[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF CARSON-NEWMAN COLLEGE]

Some Quaternary Salts of Pyrazine

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Previous communications from this Laboratory[1] have reported quaternary salts of substituted thiazoles and of hexamethylenetetramine. The present paper deals with similar derivatives of pyrazine. Since Shear and associates[2,3] have found that certain pyridinium salts damage sarcoma cells *in vivo* it appeared desirable to learn whether analogous pyrazinium salts have similar effects. Samples of the compounds described below have been submitted to the National Cancer Institute for screening tests.

Apparently no extensive study has been made on the preparation of quaternary salts from unsubstituted pyrazine.[4] The organic halides we have used include alkyl iodides, cyclohexylethyl bromide, styrene bromohydrin and various aryl haloalkyl ketones. We have found that it is desirable to carry out the reactions below about 40° since formation of dark impurities is favored by higher temperature. In the case of the liquid halides a solvent is not necessary, since an excess of the halide serves the purpose conveniently, but when using solids such as naphthacyl bromides a small volume of chloroform serves to bring the reactants into a single liquid phase and also simplifies purification of the product. The rates of reaction vary widely: some reactions take place within a few hours or less, while others are still incomplete after seventy-five days. Some yields approaching the theoretical were obtained, but the primary objective was to obtain pure samples of the compounds rather than to determine the maximum attainable yields. Most of the products were recrystallized from absolute alcohol, either by chilling or by addition of isopropyl ether or both, but in a few cases analytically pure samples were obtained without recrystallization simply by washing the crystals with chloroform. It was found that some of the salts decomposed in hot solvents and for this reason heating was avoided or minimized as far as possible.

The salts ranged from white to orange or brown in color and were readily soluble in water to give yellow, orange, red or brown solutions. Most of them were moderately soluble in alcohol.

Materials.—Pyrazine used in these experiments was donated by Mead Johnson and Company through Dr. R. C. Ellingson. Methyl iodide, ethyl iodide and β-phenylethyl iodide were purchased from Edcan Laboratories, and β-cyclohexylethyl bromide, phenacyl bromide and *p*-phenylphenacyl bromide were purchased from Eastman Kodak Company. The styrene bromohydrin was prepared by the method of Read and Reid[5] and the other aryl α-bromoalkyl ketones were prepared by the conventional Friedel–Crafts reaction or by bromination of the corresponding aryl alkyl ketone.

1-(2-Phenylethyl)-pyrazinium Iodide.—A mixture of 3.5 g. of pyrazine and 9.3 g. of phenylethyl iodide in a little chloroform deposited 2.05 g. of yellow crystals on standing seventy-five days at room temperature in a small flask from which air had been displaced by butane gas. After standing several weeks longer an additional 2.54 g. of crystals appeared. The product was recrystallized repeatedly by dissolving in hot absolute ethanol, adding a little isopropyl ether and cooling to yield yellow crystals, m. p. 180° dec., giving a red solution in alcohol. *Anal.* Calcd. for $C_{12}H_{13}IN_2$: C, 46.18; H, 4.17. Found: C, 46.37; H, 4.42.

1-Phenacylpyrazinium Bromide.—A solution of 1.69 g. of pyrazine (0.02 mole) and 3.01 g. of phenacyl bromide (0.015 mole) in 5 ml. of chloroform on standing five days deposited crystals which after washing with chloroform and drying weighed 2.67 g., m. p. 190–192° dec. Recrystallization of these white crystals from 60 ml. of boiling ethanol by cooling gave 2.27 g. of bright yellow crystals, m. p. 193–194° dec. *Anal.* Calcd. for $C_{12}H_{11}BrN_2O$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.57; H, 4.22; N, 9.87. The same product was obtained by refluxing a solution of 0.831 g. of pyrazine and 4.06 g. of phenacyl bromide in 25 ml. of methanol for six hours, cooling, removing the methanol by evaporation at room temperature and recrystallizing the residue from boiling absolute ethanol by cooling. Since the mole ratio of phenacyl bromide to pyrazine was two to one in this latter experiment the production of 1-phenacylpyrazinium bromide instead of the bis-compound seems good evidence that the latter is not readily formed.

