to the reaction product and the resulting solution made basic with excess ammonium hydroxide. The organic material was taken up in chloroform, washed with water and dried over sodium sulfate. The product was converted to a picrate by removing the chloroform at reduced pressure, dissolving the residue in a minimum of absolute ethanol and adding an excess of a chilled, saturated solution of picric acid in absolute ethanol. After standing overnight in the refrigerator the crude picrate was filtered and placed in a Soxhlet extraction cup. The material was extracted with methanol until no further crystallization from the hot solvent occurred. There was obtained 1.35 g. of orange solid, m. p. 210–212° (dec.), which evidently was the dipicrate of 3-(3′-diethylaminopropylamino)-harman. After two more recrystallizations from methanol it melted at 213.5–215° (dec.).

Anal. Calcd. for $C_{31}H_{32}N_{10}O_{14}$: C, 48.44; H, 4.20. Found: C, 48.33; H, 4.20.

Summary

3-Aminoharman is prepared from methyl harman-3-carboxylate by means of the Curtius reaction. 3-Sulfanilamidoharman and 3-(3′-diethylaminopropylamino)-harman (as the dipicrate) are prepared from 3-aminoharman.

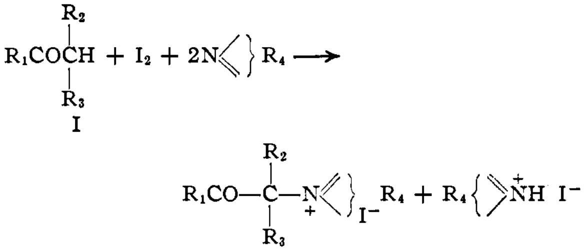
URBANA, ILLINOIS RECEIVED AUGUST 7, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Iodine and Pyridine

BY L. CARROLL KING, MARGARET MCWHIRTER AND R. L. ROWLAND

Previous papers from this Laboratory,[1] and from the National Cancer Institute,[2] have reported the preparation of quaternary salts of type (II) by means of the following reaction.



II

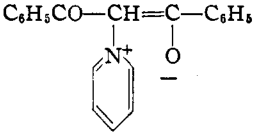
where $R_3 = R_2 = H$

Salts have been reported where R_1 was aryl[1a,1b,2] or a cyclopentanophenanthrene derivative[1a] and where $N\langle\ \rangle R_4$ was any of a number of heterocyclic nitrogeneous bases.[1c,2] In the present paper this reaction has been extended to include variation in R_2 and R_3 and additional variation in R_1.

The quaternary salts obtained when R_1 was 2- or 3-phenanthryl, thienyl or any of a variety of substituted phenyl groups are listed in Table I. When R_2 was an alkyl or aryl side chain the reaction gave the expected quaternary salt in each case but with increasing length of the alkyl side chain the salts became more difficult to purify and crystallize. A pure quaternary salt was not obtained from isobutyrophenone ($R_2 = R_3 = CH_3$). Data for these materials are also reported in Table I.

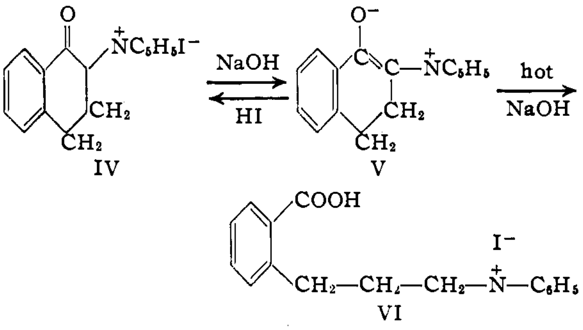
In addition to the substances reported in the tables, quaternary salts were prepared from dibenzoylmethane (R_2 = benzoyl), and from α-tetralone.

From the reaction of dibenzoylmethane with iodine and pyridine, 1-phenacylpyridinium iodide was isolated. The betaine (III) reported to be produced in 40% yield from the reaction of bromodibenzoylmethane with pyridine[3] was not observed.



III

From the reaction of α-tetralone with pyridine and iodine, 1-keto-2-tetrahydronaphthylpyridinium iodide (IV) was obtained. When (IV) was treated with cold alkali an orange betaine (V) separated. This substance could be reconverted to the salt (IV) and on prolonged alkaline hydrolysis in the presence of potassium iodide (IV) was converted to (VI). This behavior is analogous to that reported by Krollpfeiffer and Müller[4] for the corresponding pyridinium bromide.



Each of the quaternary salts reported was subjected to alkaline hydrolysis. The acids produced in these experiments are listed in Table II. No isodurylic acid was obtained from 1-(2,4,6-tri-

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(1a) King, THIS JOURNAL, **66**, 894, 1612 (1944).

(1b) King, McWhirter and Barton, *ibid.*, **67**, 2089 (1945).

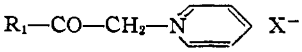
(1c) King and McWhirter, *ibid.*, **68**, 717 (1946).

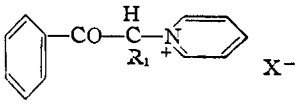
(2) Hartwell and Kornberg, *ibid.*, **68**, 868, 1131 (1946).

