	TMS	82	PPA	ClO_4	71
o	H	H	F	Br	TMS	..[b]	PPA	ClO_4	..
p	H	H	Cl	Br	TMS	84	PPA	ClO_4	84
q	H	H	Br	Br	TMS	66	PPA	ClO_4	83
r	H	H	I	Br	TMS	91	PPA	ClO_4	77
s	Cl	H	Cl	I	TMS	67	PPA	ClO_4	..[i]
t	H	Cl	Cl	I	TMS	41	PPA	ClO_4	39

[a] FA = formamide, DMF = dimethylformamide, TMS = tetramethylene sulfone, PPA = polyphosphoric acid, HBr = 48% hydrobromic acid. [b] The quaternary salt did not crystallize and was cyclized without purification. [c] In refluxing hydrobromic acid, the yield of the bromide was 65%. [d] Refluxing for 10 hours in hydrobromic acid gave no product. [e] By addition of bromine plus hydrogen bromide to the phosphoric acid mixture, the product was precipitated as the tribromide, and from this the bromide was recovered in 76% yield. [f] All cyclizations in this series were carried out at 100°. [g] This iodide was converted to the chloride before cyclization, and this represents the over-all yield for both the conversion to the chloride and the cyclization. [h] Yield of iodide rather than perchlorate. The iodide was precipitated from the phosphoric acid mixture by addition of potassium iodide solution. [i] Cyclization failed also on the chloride at 100° (24 hours), 110 to 120° (4 hours), 150 to 160° (4 hours) or 180 to 190° (2 hours).

Table II. Visible and Ultraviolet Absorption Maxima

II	Subst.	Maxima, mμ and (Log ϵ)
		Acridizinium Perchlorates
a	7-F	210^a (4.00), 248 (4.54), 365 (3.93), 384 (3.91), 404 (3.81)
b	7-Cl	225^a (4.05), 251 (4.47), 366 (3.97), 386 (3.97), 406 (3.92)
c	7-Br	203 (4.20), 229–234^a (4.22), 253 (4.43), 300^a (3.57), 366 (3.92), 387 (3.93), 407 (3.89)
d	7-I	212 (4.24), 236 (4.37), 254.5 (4.41), 347^a (3.57), 366 (3.91), 390 (3.90), 411 (3.89)
e	9-F	238 (4.60), 247^a (4.49), 357^a (3.92), 371 (4.09), 391 (383)
f	9-Cl	211^a (3.80), 243 (4.59), 254 (4.50), 271^a (4.18), 347^a (3.72), 364 (3.98), 379 (4.11), 398 (3.98)
g	9-Br	209 (3.90), 245 (4.49), 257 (4.50), 275 (4.27), 350^a (3.70), 364 (3.95), 380 (4.09), 399 (3.99)
h	9-I	209 (4.13), 239 (4.32), 261 (4.28), 283^a (4.13), 297^a (4.24), 301 (4.25), 368 (3.91), 384 (4.09), 403 (4.00)
		11-Methyl Derivatives
k	7-F	232^a (4.44), 248 (4.74), 274^a (3.80), 355^a (3.90), 369 (4.10), 385 (4.13), 406 (4.00)
l	7-Cl	238^a (4.53), 246^a (4.59), 253 (4.72), 354^a (3.92), 370 (4.12), 388 (4.15), 409 (4.07)
m	7-Br	238 (4.42), 254 (4.63), 356^a (3.83), 371 (4.07), 388 (4.10), 409 (3.94)
n	7-I	238 (4.56), 255 (4.66), 355^a (3.83), 372 (4.08), 391 (4.10), 412 (4.07)
o	9-F	237 (4.69), 248^a (4.58), 360 (4.10), 376 (4.26), 395 (3.96)
p	9-Cl	243 (4.71), 254 (4.65), 270^a (4.30), 282^a (4.22), 350 (3.83), 365 (4.09), 382 (4.25), 402 (4.11)
q	9-Br	245 (4.63), 257 (4.66), 274 (4.36), 350^a (3.80), 366 (4.08), 383 (4.26), 403 (4.12)
r	9-I	220 (4.44), 243 (4.51), 260 (4.56), 298 (4.39), 353^a (3.79), 369 (4.09), 386 (4.29), 407 (4.18)
t	8,9-Cl_2	247 (4.65), 261 (4.59), 283 (4.33), 292^a (4.48), 355^a (3.82), 370 (4.05), 388 (4.13), 407 (4.01)

[a] Shoulder.

