rylidene-imine was confirmed by hydrolyzing the salt which yielded 0.09 g. of fluorenone (purified by crystallization from petroleum ether). The small quantity of the white hydrochloride was not identified but was presumed to be the salt of a trace of unreacted 9-fluorylamine. The ether–hydrochloric acid soluble fraction was purified by sublimation and identified as fluorene. All products identified in this and subsequent experiments were compared with authentic specimens.

This reaction was also effected in an alcoholic solution of sodium ethylate. Because of the ease with which the 9-amino and hydroxy derivatives are oxidized by air in an alkaline medium, this experiment as well as those involving fluorenol were performed in a flask containing an auxiliary tube through which a gentle stream of nitrogen was flushed throughout the run. Using 0.5 g. of diazofluorene and 1.15 g. of 9-aminofluorene in about 75 cc. of an alcoholic solution of sodium ethylate, the reaction was found to be rapid. The yields of reaction products were: 0.23 g. of fluorenone ketazine, 0.40 g. of fluorylidene-imine and 0.125 g. of fluorene.

Reaction of Diazofluorene with 9-Anilinofluorene.—The quantities of materials used were 0.375 g. of diazofluorene and 0.500 g. of 9-anilinofluorene in about 10 cc. of liquid ammonia. After removal of the ammonia the reaction products were extracted with petroleum ether and the insoluble fraction upon recrystallization yielded 0.55 g. of fluorenone ketazine (76% of the theoretical). The petroleum ether extract was concentrated and the aniline was distilled *in vacuo*. The latter was identified as the tribromo derivative.

Reaction of Diazofluorene with 9-Chlorofluorene.—A reaction which appeared to be complete in approximately fifteen minutes took place between 0.5 g. of diazofluorene and 0.522 g. of 9-chlorofluorene in 10–15 cc. of liquid ammonia at room temperature. The isolated reaction products were fluorenone ketazine (0.692 g. corresponding to 74.8% of the theoretical) and a trace of fluorylidene-imine.

Reaction of Diazofluorene with 2,7-Dibromo-9-fluorenol.—The reaction between 0.5 g. of diazofluorene and 0.9 g. of 2,7-dibromo-9-fluorenol in absolute ethanol containing sodium ethylate was complete within an hour at room temperature. During the course of the reaction there was gas evolution and a gradual deposition of the yellow needle-like precipitate of 2,7-dibromofluorenone. The mixture was acidified with acetic acid and the 2,7-dibromofluorenone (0.69 g.) was separated by filtration, m. p. 203°, mixed m. p. with an authentic specimen 205°. The alcoholic filtrate and washings were steam distilled whereby 0.35 g. of fluorene was obtained. The residue from the steam distillation after triturating with a small volume of alcohol yielded an additional 0.08 g. of 2,7-dibromofluorenone. The recovered yields of fluorene and dibromofluorenone corresponded to 81 and 87.5%, respectively.

Reaction of Diazofluorene with 9-Fluorenol.—This reaction was found to be sluggish and in order to obtain satisfactory results an excess of fluorenol was used and the alcoholic solution heated at 60–70° for seven hours. The formation of ketazine due to thermal decomposition of the diazo compound was negligible. The sodium silicate formed by the action of the alkali on the glass was readily removed after acidifying the solution. The fluorenone was separated from the fluorene and excess fluorenol by converting it to the difficultly soluble fluorenone ketazine[2] and the fluorene by steam distillation. From 0.5 g. of diazofluorene and 1 g. of 9-fluorenol were obtained 0.40 g. of ketazine and 0.35 g. of fluorene.

Summary

Reactions were obtained in alkaline media, such as liquid ammonia and alcoholic sodium ethylate, between diazofluorene and 9-aminofluorene, anilinofluorene, 9-chlorofluorene and 9-fluorenol. The products formed were either fluorene and a fluorylidene derivative or fluorenone ketazine.

(2) Pinck and Hilbert, THIS JOURNAL, **57**, 2400 (1935).

