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Acridizinium Derivatives Having *meta*-Directing Substituents

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Through cyclization of suitably substituted 1-benzyl-2-(1,3-dioxolan-2-yl)pyridinium salts, acridizinium salts having nitro, carboxyl or sulfo substituents have been prepared. The 9-sulfo acridizinium derivative exists as a remarkably stable betaine.

While earlier publications have described the synthesis of acridizinium derivatives with the terminal (c) ring substituted by alkyl (2), aryl (3), or alkoxyl (4, 5) groups, there has been no published account of a derivative containing a *meta*-directing group. It seemed probable that cyclization into a ring substituted by a strongly electron-withdrawing (*meta*-directing) group would require polyphosphoric acid to effect the ring closure. Although intermediates prepared by the reaction of benzyl halides with picolinaldehyde (2) or picolinaldoxime (6) behave poorly in hot polyphosphoric acid, it was shown that the quaternary salt (III) derived from 2-(1,3-dioxolan-2-yl)pyridine (I) could be cyclized in polyphosphoric acid in 77% yield (7). It has now been found that the dioxolanylpyridine method is well suited to the synthesis of acridizinium derivatives having electron-withdrawing substituents. The results of these experiments are summarized in Table I.

The quaternization reaction with methyl *p*-(bromomethyl)benzenesulfonate afforded a betaine (III. $R_3 = SO_3^-$, no X^-) rather than the expected bromide (III. $R_3 = SO_2OCH_3$, X = Br). Refluxing hydrobromic acid was found adequate to induce cyclization into mildly deactivated rings, and yields of 74-79% were observed when the carboxyl or sulfo group was present. With the nitrile group, hydrolysis occurred, probably prior to cyclization, and only the carboxylic acid was recovered. The low yield (35%) of acridizinium-7-carboxylic acid (IV. $R_1 = COOH$, $R_3 = H$) was due in part to difficulty in removing the ammonium bromide which is formed as a by-product in the reaction.

It proved mandatory in the case of the nitro compounds, that a more effective cyclizing agent be used, and in these cases, polyphosphoric acid, at temperatures of 120-130° proved effective. It was hoped that the new nitro derivatives might be reduced to the hitherto unknown acridizinium amines, but polarographic reduction of the 9-nitro derivative carried out in this laboratory (8), seemed to indicate that reduction of the acridizinium nucleus commences at approximately the same potential as that required for reduction of the nitro group.

Only one benzyl quarternary salt (IIIf), derived from 2,4-dinitrobenzyl bromide, could not be cyclized in either hydrobromic or polyphosphoric acid. No cyclization of this highly deactivated system was observed even at temperatures (170°) at which pronounced decomposition occurs.

Perhaps the most interesting product obtained in this study is the betaine (IV. $R_3 = SO_3^-$, no Y^-) of 9-sulfoacridizinium hydroxide. This new salt manifests a thermal stability rare in the acridizinium series, undergoing no decomposition below 350°, and melting at 401-402°. Evidently a strongly acidic function is needed to form a betaine in the acridizinium series, for an attempt to convert 9-carboxyacridizinium bromide (IVd) to the zwitterion by action of an aqueous slurry of silver oxide resulted in the destruction of the acridizinium salt. The acridizinium ion is so sensitive to base that any stable betaine must be one that can be formed at low *p*H.

The 7-carboxyacridizinium (IV. $R_1 = COOH$, $R_3 = H$) bromide, unlike the 9 analog (IVd) could not be esterified by the Fischer method (steric hindrance?), but it could be converted to the acid chloride which formed the ester normally.

Data concerning the ultraviolet absorption spectra of the new acridizinium salts (IV) are in Table II.

EXPERIMENTAL

All analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany. The melting points were taken on the Mel-Temp apparatus and are uncorrected. Ultraviolet absorption spectra were measured in 95% ethanol using a Cary Model 14 Spectrophotometer and 1 cm. quartz cells.