Table III. Ultraviolet Absorption Maxima (mμ) of Monohalogen Derivatives of Acridizinium and 11-Methylacridizinium Salts

	7-Substituted		9-Substituted	
Halogen	Acridizinium	11-Me-acridizinium	Acridizinium	11-Me-acridizinium
F	248	248	238	237
Cl	251	253	243	243
Br	253	254	257	257
I	254.5	255	261^a	260

[a] This absorption (log ϵ 4.28) is lower in intensity than the actual maximum at 239 mμ (log ϵ 4.32), but analogy suggests that the absorption at 261 mμ corresponds to the band being observed in the other iodo derivatives.

Table IV. Cyclization Intermediates

Formula, Table I	Subst.	*X*	M.P.^{a}	Reaction Time, Days	Formula	C, %		H, %		N, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
				1-Benzyl-2-(1,3-dioxolan-2-yl)pyridinium Salts (I)							
c	2-Br	Br	142–143.5^b	17	$C_{15}H_{15}Br_2NO_2$	44.88	44.95	3.74	3.71	3.49	3.67
c	2-Br	ClO_4	123–124^c		$C_{15}H_{15}BrClNO_6$	42.85	43.12	3.57	3.62	3.33	3.42
d	2-I	Br	172–173^d	19	$C_{15}H_{15}BrINO_2$	40.20	40.32	3.37	3.49	3.12	3.21
d	2-I	ClO_4	140.5–141.5^c		$C_{15}H_{15}ClINO_6$	38.52	38.70	3.23	3.15	3.00	3.48
e	4-F	Br	132–133.5^e	19	$C_{15}H_{15}BrFNO_2$	52.95	53.25	4.44	4.48	4.12	4.12
g	4-Br	Br	154–155^d	35	$C_{15}H_{15}Br_2NO_2$	44.91	45.31	3.77	3.90	3.49	3.60
g	4-Br	ClO_4	169–170^e		$C_{15}H_{15}BrClNO_6$	42.85	43.22	3.57	3.77	3.33	3.43
h	4-I	Br	177–178.5^e	18	$C_{15}H_{15}BrINO_2$	40.20	40.32	3.37	3.55	3.12	3.19
h	4-I	ClO_4	184–185^e		$C_{15}H_{15}ClINO_6$	38.52	38.81	3.23	3.42	2.99	3.02
i	2,4-Cl_2	I	151–152^{e,f}	1	$C_{15}H_{14}Cl_2INO_2$	41.12	41.21	3.22	3.24	3.20	3.51
j	3,4-Cl_2	ClO_4	121–122^e		$C_{15}H_{14}Cl_3NO_6$	43.87	43.96	3.44	3.54	3.41	3.57
				1-Benzyl-2-(2-methyl-1,3-dioxolan-2-yl)pyridinium Salts (III)							
k	2-F	I	123–124^{c,f}	7	$C_{16}H_{17}FINO_2$	47.89	47.74	4.27	4.12	3.49	3.80
k	2-F	ClO_4	105–106^e		$C_{16}H_{17}ClFNO_6$	51.41	51.38	4.58	4.41	3.75	3.82
l	2-Cl	Br	143–144^c	5	$C_{16}H_{17}BrClNO_2$	51.84	51.87	4.62	4.78	3.78	3.92
l	2-Cl	ClO_4	138–138.5^c		$C_{16}H_{17}Cl_2NO_6$	49.24	49.47	4.39	4.50	3.59	3.81
m	2-Br	Br	152–152.5^b	14	$C_{16}H_{17}Br_2NO_2$	46.29	46.41	4.13	3.99	3.37	3.62
m	2-Br	ClO_4	150.5–151^c		$C_{16}H_{17}BrClNO_6$	44.21	44.34	3.94	3.80	3.22	3.52
n	2-I	Br	143.5–144.5	14	$C_{16}H_{17}BrINO_2$	41.58	41.77	3.71	3.68	3.03	3.11
n	2-I	ClO_4	149–150^d		$C_{16}H_{17}ClINO_6$	39.89	39.98	3.56	3.48	2.91	3.12
p	4-Cl	Br	130–130.5^b	11	$C_{16}H_{17}BrClNO_2$	51.84	51.66	4.62	4.33	3.78	4.07
p	4-Cl	ClO_4	128–129^c		$C_{16}H_{17}Cl_2NO_6$	49.24	49.15	4.39	4.50	3.59	3.93
q	4-Br	Br	140–141^b	14	$C_{16}H_{17}Br_2NO_2$	46.29	46.42	4.13	4.15	3.37	3.57
q	4-Br	ClO_4	151–152^c		$C_{16}H_{17}BrClNO_6$	44.21	44.08	3.94	4.09	3.22	3.50
r	4-I	Br	167–167.5^c	14	$C_{16}H_{17}BrINO_2$	41.58	41.69	3.71	3.47	3.03	3.33
r	4-I	ClO_4	157–158^c		$C_{16}H_{17}ClINO_6$	39.89	40.17	3.56	3.57	2.91	3.11
s	2,4-Cl_2	I	145–146^{f,g}	3	$C_{16}H_{16}Cl_2INO_2$	42.50	42.46	3.57	3.58	3.10	3.24
s	2,4-Cl_2	ClO_4	217.5–218^b		$C_{16}H_{16}Cl_3NO_6$	45.25	45.37	3.80	3.99	3.30	3.46
t	3,4-Cl_2	I	127–127.5^{f,g}	3	$C_{16}H_{16}Cl_2INO_2$	42.50	42.41	3.57	3.43	3.10	3.42
t	3,4-Cl_2	ClO_4	137.5–138^e		$C_{16}H_{16}Cl_3NO_6$	45.25	45.42	3.80	3.60	3.30	3.47
u	4-NO_2	Br	161–162^b	7	$C_{16}H_{17}BrN_2O_4$	50.40	50.42	4.50	4.66	7.35	7.58
u	4-NO_2	ClO_4	229–229.5^c		$C_{16}H_{17}ClN_2O_8$	47.95	48.17	4.28	3.93	6.99	7.12