(3) Kröhnke, *Ber.*, **68**, 1177 (1935). However, this betaine was obtained when Kröhnke's procedure was used.

(4) Krollpfeiffer and Müller, *ibid.*, **68**, 1169 (1935)

TABLE I



R_1	X⁻	Yield, %	Recrystn. solvent[k]	M. p.,[a] °C.	Formula	Percentage composition[b]			
						Calcd.	Found	Calcd.	Found
p-F—C_6H_4—	I	20	W	179–180	$C_{13}H_{11}ONIF$	N, 4.08	3.80	I, 37.0	37.2
p-F—C_6H_4—	ClO_4		W	125–126	$C_{13}H_{11}O_5NClF$	C, 49.46	49.49	H, 3.51	3.94
p-Cl—C_6H_4—	I	72	W, A	217–218	$C_{13}H_{11}ONICl$	I, 35.3	35.0		
p-Cl—C_6H_4—	ClO_4		W, E	211–212	$C_{13}H_{11}O_5NCl_2$	C, 47.00	47.18	H, 3.34	3.39
p-Br—C_6H_4—	I	73	W, A	233–235	$C_{13}H_{11}ONIBr$	I, 31.4	31.1		
p-Br—C_6H_4—[c]	ClO_4		W, E	238–240	$C_{13}H_{11}O_5NClBr$	C, 41.46	41.85	H, 2.94	3.10
p-I—C_6H_4—	I	82	E	237–238	$C_{13}H_{11}ONI_2$	I, 28.1	28.2		
p-I—C_6H_4—	ClO_4		E	269–270	$C_{13}H_{11}O_5NICl$	C, 36.86	37.20	H, 2.62	2.79
p-CH_3—C_6H_4—	I	89	A	200–203	$C_{14}H_{14}ONI$	I, 37.4	37.1		
p-CH_3—C_6H_4—	ClO_4		A	152–153	$C_{14}H_{14}O_5NCl$	C, 53.94	54.27	H, 4.53	4.59
p-CH_3—OC_6H_4—[d]	I	71	W, A	218–219	$C_{14}H_{14}O_2NI$	I, 35.7	35.9		
p-CH_3—S—C_6H_4—	I	75	A	185–186	$C_{14}H_{14}ONIS$	I, 34.2	34.0	N, 3.78	3.96
p-CH_3S—C_6H_4—	ClO_4		W	181–182	$C_{14}H_{14}O_5NClS$	C, 48.91	49.07	H, 4.10	4.36
p-NO_2—C_6H_4—	I	78	W	211–212	$C_{13}H_{11}O_3N_2I$	I, 34.7	34.6	N, 7.57	7.35
p-NO_2—C_6H_4—[e]	ClO_4		W	183–185	$C_{13}H_{11}O_7N_2Cl$	N, 8.18	8.25		
p-C_6H_5—C_6H_4—	I	80	W, A	204–205	$C_{19}H_{16}ONI$	I, 31.6	31.7	N, 3.49	3.43
p-C_6H_5—C_6H_4—	ClO_4		W, A	241–242	$C_{19}H_{16}O_5NCl$	C, 61.05	61.48	H, 4.31	4.27
Mesityl	I	87	A, E	267–268	$C_{16}H_{18}ONI$	I, 34.6	34.4		
Mesityl[f]	ClO_4		A, E	276–277	$C_{16}H_{18}O_5NCl$	C, 56.56	56.68	H, 5.34	5.51
3-Phenanthryl	I	20	W	219–220	$C_{21}H_{16}ONI$	N, 3.29	3.56		
3-Phenanthryl	ClO_4		A, E	257–258	$C_{21}H_{16}O_5NCl$	N, 3.52	3.97		
2-Phenanthryl	I	30	M	223–224	$C_{21}H_{16}ONI$	N, 3.29	3.24		
2-Phenanthryl	ClO_4		W, E	240–242	$C_{21}H_{16}O_5NCl$	N, 3.52	3.66		
Thienyl	I	76	W, A	210–212	$C_{11}H_{10}ONIS$	I, 38.3	38.6		
Thienyl	ClO_4		W, A	215–217	$C_{11}H_{10}O_5NClS$	C, 43.51	43.52	H, 3.32	3.38
									
CH_3—[i]	I	40–60	....	....	....	......	...	.....	...
C_2H_5—	I	70	W	152–153	$C_{15}H_{16}ONI$[m]	C, 51.00	50.64	H, 4.56	4.73
C_2H_5—	ClO_4		W	133–134	$C_{15}H_{16}O_5NCl$	C, 55.30	55.57	H, 4.95	5.02
n-C_3H_7—[h]	I	80		Glass[g]	$C_{16}H_{18}ONI$[n]	C, 52.33	52.38	H, 4.93	4.84
n-C_4H_9—[h]	I	30	Ac, Et	123–125	$C_{17}H_{20}ONI$	I, 33.3	33.3	N, 3.67	3.49
C_6H_5—	I	80	W, A	158–162	$C_{19}H_{16}ONI$	I, 31.6	31.5		
C_6H_5—	ClO_4		W, A	175–176	$C_{19}H_{16}O_5NCl$	C, 61.05	61.47	H, 4.31	4.60
CH_3—, CH_3—[l]	I	60		Viscous glass[j]	$C_{15}H_{16}ONI$	I, 36.0	38.9		