Quaternization.

Quaternizations were carried out at room temperature in the absence of light and in stoppered flasks. The volume of solvent (dimethylformamide or tetramethylenesulfone) used (in milliliters) was roughly equal to the weight in grams of the benzyl halide (9-11) employed. It is disadvantageous to use larger volumes of solvent unless a homogeneous mixture cannot be made otherwise. At the end of the reaction period, ether or ethyl acetate was added to complete the precipitation of the salt which was usually crystallized from methanol-ethyl acetate.

Cyclization. Procedure A.

A solution containing 10 ml. of 48% hydrobromic acid per gram of quaternary salt was refluxed for at least six hours. Removal of the hydrobromic acid in a rotary evaporator *in vacuo* (aspirator) produced the acridizinium salt as a residue which usually could be crystallized from methanol-ethyl acetate. This is the preferred method when either procedure A or B can be used.

Procedure B.

The quaternary salt (III) was placed in a round-bottomed flask and the combined weight noted. Polyphosphoric acid was added, 30 g. for the first 2 g. of salt, and 10 g. for each additional gram. The mixture was stirred on the steam bath until hydrogen bromide was no longer evolved and the solution was homogeneous. Less decomposition occurred if cyclization was carried out on the steam bath, but when higher temperatures were used it was found important that the mixture be stirred vigorously to prevent localized overheating.

After cyclization was complete, the mixture was cooled to room temperature and a quantity of ice water equal in weight to the polyphosphoric acid used, was added with vigorous stirring. Digestion of the resulting solution on the steam bath for two hours was carried out to insure complete hydrolysis of the polyphosphoric acid and to prevent coprecipitation of polyphosphate salts. The acridizinium derivatives were isolated from phosphoric acid solution by either of two procedures.

(1) Isolation as the perchlorate.

Dropwise addition of 35% perchloric acid to the cool solution usually precipitated the perchlorate which could be recrystallized.

(2) Isolation as the tribromide.

Dropwise addition of a mixture, consisting of three volumes of 48% hydrobromic acid to one volume of bromine (the $HBr-Br_2$ reagent), to the phosphoric acid solution with rapid stirring afforded the very insoluble tribromide salt. After cooling the mixture, the salt was collected, washed in cold water, and