[a] Melting point of analytical sample. Unless otherwise indicated, all crystals were colorless and crystallized from methanol–ethyl acetate. [b] Prisms. [c] Platelets. [d] Irregular prisms. [e] Needles. [f] Pale yellow. [g] Powder.

Table V. Cyclization Products

Compd. (II)	Subst.	Y	Temp.	Time, Hr.	Proc.[a]	M.P.[b]	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
							Acridizinium Derivatives						
a	7-F	ClO_4	105	3	B	233.5–235[c]	$C_{13}H_9ClFNO_4$	52.45	52.55	3.05	3.08	4.70	4.99
b	7-Cl	ClO_4	95	4	B	209–212[d]	$C_{13}H_9Cl_2NO_4$	49.84	49.65	2.87	2.81	4.47	4.73
c	7-Br	ClO_4	105	4	B	206–208[c]	$C_{13}H_9BrClNO_4$	43.57	43.65	2.51	2.52	3.91	4.20
d	7-I	Br	126[e]		A	259–259.5[d]	$C_{13}H_9BrIN$	40.45	40.30	2.35	2.46	3.63	3.82
d	7-I	ClO_4				229–230[f]	$C_{13}H_9ClINO_4$	38.49	38.31	2.23	2.16	3.45	3.81
d	7-I	Pic.[g]				231–232[h]	$C_{19}H_{11}INO_7$	42.71	42.68	2.07	2.09	10.48	10.44
e	9-F	ClO_4	105	2	B	177–178[d]	$C_{13}H_9ClFNO_4$	52.45	52.80	3.04	3.08	4.70	4.81
f	9-Cl[i]	ClO_4	85		B	224.5–226[d]	$C_{13}H_9Cl_2NO_4$	49.70	49.65	2.88	3.23	4.46	4.51
g	9-Br	Br	126	30	A	262–263[h,j]	$C_{13}H_9Br_2N \cdot H_2O$	44.74	44.22	3.18	3.08	4.01	4.39
g	9-Br	ClO_4				218–220[d]	$C_{13}H_9BrClNO_4$	43.57	43.71	2.51	2.73	3.91	4.22
g	9-Br	I				257–258[k]	$C_{13}H_9BrIN$	40.44	40.55	2.35	2.54	3.62	3.97
h	9-I	Br	126		A	256–257[j,l]	$C_{13}H_9BrIN \cdot \frac{1}{2}H_2O$	39.52	39.61	2.55	2.59	3.55	3.68
h	9-I	ClO_4				257–258[c]	$C_{13}H_9ClINO_4$	38.49	38.59	2.23	2.26	3.45	3.82
h	9-I	Pic.				248–249[f]	$C_{19}H_{11}IN_4O_7$	42.71	42.86	2.07	2.12	10.48	10.30
i	7,9-Cl₂	ClO_4	115	11	B	229–230[c]	$C_{13}H_8Cl_3NO_4$	44.79	44.85	2.31	2.39	4.02	4.25
j	8.9-Cl₂	ClO_4	145	19	B	231–232[k]	$C_{13}H_8Cl_3NO_4$	44.79	44.91	2.31	2.26	4.02	4.00
j	8.9-Cl₂	Br				>250[d,m]	$C_{13}H_8BrCl_2N$	47.45	47.56	2.45	2.69	4.26	4.33
							11-Methylacridizinium Perchlorates (IV)						