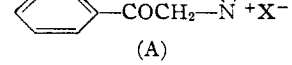
BELTSVILLE, MARYLAND RECEIVED JANUARY 24, 1946

[CONTRIBUTION FROM THE NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

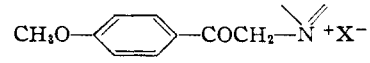
Some Quaternary Ammonium Salts of Heterocyclic Bases[1,2]

BY JONATHAN L. HARTWELL AND SYLVIA R. L. KORNBERG

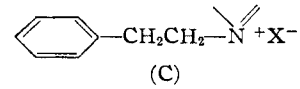
The biological results obtained by our collaborators[2] with some of the α,β-diphenylethylamines[3] made desirable the synthesis of several series of compounds which, while retaining certain features of the α,β-diphenylethylamines, would have other features modified. Three series of compounds, A, B and C, were chosen for synthesis. Each of these resembled the α,β-diphenylethylamines in possessing two aromatic rings separated by two carbon atoms on one of which was attached a nitrogen atom. They differed, however, in several respects that are obvious on comparison. The present paper reports the synthesis and properties of these three series of quaternary ammonium compounds formed by adding the elements of



(A)



(B)



(C)

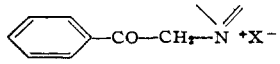
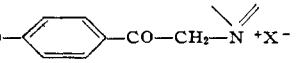
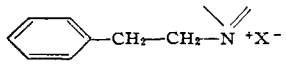
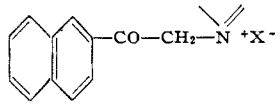
phenacyl (series A), *p*-methoxyphenacyl (series B) and β-phenethyl (series C) halide to a number of tertiary heterocyclic bases of the pyridine, quinoline and isoquinoline groups. In addition, one member of the naphthalene series and several oximes were prepared. An attempt to prepare a styryl series by the addition of β-bromostyrene to the heterocyclic bases resulted in too small yields of products for the reaction to be preparatively useful.

(1) Paper XII in the series entitled "Chemical Treatment of Tumors." Paper XI in this series: Hartwell and Kornberg, THIS JOURNAL, **67**, 1606 (1945).

(2) Material contained in this paper was presented, in part, at the A. A. A. S., Gibson Island Conference on Cancer at Gibson Island, Maryland, on August 3, 1945.

(3) Paper XI.