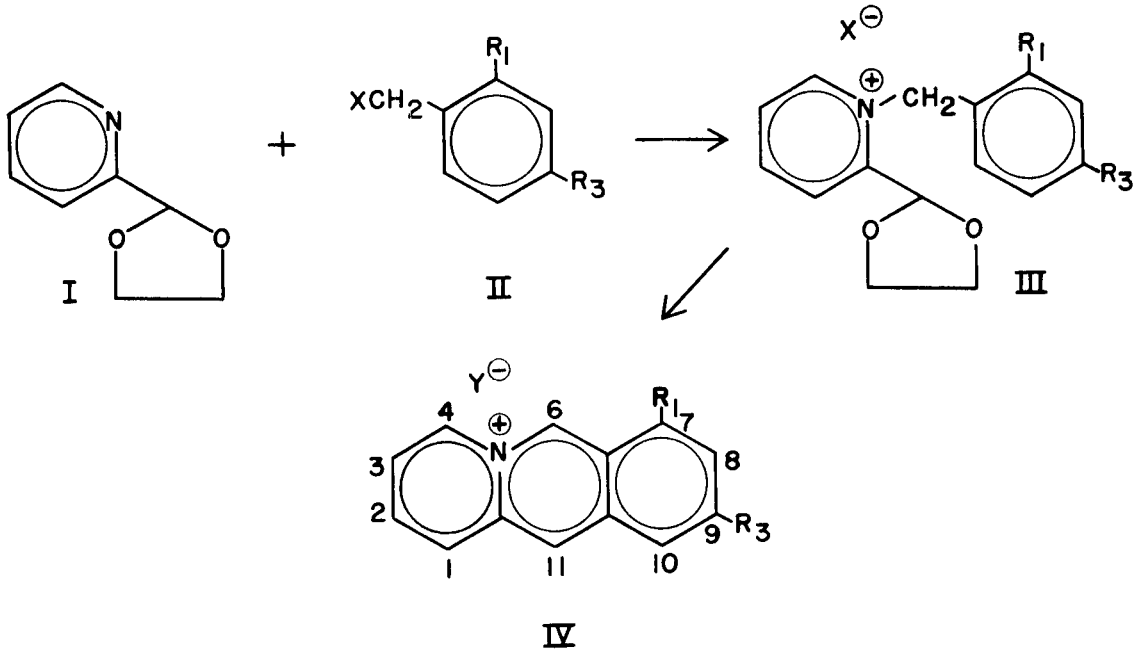

Table I

Synthesis of Acridizinium Salts Having Deactivating Groups

	II Substituents		III			IV		
	R_1	R_3	X^-	Solvent (a)	Yield, %	H^+	Y^-	Yield, %
a	CN	H	Br	TMS	96	HBr (c)	Br	35 (d)
b	NO_2	H	Br	TMS	86	PPA	ClO_4	37
c	H	NO_2	Br	DMF	88	PPA (e)	ClO_4	56
d	H	COOH	Br	TMS	88	HBr	Br	79
e	H	SO_3CH_3 (b)	(Br) (b)	TMS	22	HBr	(b)	74
f	NO_2	NO_2	Br	TMS	87	PPA (f)		0

(a) DMF = dimethylformamide, TMS = tetramethylene sulfone. (b) The quaternization product was not the expected bromide containing the sulfo methyl ester, but instead a sulfo betaine. This was cyclized to a sulfoacridizinium betaine. (c) No product was isolated in an attempted polyphosphoric acid cyclization. (d) The product isolated was the acridiziniumcarboxylic acid (IV. R_1 = COOH) instead of the nitrile. (e) Refluxing of the quaternary salt in hydrobromic acid for 48 hr. gave no cyclization product. (f) The conditions tried were 140-170° for 4-21 hr. Decomposition occurred before cyclization.

Table II

Ultraviolet Absorption Maxima (mμ) and (Log ε) for Acridizinium (IV) Perchlorates

7-Carboxy	209 (a)	242	383 (a)	343 (a)	361	381	402			
	(3.88)	(4.62)	(3.76)	(3.71)	(4.01)	(4.06)	(4.03)			
7-Carbo-	205	239	263	343 (a)	367	382	403			
methoxy	(4.00)	(4.62)	(4.35)	(3.74)	(4.02)	(4.08)	(4.04)			
7-Nitro	215	239	267-269 (a)	276-279 (a)	327-330	344	358	390	401 (a)	
(IVb)	(4.25)	(4.28)	(3.89)	(3.86)	(3.40)	(3.64)	(3.92)	(3.79)	(3.78)	
9-Nitro	214 (a)	241	257	290 (a)	324	339	356	385 (a)	403	424
(IVc)	(4.02)	(4.26)	(4.28)	(3.83)	(3.56)	(3.62)	(3.72)	(3.60)	(3.81)	(3.81)
9-Carboxy	246	276-278 (a)	286-288 (a)	324	341	357	368	389	410	
(IVd)	(4.62)	(4.05)	(4.02)	(3.44)	(3.63)	(3.89)	(3.81)	(4.05)	(4.10)	
9-Carbo-	245	274 (a)	323	339	357	370	390	412		
methoxy (b)	(4.60)	(4.28)	(3.44)	(3.67)	(3.91)	(3.78)	(4.08)	(4.16)		
9-Sulfo (c)	215 (a)	245	253	267 (a)	347 (a)	360	380	399		
(Betaine)	(3.70)	(4.62)	(4.58)	(4.31)	(3.68)	(3.92)	(4.02)	(4.01)		

(a) Shoulder (b) Spectrum for bromide rather than perchlorate. (c) Betaine of 9-sulfoacridizinium hydroxide rather than perchlorate salt.