k	7-F	ClO_4	100	24	B	206.5–207.5[f]	$C_{14}H_{11}ClFNO_4$	53.94	53.97	3.56	3.85	4.49	4.58
l	7-Cl	ClO_4	100	12	B	244–244.5[f]	$C_{14}H_{11}Cl_2NO_4 \cdot \frac{1}{2}CH_3CN$	51.67	51.59	4.04	3.78	6.02	5.93
m	7-Br[n]	ClO_4	100	17	B	261.5–262[j]	$C_{14}H_{11}BrClNO_4$	45.12	45.03	2.98	2.95	3.76	4.09
n	7-I	ClO_4	100	5	B	273–274[j,k]	$C_{14}H_{11}ClINO_4$	40.07	40.43	2.64	2.74	3.34	3.59
o	9-F[o]	ClO_4	100	27	B	250.5–252[f,j]	$C_{14}H_{11}ClFNO_4$	53.94	54.29	3.56	3.71	4.49	4.67
p	9-Cl	ClO_4	100	18	B	293.5–294[h]	$C_{14}H_{11}Cl_2NO_4$	51.24	51.35	3.38	3.45	4.27	4.55
q	9-Br	ClO_4	100	4	B	286–287[f,j]	$C_{14}H_{11}BrClNO_4$	45.12	45.14	2.98	3.30	3.76	3.93
r	9-I	ClO_4	100	17	B	293–294[j,k]	$C_{14}H_{11}ClINO_4$	40.07	40.16	2.64	2.55	3.34	3.58
t	8,9-Cl₂	ClO_4	100	10	B	302–303[f,j]	$C_{14}H_{10}Cl_3NO_4$	46.37	46.78	2.78	2.99	3.86	4.00

[a] Procedure A, hydrobromic acid cyclication, procedure B, polyphosphoric acid. [b] Melting point of the analytical sample. The yields reported in Table I are for compounds melting within 10 degrees of this m.p. Unless otherwise stated, the samples were yellow and were crystallized from methanol-ethyl acetate or methanol-acetonitril ethyl acetate. [c] Prisms. [d] Needles. [e] Refluxing. [f] Platelets. [g] Picrate. [h] Microcrystalline. [i] A small quantity of this compound has been prepared in this laboratory by J. H. Jones (2), via the quaternary salt derived from picolinaldehyde. [j] Melts with decomposition. [k] Irregular prisms. [l] Granules. [m] This product decomposed rather than melted. [n] This perchlorate salt was prepared from the iodide (see Experimental). [o] Prepared from crude oily quaternary salt.

benzyl bromide with the ketal, Table IV) which could not be cyclized, although the corresponding acetal has been reported (*1*) to cyclize in 56% yield. The visible and ultraviolet absorption spectra of the new acridizinium salts may be found in Table II.

