[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation of 2-Substituted Vinyl Quaternary Salts

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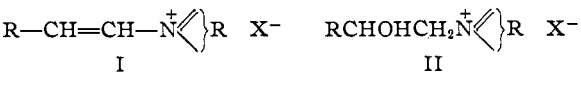
2-Substituted vinyl quaternary salts, I, were prepared for testing as tumor damaging agents.[1] The compounds prepared, their yields, melting points, and analytical data are listed in the accompanying table. Except where noted these are new compounds.



I II

Most of the type I compounds were obtained by dehydration of the 2-substituted-2-hydroxyethyl quaternary salts, II, using benzoyl chloride at 180–200° as the dehydrating agent.[2,3] 1-Styrylpyridinium bromide was also prepared by treating 1-(2-phenyl-2-chloroethyl)-pyridinium bromide with alcoholic potassium hydroxide. 1-(3,4-Dimethoxystyryl)-pyridinium iodide was obtained directly from the reaction between veratraldehyde and phenacylpyridinium iodide.

The compounds of type II were prepared by the action of a heterocyclic base on styrenebromohydrin[4] (Method A) and by the action of a suitable aldehyde on a phenacylpyridinium salt or methylpyridinium salt[4] (Methods B and C).

Kröhnke[2] reported the melting point of 1-styrylpyridinium bromide as 101–102°. In this Laboratory the monohydrate of this compound melted at 99–100°. When this substance was dried *in vacuo* at 100° the anhydrous salt melting at 154–156° was obtained.

This work was partially supported by a grant-in-aid from the National Cancer Institute of the United States Public Health Service.

Experimental

The following examples are representative of the general methods used in preparing the 2-substituted-2-hydroxyethyl quaternary salts.

Method A. 1-(2-Phenyl-2-hydroxyethyl)-4-pentylpyridinium Bromide.—A mixture of 10 g. (0.05 mole) of styrenebromohydrin[5] and 8 g. (0.05 mole) of 4-*n*-amylpyridine was heated for twenty hours at 100°. The resulting solid was ground in a mortar and the product washed with acetone until nearly colorless. Ten grams of crude product melting at 165–166° was obtained. Crystallization from 55 cc. of warm water gave 8.5 g. (48%) of pure product melting at 166–167°. The picrate, iodide and perchlorate salts of this compound were oils.

Method B. 1-[2-(2-Thienyl)-2-hydroxyethyl]-pyridinium Iodide.—To a suspension of 15 g. (0.046 mole) of phenacylpyridinium iodide[6] in a solution of 15 g. (0.11 mole) of 2-thiophenaldehyde[7] and 50 cc. of ethanol at 0° was added 4.5 cc. (0.045 mole) of 10 *N* sodium hydroxide. The temperature was maintained at 0° for three hours. The product which precipitated was removed by filtration and crystallized first from dilute alcohol and then from water. The yield was 4.6 g. (30%) of product melting at 236–237°.

Method C. 1-[2-(2-Thienyl)-2-hydroxyethyl]-pyridinium Bromide.—A solution of 17.5 g. (0.1 mole) of methylpyridinium bromide, 15 g. (0.11 mole) of 2-thiophenealdehyde[7] and 1 cc. of piperidine in 50 cc. of absolute ethanol was refluxed for sixteen hours. Upon cooling the reaction mixture 10 g. of crude product separated. After crystallization from dilute ethanol the pure product weighed 7.7 g. (27%) and melted at 232–233°.

1-Styryl-3-picolinium Bromide.—This example is typical of the dehydration of the 2-substituted-2-hydroxyethyl quaternary salts. A mixture 16 g. (0.057 mole) of 1-(2-phenyl-2-hydroxyethyl)-3-picolinium bromide, and 30 cc. of benzoyl chloride was heated at 190–200° for one hour. The reaction mixture was cooled to 0°. The product was collected and washed with acetone and ether. The weight of crude product melting at 185–188° was 14 g. After crystallization from absolute ethanol–ether the weight was 12.5 g. (83%); m. p. 186–188°.