TABLE I

No.	Amine used	X	Appearance, crystallizing solvent		M. p., °C. (cor.)[a]	Yield, crude, %	Empirical formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
					Series A, 						
1[c]	Pyridine	I	White pr.	Water	215.0–216.0 (dec.)	84	.....	..	..	...	...
2	α-Picoline	I	Cream pr.	Water	206.4–207.1 (dec.)	8	$C_{14}H_{14}INO$	49.6	50.0	4.2	4.4
3	β-Picoline	I	Lt. yel. pr.	Water	183.7–184.7 (dark.)	29	$C_{14}H_{14}INO$	49.6	49.8	4.2	4.1
4	γ-Picoline	Br	White ne.	Alcohol	261.2–261.8 (dec.)	67	$C_{14}H_{14}BrNO$	57.6	56.1	4.8	4.8
5	γ-Picoline	I	Buff pl.	Alc. or pyridine	201.1–201.9 (dec.)	36	$C_{14}H_{14}INO \cdot H_2O$	45.5	45.8	4.7	5.1
6	γ-Picoline	ClO_4	Pale yel. pr.	Water	175.4–176.1	100[h]	$C_{14}H_{14}ClNO_5$	53.9	54.4	4.5	4.5
7	Nicotinamide	Br	Pale yel. ne.	85% Alcohol	235.8–238.2 (dark.)	90	$C_{14}H_{13}BrN_2O_2$	52.3	52.1	4.1	4.0
8	Pyridoxine	Br	Pale yel. pr.	Alcohol	208–210 (dec.)	44	$C_{15}H_{18}BrNO_4$	52.2	52.2	4.9	5.2
9[d]	Quinoline	Br	Pale yel. ne.	Alcohol	191.0–192.6	68	$C_{17}H_{14}BrNO \cdot H_2O$	59.0	59.0	4.7	5.0
10	Isoquinoline	I	Yel. pr.	Water	178.7–180.0 (dark.)	40	$C_{17}H_{14}INO$	54.4	54.0	3.8	4.0
11	3-Methylisoquinoline	I	Yel. pr.	Alcohol	199.0–199.7 (dec.)	56	$C_{18}H_{16}INO$	55.5	55.4	4.1	4.4
					Series B, CH_3O– 						
12	Pyridine	I	Lt. yel. pr.	Water	211.5–214.5 (dec.)	79	$C_{14}H_{14}INO_2$	47.3	47.6	4.0	4.1
13	Pyridine	ClO_4	Yel. pl.	Water	201.0–202.2	87[g]	$C_{14}H_{14}ClNO_6$	51.3	51.7	4.3	4.5
14	α-Picoline	I	Buff pl.	Water	204.9–205.9 (dec.)	9	$C_{15}H_{16}INO_2$	48.8	49.1	4.4	4.3
15	β-Picoline	I	Lt. pink pr.	Alcohol	202.3–203.5	57	$C_{15}H_{16}INO_2$	48.8	48.7	4.4	4.3
16	γ-Picoline	I	Pink pr.	Water	230.8–232.2 (dark.)	8	$C_{15}H_{16}INO_2$	48.8	48.8	4.4	4.4
17	Quinoline	Br	Yel. pr.	Alcohol	227.3–228.5 (dec.)	49	$C_{18}H_{16}BrNO_2 \cdot H_2O$	58.9	58.9	4.7	5.1
18	Quinoline	ClO_4	Pink ne.	Water	224.7–226.4 (dec.)	87[h]	$C_{18}H_{16}ClNO_6$	57.2	57.5	4.3	4.5
19	Isoquinoline	I	Yel. pr.	Water	234.7–235.7 (dark.)	58	$C_{18}H_{16}INO_2$	53.3	53.5	4.0	4.0
20	3-Methylisoquinoline	I	Yel. pr.	Water	225.7–226.9 (dec.)	57	$C_{19}H_{18}INO_2$	54.4	54.8	4.3	4.2
					Series C, 						
21[e]	Pyridine	Br	White pl.	Alcohol + ether	125.9–126.5	89	.....	..	...	..	...
22	α-Picoline	Br	White pr.	Alcohol	198.1–198.9	93	$C_{14}H_{15}BrN$	60.4	60.85	5.8	6.0
23	β-Picoline	Br	White ne.	Methyl ethyl ketone	123.3–127.5	100	$C_{14}H_{16}BrN$	60.4	59.6	5.8	5.7
24	γ-Picoline	Br	White pr.	Alcohol + ether	88.8–91.0	76	$C_{14}H_{16}BrN \cdot {}^2/_3 H_2O$	58.0	58.0	6.0	6.4
25	γ-Picoline	ClO_4	White ne.	Water	126.9–127.5	28[h]	$C_{14}H_{16}ClNO_4$	56.5	56.0	5.4	5.5
26[f]	Quinoline	Br	Cream pr.	Alcohol + ether	127.3–128.3	84	.....	..	...	...	...
27	Isoquinoline	Br	Buff pr.	Water	72.7–73.9	80	$C_{17}H_{18}BrN \cdot {}^4/_3 H_2O$	60.5	60.4	5.6	5.7
28	Isoquinoline	ClO_4	White ne.	Water	170.4–171.1	100[h]	$C_{17}H_{15}ClNO_4$	61.2	61.0	4.8	4.8
29	3-Methylisoquinoline	Br	White pr.	Alcohol	249.0–250.2 (dec.)	84	$C_{18}H_{18}BrN$	65.9	65.7	5.5	5.5
											
30	Pyridine	I	Lt. yel. pr.	Water	217.0–217.8 (dec.)	85	$C_{17}H_{14}INO$	54.4	54.7	3.8	3.9

[a] All melting points reported in this paper were determined with the Hershberg apparatus, *Ind. Eng. Chem., Anal. Ed.*, 8, 312 (1936). [b] The microanalyses reported in this paper were performed by Arlington Laboratories, Fairfax, Va. [c] Ref. 5. [d] Ref. 6. [e] Kröhnke, *Ber.*, **67**, 656 (1934); Sugasawa and Sugimoto, *Ber.*, **72**, 977 (1939). [f] Sugasawa, *J. Pharm. Soc. Japan*, **57**, 296 (1937). [g] Based on the iodide. [h] Based on the bromide. [i] Other analyses on this compound are: Calcd. for N, 5.0; Br, 28.7. Found: N, 5.0; Br, 29.2.