Comparison of the ultraviolet absorption maxima of the monohaloacridizinium derivatives (II) with those observed in the 11-methyl series (IV) is made in Table III. With only one adjustment (noted in the table), there is close correspondence in absorption maxima between the compounds with and without the alkyl group. More remarkable is the effect of the position of the halogen atom on the shift of the maximum observed as halogen is varied from fluorine to iodine. The shift in the 7-halogen series amounts to about 7 mμ, while in the 9-halogen series the shift amounts to 23 mμ.

EXPERIMENTAL

Quaternization and Cyclization. General procedures have been described (*1*). Experimental data have been summarized in Tables IV and V.

Benzyl Iodides. Commercially available benzyl chlorides too unreactive for the quaternization reaction were first converted to the iodide. The benzyl chloride was added to an acetone solution containing a slight excess of sodium iodide and the mixture refluxed for 10 minutes. The solution was filtered, and the acetone removed in vacuo without heat. The residue was dissolved in ether, the solution filtered, and the ether removed in vacuo. The residual benzyl iodide was used immediately in the quaternization reaction.

Conversion of Quaternary Iodides (III) to Chlorides. A tenfold excess of freshly precipitated and washed silver chloride was stirred for six hours with a solution of the iodide (III) in water or methanol. The mixture was filtered and concentrated. The residue was used directly in the cyclization reaction.

Spectra. The ultraviolet absorption spectra were determined in 95% ethanol using a Cary Model 14 spectrophotometer.

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Adsorption Study of Ferrimetaphosphate

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Preparation methods for an active ferric metaphosphate are given, and the optimum method is noted. The ferrimetaphosphate has a very high capacity for water adsorption and can be regenerated with small amounts of energy. The ferrimetaphosphate has a high capacity for adsorption of ammonia; however, the ammonia is taken up irreversibly and the absorbent is converted into an inactive material. Static water and ammonia adsorption values show that the specific surface is large; about 640 sq. meters per gram for a monomolecular layer. From the data, an estimation is made that the adsorbed layer of water molecules surrounding the compound is about 8 molecules thick.

ADDITION of a solution of sodium polyphosphate glass to an aqueous solution of a ferric salt precipitates ferrimetaphosphate which exhibits adsorptive behavior toward water and ammonia. By careful attention to the method of preparation, a solid with a large specific surface can be obtained. The results of such an investigation are reported here.

PREPARATION

Direct Method. A solution of $(NaPO_3)_n$ was prepared by dissolving 30.5 grams of R-S Unadjusted Calgon in rapidly stirred water, total volume 100 ml. End group titrations indicated an average chain length of 9. The formula weight of the glass was chosen as 612, thus, such solutions can be referred to as $0.5M$. With continuous stirring, the solution of the phosphate glass was added to a freshly prepared $0.5M$ ferric chloride solution until the flocculent, yellow precipitate which first formed changed to a fine, white precipitate. The total addition of phosphate was kept

Table I. Effect of Preparation Variables on Activity of Ferrimetaphosphates

Condition	H_2O Adsorbed, Mg./G. (Relative Humidity, 100%)
$0.2M$ $FeCl_3$ *vs.* $0.5M$ $(NaPO_3)_n$	90.0
Both solutions $0.25M$	116.8
Both solutions $0.5M$	132.5

All were dried to constant weight before being placed in atmosphere for 4 hours.

Table II. Effect of Drying on Activity of Ferrimetaphosphate

Drying Treatment at 108 ± 2° C.	H_2O Adsorbed, Mg./G. (Relative Humidity, 100%)
Dried to constant weight	197.5
Dried 1½ hours	274.5
Dried 1 hour	344.0

All samples prepared by direct method using $0.5M$ solutions; samples in atmosphere for 12 hours.

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