1-(2-Phenyl-2-chloroethyl)-pyridinium Bromide.—Ten grams (0.036 mole) of 1-(2-phenyl-2-hydroxyethyl)-pyridinium bromide was treated portionwise with 10 cc. of thionyl chloride and then heated at 100° for five minutes. The excess thionyl chloride was removed *in vacuo* and the residual oil dissolved in hot acetone. An equal volume of ether was added whereupon the product crystallized. The weight of crude product was 6 g.; m. p. 151°. Crystallization from absolute ethanol–ether gave 5.5 g. (51%) of pure product melting at 153°.

Anal. Calcd. for $C_{13}H_{13}ClBrN$: N, 4.69. Found: N, 4.78.

The perchlorate salt was prepared from the above bromide by metathetical reaction with perchloric acid. The pure salt, after crystallization from water, melted at 175–176°.

Anal. Calcd. for $C_{13}H_{13}Cl_2NO_4$: N, 4.40. Found: N, 4.10.

1-Styrylpyridinium Bromide.—A 10% ethanolic potassium hydroxide solution was added dropwise to a solution of 5.5 g. of 1-(2-phenyl-2-chloroethyl)-pyridinium bromide in 25 cc. of ethanol until a permanent alkaline reaction to Alkacid paper was obtained. The solution was filtered and acidified with concentrated hydrobromic acid. The resulting red solution was evaporated in an air stream and the residual solids washed with acetone. The weight of the crude monohydrate was 4.5 g.; m. p. 96–98°. After crystallization from *n*-amyl alcohol the product weighed 3.5 g. (64%) and melted at 99–100°. This product lost one molecule of water on heating *in vacuo* at 100° over phosphorus pentoxide. The anhydrous compound melted at 154–156°.

(1) To be examined by the Chemotherapy Section of the National Cancer Institute for activity against sarcoma 37.

(2) Kröhnke, German Patent, 682,255 (1939), prepared 1-styrylpyridinium bromide by heating 1-(2-phenyl-2-hydroxyethyl)-pyridinium bromide with benzoyl bromide at 160–180°.

(3) By heating the hydroxy compounds at 150° for a short time with benzoyl chloride or *p*-nitrobenzoyl chloride, the intermediate esters could be obtained. Thus, 2-phenyl-2-benzoxyethylpyridinium bromide, m. p., 123–125° (*Anal.* Calcd. for $C_{20}H_{18}BrNO_2$: Br, 20.8. Found: Br, 20.8; perchlorate, m. p. 157–158°. *Anal.* Calcd. for $C_{20}H_{18}ClNO_6$. N, 3.47. Found: N, 3.14) and 2-phenyl-2-*p*-nitrobenzoxyethylpyridinium bromide, m. p. 246–248° (*Anal.* Calcd. for $C_{20}H_{17}BrN_2O_4$: Br, 18.6. Found: Br, 18.4), were obtained.

(4) (a) Kröhnke, *Ber.*, **66**, 607 (1933); (b) **67**, 656 (1934); (c) **68**, 1351 (1935); (d) **72**, 2000 (1939).

(5) Read and Reid, *J. Chem. Soc.*, 1487 (1928). The crude product was used without distillation.

(6) King, THIS JOURNAL, **66**, 894 (1944).

(7) Generously supplied by Abbott Laboratories, North Chicago, Illinois.