Table III

1-(Benzyl)-2-(1,3-dioxolan-2-yl)pyridinium Salts (III)

II	Subst.	X^-	M.P. (d)	Time, Days	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
d	2-CN (a)	Br	157-158 (e)	10	$C_{16}H_{15}BrN_2O_2 \cdot 3/4H_2O$	53.26	53.26	4.61	4.48	7.85	7.95
a	2-CN	ClO_4	161-162 (e)		$C_{16}H_{15}ClN_2O_6$	52.39	52.74	4.12	4.11	7.63	7.72
b	2-NO_2 (b)	Br	162-163	11	$C_{15}H_{15}BrN_2O_4$	49.05	49.25	4.11	4.26	7.63	7.63
b	2-NO_2	ClO_4	189-190		$C_{15}H_{15}ClN_2O_8$	46.63	46.74	3.88	3.86	7.25	7.25
c	4-NO_2	Br	163-165	18	$C_{15}H_{15}BrN_2O_4$	49.04	49.41	4.08	4.15	7.62	7.81
c	4-NO_2	ClO_4	133.5-134.5 (f)		$C_{15}H_{15}ClN_2O_8$	46.64	47.08	3.88	3.86	7.25	7.22
d	4-COOH	Br	168-169 (g)	14	$C_{16}H_{16}BrNO_4$	52.47	52.45	4.40	4.39	3.82	3.87
	4-SO_3 (c)		237-237.5 (h)	2	$C_{15}H_{15}NO_5S$	56.06	55.70	4.70	4.71	4.36	4.79
f	2,4-$(NO_2)_2$	Br	145-146 (f)	4	$C_{15}H_{14}BrN_3O_6$	43.70	43.82	3.42	3.48	10.19	10.28

(a) Reference 9. (b) Reference 10. (c) The starting material was methyl 4-(bromomethyl)benzenesulfonate, but the product was the betaine (III. $R_1 = H$, $R_3 = SO_3^-$, no X^-) of 1-(4-sulfobenzyl)-2-(1,3-dioxolan-2-yl)pyridinium hydroxide. (d) Melting point of analytical sample. Unless otherwise indicated, all crystals were colorless and crystallized as needles from methanol-ethyl acetate. (e) Irregular prisms. (f) Platelets. (g) Prisms. (h) Granules, which melted with decomposition.

Table IV

Acridizinium Derivatives (IV)

Comp.	Subst.	Y^-	Temp.	Time Hr.	Proc. (a)	M.P. (b)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
	7-COOH	Br	126	18	A	281-282 (d)	$C_{14}H_{10}BrNO_2$	55.28	55.76	3.31	3.43	4.60	4.79
	7-COOH	ClO_4				236-237 (d)	$C_{14}H_{10}ClNO_6$	51.94	52.07	3.11	3.21	4.32	4.50
b	7-NO_2	ClO_4	125	6	B	216.5-217.5 (e)	$C_{13}H_9ClN_2O_6$	48.08	48.15	2.79	2.82	8.63	8.66
c	9-NO_2	ClO_4	115	7	B	240.5-241 (e)	$C_{13}H_9ClN_2O_6$	48.14	48.40	2.78	2.82	8.64	8.35
c	9-NO_2	Pic.				244-245 (f,e)	$C_{19}H_{11}N_5O_9$	50.33	50.66	2.44	2.72	15.45	15.08
d	9-COOH	Br	126	11	A	255 (g)	$C_{14}H_{10}BrNO_2 \cdot 1/2H_2O$	53.95	54.17	3.54	3.91	4.47	4.41
d	9-COOH	ClO_4				250-253 (g)	$C_{14}H_{10}ClNO_6$	51.94	52.21	3.11	3.46	4.32	4.33
	9-SO_3^-	(c)	126	21	A	401-402 (e)	$C_{13}H_9NO_3S$	60.22	60.18	3.50	3.67	5.40	5.60