Analyses.—The nitrogen analyses, except that on 1-phenacylpyrazinium bromide, were carried out by a modified semi-micro Kjeldahl method, involving digestion of the sample for three to four hours in boiling sulfuric acid–potassium acid sulfate solution in the presence of selenium catalyst. Previous experience had shown that the usual short period of digestion was insufficient for quaternary salts of some heterocyclic nitrogen compounds. Even this period of digestion did not give correct results in every case, for the Kjeldahl analyses on both the styrenebromohydrin and *p*-*t*-butylphenacyl bromide derivatives of pyrazine gave low values for nitrogen, while combustion analyses for carbon and hydrogen carried out by Mrs. M. M. Ledyard at the National Cancer Institute agreed with the theoretical.

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(1) Bahner and Pickens, *J. Tenn. Acad. Sci.*, **23**, 104 (1948); Bahner, Pickens and Bales, THIS JOURNAL, **70**, 1652 (1948); Bahner, Pickens, Pickens and Easley, *ibid.*, **72**, 2266 (1950).

(2) Shear, *et al.*, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 236 ff.

(3) Hartwell and Kornberg, THIS JOURNAL, **68**, 1131 (1946).

(4) See Stoehr, *J. prakt. Chem.*, [2] **49**, 402 (1894); **51**, 462 (1895).

(5) Read and Reid, THIS JOURNAL, **50**, 1487 (1928).

TABLE I

PYRAZINIUM SALTS

Salt of pyrazine with	Reaction time[a]	Yield, %	Recrystallized from	Color	M. p., °C.[b]	Formula	Analyses, % Calcd.	Found
Methyl iodide[4]	6 d.	38	Abs. EtOH	Bright yellow	136	$C_5H_7IN_2$	C, 27.06	27.17
							H, 3.16	3.38
Ethyl iodide	122 d.	92[c]	Abs. EtOH	Bright yellow	162	$C_6H_9IN_2$	C, 30.53	30.50
							H, 3.82	3.88
β-Cyclohexylethyl bromide	79 d.	23	Abs. EtOH + isoprop. eth.	Tan	176	$C_{12}H_{19}BrN_2$	N, 10.29	10.29
β-Phenylethyl iodide	75 d.	16[c]	Abs. EtOH + isoprop. eth.	Bright yellow	182	$C_{12}H_{13}IN_2$	C, 46.18	46.37
	.....	34					H, 4.17	4.42
Styrene bromohydrin	71 d.	6	Abs. EtOH	White	206	$C_{12}H_{13}BrN_2O$	C, 51.26	51.36
							H, 4.63	4.71
							N, 9.97	9.51
Phenacyl bromide	5 d.	62[c]	Abs. EtOH	White[d] yellow	193–194	$C_{12}H_{11}BrN_2O$	C, 51.63	51.57
		53					H, 3.97	4.22
							N, 10.04	9.87
p-t-Butylphenacyl bromide	5 min.	72[c]	Abs. EtOH + isoprop. eth.	Bright yellow	200	$C_{16}H_{19}BrN_2O$	C, 57.32	57.24
							H, 5.71	5.68
							N, 8.35	7.45
p-Fluorophenacyl bromide	10 d.	15	Abs. EtOH	Light brown	185	$C_{12}H_{10}BrFN_2O$	N, 9.32	9.30
p-Chlorophenacyl bromide	18 hr.	77[c] 56	Abs. MeOH + isoprop. eth.	Light tan	234	$C_{12}H_{10}BrClN_2O$	N, 8.93	8.73
p-Bromophenacyl bromide	18 hr.	69[c]	Washed with $CHCl_3$	Light brown	254[e]	$C_{12}H_{10}Br_2N_2O$	N, 7.82	7.75
p-Iodophenacyl bromide	7 d.	20	Washed with $CHCl_3$	White	249	$C_{12}H_{10}BrIN_2O$	C, 35.56	35.39
							H, 2.47	2.68
m-Nitrophenacyl bromide	4 d.[f]	58	Washed with $CHCl_3$	White	205–208	$C_{12}H_{10}BrN_3O_3$	C, 44.46	44.59
							H, 3.11	3.28
p-Methoxyphenacyl bromide	41 d.[f]	83	MeOH and isoprop. eth.	Tan	217	$C_{13}H_{13}BrN_2O_2$	N, 9.06	8.91
p-Phenylphenacyl bromide	30 d.	43	Abs. EtOH + isoprop. eth.	Orange	186	$C_{18}H_{15}BrN_2O$	N, 7.89	7.92
α-Bromopropiophenone	13 d.	22	Abs. EtOH	Grayish brown	186–187	$C_{13}H_{13}BrN_2O$	N, 9.78	9.70
α-Naphthacyl bromide	3 d.	67[c] 30	Abs. EtOH + isoprop. eth.	Light brown	193	$C_{16}H_{13}BrN_2O\cdot H_2O$	N, 8.07	7.98
β-Naphthacyl bromide	40 d.	68[c]	Abs. EtOH	Light brown	210	$C_{12}H_{11}BrN_2O\cdot{}^1/_2H_2O$	N, 8.29	8.07
	(3 d.	49)						
5,6,7,8-Tetrahydro-β-naphthacyl bromide	2 d.	78[c] 59	Abs. MeOH + isoprop. eth.	Pale yellow	218	$C_{16}H_{17}BrN_2O$	N, 8.41	8.26
1-Bromoethyl-β-naphthyl ketone	39 d.	19	Abs. EtOH + isoprop. eth.	Tan	205	$C_{17}H_{15}BrN_2O$	N, 8.16	8.37