TABLE I

$RCHOHCH_2N\langle\rangle R'\ X^-$

R	N⟨⟩R'	X⁻	Yield, %[a]	M. p., °C.[b]	Formula	Halogen, % Calcd.	Halogen, % Found	Nitrogen,[c] % Calcd.	Nitrogen,[c] % Found
Phenyl	Pyridine	Br	76[d]	234–235[e]	$C_{13}H_{14}BrNO$	28.53	28.4	..	..
Phenyl	Pyridine	I	59,[f] 46[g]	253–254	$C_{13}H_{14}INO$	38.80	39.1	4.28	4.17
Phenyl	Pyridine	ClO_4	....	217–218[h]	$C_{13}H_{14}ClNO_5$	...	..	4.67	4.69
Phenyl	β-Picoline	Br	56[d]	165–166	$C_{14}H_{16}BrNO$	27.17	26.9	..	..
Phenyl	β-Picoline	ClO_4	....	181–182	$C_{14}H_{16}ClNO_5$	...	..	4.47	4.22
Phenyl	4-*n*-Amylpyridine	Br	48[d]	166–167	$C_{18}H_{24}BrNO$	22.81	22.5	..	..
Phenyl	Isoquinoline	Br	49[d]	166–168[i]	$C_{17}H_{16}BrNO$	24.20	23.8	..	..
Phenyl	Isoquinoline	ClO_4	....	211	$C_{17}H_{16}ClNO_5$	...	..	4.01	3.97
2-Thienyl	Pyridine	Br	27[g]	232–233	$C_{11}H_{12}BrNOS$	27.9	27.9	..	..
2-Thienyl	Pyridine	I	30[f]	236–237	$C_{11}H_{12}INOS$	38.2	38.5	..	..
2-Thienyl	Pyridine	ClO_4	....	206	$C_{11}H_{12}ClNO_5S$	...	..	4.58	4.50
	$RCH{=}CHN^+\langle\rangle R'\ X^-$								
Phenyl	Pyridine	Br	64,[j] 68[k]	99–100[l]	$C_{13}H_{12}BrN{\cdot}H_2O$	28.5	28.5	..	..
Phenyl	Pyridine	Br	....	154–156	$C_{13}H_{12}BrN$	30.5	30.5	..	..
Phenyl	Pyridine	ClO_4	....	171–172[m]	$C_{13}H_{12}ClNO_4$	...	..	4.97	5.30
Phenyl	β-Picoline	Br	83[k]	186–188	$C_{14}H_{14}BrN$	28.9	28.6	..	..
Phenyl	β-Picoline	ClO_4	....	150–151	$C_{14}H_{14}ClNO_4$	...	..	4.74	4.52
Phenyl	4-*n*-Amylpyridine	Br	50[k]	186–187	$C_{18}H_{22}BrN$	24.0	23.6	..	..
Phenyl	4-*n*-Amylpyridine	ClO_4	....	144–145	$C_{18}H_{22}ClNO_4$	...	..	3.98	4.19
Phenyl	Isoquinoline	Br	60[k]	219–220	$C_{17}H_{14}NBr{\cdot}H_2O$	24.2	24.1	..	..
Phenyl	Isoquinoline	ClO_4	....	212–213	$C_{17}H_{14}NClO_4$	...	..	4.22	4.13
2-Thienyl	Pyridine	Br	68[k]	98–100	$C_{11}H_{10}BrNS{\cdot}H_2O$	27.9	27.8	..	..
2-Thienyl	Pyridine	Br	....	180–181	$C_{11}H_{10}BrNS$	29.8	29.5	..	..
2-Thienyl	Pyridine	ClO_4	....	179–180	$C_{11}H_{10}ClNO_4S$	...	..	4.87	4.68
3,4-Dimethoxyphenyl	Pyridine	I	10[n]	263–264	$C_{15}H_{16}INO_2$	34.4	34.6	..	..
3,4-Dimethoxyphenyl	Pyridine	ClO_4	....	261–262	$C_{15}H_{16}ClNO_6$	...	..	4.10	4.19

[a] Yields are of pure compounds. [b] M. p.'s are uncorrected. [c] Nitrogen analyses by Misses R. Guy and V. Hobbs. [d] Prepared by Method A. [e] Kröhnke[3b] reported 231.5°. [f] Prepared by Method B. [g] Prepared by Method C. [h] Kröhnke[4a] reported 212–215°. [i] Kröhnke[4b] reported 170–172°. [j] Prepared from 2-phenyl-2-chloroethylpyridinium bromide. [k] Prepared by dehydration of type II compound with benzoyl chloride. [l] Kröhnke[2] reported 101–102° for the anhydrous compound. [m] Kröhnke[2] reported 171–172°. [n] See Experimental for preparation.

1-(3,4-Dimethoxystyryl)-pyridinium Iodide.—To a suspension of 15 g. (0.046 mole) of phenacylpyridinium iodide, 15 g. (0.09 mole) of veratraldehyde in 100 cc. of 90% ethanol at 0° was added 4.5 cc. (0.045 mole) of a 10 *N* sodium hydroxide solution. The solution was allowed to stand at 5° for four days during which time only a slight amount of product separated. It was evaporated *in vacuo* on the steam-bath and the residue dissolved in acetone. A yellow crystalline product separated. The weight was 3.2 g. and the m. p. was 255°. After two crystallizations from water 1.7 g. (10%) of product melting at 263–264° was obtained.

Summary

A series of 2-substituted vinyl quaternary salts has been prepared by the dehydration of 2-substituted-2-hydroxyethyl quaternary salts.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 14, 1949