(a) Procedure A, hydrobromic acid cyclization, procedure B, polyphosphoric acid. (b) Melting point of the analytical sample. All samples melted with decomposition. The yields reported in Table I are for compounds melting within ten degrees of this m.p. Unless otherwise stated the samples were yellow and were crystallized from methanol-ethyl acetate. (c) This product is the betaine (IV. $R_1 = H$, $R_3 = SO_3^-$) produced by cyclization of the betaine of 1-(4-sulfobenzyl)-2-(1,3-dioxolan-2-yl)pyridinium hydroxide (Table III). (d) Microcrystalline. (e) Needles. (f) Prisms (g) Granules.

then suspended in a mixture of acetone and methanol. The resulting mixture was heated on the steam bath (hood) with stirring until the salts dissolved, and the bromide was crystallized from the solution in the usual way.

9-Carbomethoxyacridizinium Bromide (IV. R_1 H, R_3 $COOCH_3$, Y = Br).

The esterification of 1.21 g. of 9-carboxyacridizinium bromide (IVd) may be accomplished by refluxing it for 2 hr. in 100 ml. of methanol saturated with hydrogen bromide. Recrystallization of the product from methanol-ethyl acetate afforded 1.09 g. (86%) of the ester, m.p. 230–233° dec. The analytical sample had a m.p. of 230° with decomposition, gas evolution, and previous charring.

Anal. Calcd. for $C_{15}H_{12}BrNO_2$: C, 56.62; H, 3.80; N, 4.40. Found: C, 56.36; H, 3.89; N, 4.75.

The perchlorate crystallized as bright yellow needles from methanol-ethyl acetate, m.p. 236–237°.

Anal. Calcd. for $C_{15}H_{12}ClNO_6$: C, 53.34; H, 3.58; N, 4.14. Found: C, 53.15; H, 3.53; N, 4.50.

7-Carbomethoxyacridizinium Perchlorate (IV. R_1 $COOCH_3$, R_3 H, Y ClO_4).

Direct esterification of 7-carboxyacridizinium bromide in the manner of the 9 isomer failed, but esterification could be accomplished *via* the acid chloride. A slurry of 1.5 g. of 7-carboxyacridizinium bromide in a mixture of 1 ml. of oxalyl chloride and 70 ml. of acetyl chloride was stirred for 27 hr. at room temperature in a flask protected from moisture. The acetyl chloride was removed *in vacuo* (aspirator) and 70 ml. of reagent grade methanol added. The solution was stirred for 4 hr., charcoaled, and the solvent removed. The residue was dissolved in water and precipitated as the perchlorate by addition of 37% perchloric acid. Recrystallized from methanol-ethyl acetate, the precipitate afforded 1.0 g. (60%) of material, m.p. 204–205°. The analytical sample formed pale yellow platelets from methanol-ethyl acetate, m.p. 211–212°.

Anal. Calcd. for $C_{15}H_{12}ClNO_6$: C, 53.34; H, 3.58; N, 4.14. Found: C, 53.68; H, 3.68; N, 4.52.

The bromide was obtained by dropwise addition of a mixture of 3 volumes of 48% hydrobromic acid to 1 volume of bromine to an aqueous solution of the perchlorate. The tribromide salt which formed was converted to the bromide by heating it with acetone-methanol mixture. The analytical sample was obtained as yellow irregular prisms, m.p. >400° (color change to red above 190° and gradual charring).

Anal. Calcd. for $C_{15}H_{12}BrNO_2$: C, 56.62; H, 3.80; N, 4.40. Found: C, 56.38; H, 3.66; N, 4.68.

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