Experimental

Intermediates.—Acetophenone, *p*-methoxyacetophenone, methyl β-naphthyl ketone, phenacyl bromide, β-phenylethyl bromide, β-bromostyrene and the heterocyclic bases were obtained from commercial sources. *p*-Methoxyphenacyl bromide was prepared by bromination of the corresponding methyl ketone in carbon disulfide at room temperature, using the theoretical quantity of bromine; the product was recrystallized from hexane and had a melting point of 69.4–70.5° cor.

Preparation of the Iodides (Series A and B, and compound 30, Table I).—The procedure was that of King.[4] Only 1-phenacylpyridinium iodide (compound 1) had been reported before.[5] The reaction proceeded well with the other bases except with quinoline; in this case the usual methods of isolation failed to produce a crystalline product from the dark, viscous reaction mixture with acetophenone (reaction was not tried with *p*-methoxyacetophenone).

1-Phenacyl-2-picolinium iodide (compound 2) crystallized in two forms which came out simultaneously but in separate crystals, colorless transparent prisms and light yellow transparent prisms, which could be separated by hand. Each form had the same melting point and the melting point of a mixture showed no depression.

Of the iodides, only 1-phenacyl-4-picolinium iodide (compound 5) was difficult to obtain pure. It seemed to be persistently contaminated with an unstable substance of higher iodine content. Treatment with sodium bisulfite

(4) (a) King, THIS JOURNAL, **66**, 894 (1944). (b) Some of the compounds reported in the present paper were prepared simultaneously and independently by Dr. King and are described in THIS JOURNAL, **68**, 717 (1946).

(5) Kröhnke, *Ber.*, **66**, 1386 (1933); also King, ref. 4a.

TABLE II

OXIMES

No.	Prep. from no.	Appearance, crystallizing solvent		M. p., °C. (cor.)	Yield, crude %	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
31	1	White pr.	Water	166.7–168.3 (dec.)	97	$C_{13}H_{13}IN_2O$	45.9	45.8	3.9	3.9	8.2	8.3
32	12	White pr.	Alcohol	113.4–115.0 (dark.)	57	$C_{14}H_{15}IN_2O_2 \cdot 0.5H_2O$	44.3	44.2	4.2	4.9	7.4	7.5
33	30	Pale yel. ne.	Water	203–205 (dec.)[a]	63	$C_{17}H_{15}IN_2O$	52.3	52.5	3.9	4.1	7.2	6.5

[a] The melting point varies with the rate of heating.

solution followed by repeated crystallization from pyridine finally yielded a product, probably still not pure, which gave analytical figures for a hydrate. Attempts to convert it to the perchlorate by double decomposition following the procedure of King[4a] failed. A pure bromide was prepared by the addition reaction (below) and from it the perchlorate was readily obtained by double decomposition.

The iodides were quite soluble in water at room temperature with the exception of compound 16 which was soluble in hot water and compounds 11, 19, 20 and 30 which were only slightly soluble in hot water.

Preparation of Bromides (Series A and B, Table I).—The bromides (compounds 4, 7, 8, 9 and 17) were prepared by adding phenacyl bromide or *p*-methoxyphenacyl bromide to the theoretical quantity of the amine, warming on the steam-bath for periods of a few minutes to one-half hour, and crystallizing the products from alcohol. Pyridoxine (vitamin B_6) was obtained from the commercial hydrochloride by warming a suspension in absolute alcohol with an excess of sodium bicarbonate until evolution of carbon dioxide ceased, filtering off the insoluble sodium salts and evaporating the mother liquor to dryness under vacuum; the crystalline pyridoxine so obtained was used directly.

1-Phenacylquinolinium bromide (compound 9) has been reported in the literature several times,[6] either anhydrous or hydrated, with melting points ranging from 115 to 212°. The compound reported here (compound 9) melted constantly, after drying in a desiccator at 80°, at 191.0–192.6° (cor.) and gave analytical values for a monohydrate. 1-(*p*-Methoxyphenacyl)-quinolinium bromide (compound 17) also retained water tenaciously (at 100°). No attempt was made to prepare the completely anhydrous compounds.