[a] At 35–40°. [b] Determined by rapid heating. Decomposition accompanied melting in nearly all cases. [c] Crude yields. All other yields refer to purified material. [d] White when first obtained from chloroform. Yellow on recrystallization. [e] Darkens at 235°. [f] Reaction much more rapid than time suggests.

Summary

A series of quaternary salts of pyrazine have been prepared for screening as oncolytic agents. The salts formed readily from pyrazine, and the appropriate organic halide, but only one of the two nitrogen atoms of the pyrazine was ever found to have reacted.

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[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Acyl Aldehydes. The Synthesis of Para-Acetylbenzaldehyde

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This work was undertaken to determine the applicability of certain useful aldehyde and ketone synthetic methods for the preparation of acetylbenzaldehydes, specifically *p*-acetylbenzaldehyde. This particular isomer was chosen since it was believed to represent the maximum reactivity possible with those substituent groups and yet one likely to yield polymolecular products on self-condensation.[2] Thus the *o*-isomer would be expected to cyclize monomolecularly while in the *m*-isomer the groups are not mutually activating. Furthermore, in *p*-acetylbenzaldehyde itself, there are present no basic substituents (—OH or —OCH_3, for example) which may diminish the reactivity of either or both carbonyl groups.[2b,3] The process by which the two groups interact is of the aldol type and takes place under the influence of both acids and bases and at high temperatures. This seemed to limit the choice of methods immediately if the monomeric ketoaldehyde were to be the main product.

The only method tried which led to a pure product in reasonable yield was the Rosenmund reduction of *p*-acetylbenzoyl chloride. The pres-

(1) Taken from the M.S. thesis of W. K. Detweiler, February, 1949.

(2) (a) Hass and Bender, THIS JOURNAL, **71**, 1767 (1949), obtained the polychalcone instead of acetylbenzaldehyde by reaction of *p*-acetylbenzyl bromide with sodium 2-propane-nitronate. (b) See also Russell, *ibid.*, **70**, 2864 (1948).

(3) Gray and Bonner, *ibid.*, **70**, 1249 (1948).