Preparation of Bromides (Series C, Table I).—These bromides were prepared in general by adding β-phenylethyl bromide to a 20% excess of amine, warming on the steam-bath for periods ranging from forty-five minutes to sixteen hours depending on the reactivity of the amine, and working up the reaction mixture with alcohol with or without the addition of ether.

Of these bromides, compounds 24 and 27 gave analytical values indicating the presence of water although they had been crystallized to constant melting point and dried under vacuum usually at 100° before analysis. Samples of these bromides were therefore converted into the perchlorates. The latter proved to be anhydrous and better adapted for characterization.

Exceptional behavior was noted in the reaction of β-phenylethyl bromide with β-picoline. Using the conditions outlined above, a white crystalline product could be obtained, crystallizable from alcohol–ether or water, melting at 109–110° (cor.); this product, however, although containing more than 20% of bromine, did not have this element in ionizable form (negative silver nitrate test) and thus did not appear to be the expected quaternary ammonium salt. When the reactants were refluxed together in alcohol solution for forty-eight hours and the mixture worked up by boiling off most of the alcohol and adding ether, a product was obtained in practically theoretical yield which, after crystallizing from methyl ethyl ketone, gave white needles melting at 123.3–127.5° (cor.) and giving a strongly positive silver nitrate test. The latter product was assumed to be the desired quaternary ammonium salt (compound 23). This compound, however, was quite labile and tended to go over into the 109–110° product even on recrystallization; an attempt to make the perchlorate by double decomposition with perchloric acid in aqueous solution yielded the lower-melting compound. The latter compound is being further studied and will be reported on at a later date.

After the experiences described in the preceding paragraph, all the other compounds prepared from β-phenylethyl bromide as well as the other compounds prepared from β-picoline were tested with silver nitrate solution. Their aqueous solutions all gave copious precipitates of silver halide, and their assignment as quaternary ammonium salts was thus confirmed.

Preparation of Perchlorates (Series A, B, and C. Table I).—The perchlorates were readily prepared from the bromides by double decomposition. To a warm aqueous solution of 1.0 g. of the bromide was added a 50% excess of perchloric acid. In all cases, pure white needles of the product separated at once or upon cooling. The products were purified by recrystallization from water and were found to be halide-free on testing with silver nitrate solution. One iodide, 1-(*p*-methoxyphenacyl)-pyridinium iodide (compound 12), was converted into a perchlorate in this manner, in order to provide an authentic sample for comparison. Another iodide, 1-phenacyl-4-picolinium iodide (compound 5), was recovered unchanged after an attempt to prepare the perchlorate by this procedure.

Preparation of Oximes (Table II).—A nearly saturated hot aqueous solution of the keto-iodide was treated with a 15% excess of hydroxylamine hydrochloride and sodium acetate and the mixture left on the steam-bath for two hours. On cooling, the oximes separated in crystalline form.

While compounds 31 and 33 occurred in an anhydrous condition, compound 32 had firmly bound water of crystallization. An attempt to form the perchlorate by adding perchloric acid to a hot aqueous solution of the oxime yielded a new product crystallizing in yellow plates, m. p. 201.0–202.2° (cor.). A mixed melting point determination with an authentic sample of 1-(*p*-methoxyphenacyl)-pyridinium perchlorate (compound 13, Table I), m. p. 199.7–200.8° (cor.) before recrystallization, showed no depression. The oximino group had therefore been hydrolyzed to the ketone. Substitution of sodium perchlorate for perchloric acid yielded an oil from which nothing crystalline could be obtained.

Summary

1. The synthesis and properties of several new quaternary ammonium salts, prepared in the course of studies in the chemotherapy of cancer, are reported. They were formed by adding the elements of phenacyl, *p*-methoxyphenacyl, β-naphthacyl and β-phenylethyl halides to aromatic heterocyclic bases of the type of pyridine, quinoline and isoquinoline.

2. Oximes of some of the ketonic compounds are also described.

BETHESDA, MARYLAND RECEIVED FEBRUARY 1, 1946

(6) Bamberger, *Ber.*, **20**, 3340 (1887); Ihlder, *Arch. Pharm.*, **240**, 692 (1902); Kröhnke, *Ber.*, **68**, 1177 (1935).