[a] All melting points were observed on a Fisher–Jones melting point block. [b] Analyses by M. Ledyard and P. Craig. [c] Kröhnke, *Ber.*, **68**, 1187 (1934); m. p. 241–242°, no analysis reported. [d] Hartwell and Kornberg, THIS JOURNAL, **68**, 868 (1946). [e] Kröhnke and Heffe, *Ber.*, **70B**, 875 (1937); m. p. 185–186°, no analysis reported. [f] Kröhnke and Heffe, *ibid.*, **70B**, 874 (1937); m. p. 275°, no analysis reported. [g] Obtained as crystals from acetone-ether by cooling in a Dry Ice–acetone bath. These crystals became glass-like on warming to room temperature. [h] Perchlorate derivatives could not be obtained. [i] Reported in ref. 1a. [j] This compound was not obtained pure. [k] Symbols denote solvents as follows: W = water, E = ethylene glycol, A = alcohol, M = ethylene glycol monomethyl ether, Ac = acetone, Et = ethyl ether. Combinations of these symbols denote crystallization from the mixed solvents. [l] In this compound both of the hydrogens α- to the carbonyl group were replaced by methyl groups. [m] Calcd.: I, 35.9. Found: 36.0. [n] Calcd.: I, 34.6. Found: 34.2.

methylphenacyl)-pyridinium iodide by alkaline hydrolysis. This is consistent with the observation of Fuson[5] and co-workers for the corresponding pyridinium chloride.

This investigation was partially supported by a grant from the Abbott fund of Northwestern University and by a Grant-in-aid from the National Cancer Institute.

Experimental

Preparation of Ketones.—The ketones, with the exception of *p*-methylmercaptoacetophenone, are known. 2- and 3-acetophenanthrene were prepared by the procedure of Mosettig and van de Kamp,[6] and *p*-nitroacetophenone by the method of Walker and Hauser.[7] α-Tetralone, methyl thienyl ketone and dibenzoylmethane were prepared by methods described in "Organic Syntheses." The other ketones were prepared by Friedel–Craft reactions

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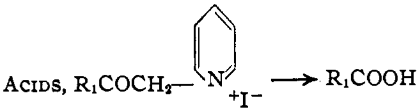
(5) Babcock, Nakamura and Fuson, THIS JOURNAL, **54**, 4407 (1932).

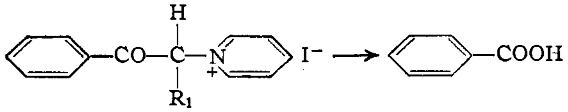
(6) Mosettig and van de Kamp, *ibid.*, **52**, 3704 (1930).

(7) Walker and Hauser, *ibid.*, **68**, 1386 (1946).

TABLE II



R_1	Yield, %	M. p., °C.	Melting point reported, °C.
p-FC_6H_4-	70	181–182	186[a]
p-ClC_6H_4-	99	242–243	243[b]
p-BrC_6H_4-	87	249–250	250–251[c]
p-IC_6H_4-	83	268–269	266–267[d]
p-$CH_3C_6H_4$-	94	176–179	179[e]
p-$CH_3OC_6H_4$-	80	183–184	183–185[f]
p-CH_3S—C_6H_4	80	190–191	192[g]
p-NO_2—C_6H_4-	30	239–240	241[k]
p-C_6H_5—C_6H_4-	55	221–222	224[h]
3-Phenanthryl-	85	269–270	270[i]
2-Phenanthryl-	80	258–259	258.5–260[i]
Thienyl-	99	127–128	126–127[j]



R_1	Yield, %	M. p., °C.
Ethyl-	71	122
Propyl-	73	122
Butyl-	60	121
Phenyl-	70	121
CH_3- CH_3-[l]	25	121

[a] Schiemann and Wirkelmuller, "Organic Synthesis," Coll. Vol. II, 299. [b] Davies and Wood, *J. Chem. Soc.*, 1126 (1928). [c] Van Arendonk and Cupery, THIS JOURNAL, **53**, 3184 (1931). [d] Whitmore and Woodward, "Organic Syntheses," Coll, Vol. I, 325. [e] Gattermann, *Ann.*, **244**, 51 (1888). [f] Oppenheim and Pfaff, *Ber.*, 8, 890 (1875). [g] Zincke and Jorg, *ibid.*, **43**, 3448 (1910). [h] Ciamician and Silber, *ibid.*, **28**, 1555 (1895). [i] Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930). [j] Schorigin, *Ber.*, **43**, 1942 (1910). [k] Fischer, *Ann.*, **127**, 140 (1863). [l] In this compound, both R_1 and the hydrogen alpha to the carbonyl group, were replaced by methyl groups.

using benzene or a substituted benzene and the appropriate acid chloride. In general the boiling point or melting point data for each of the ketones was in good agreement with that recorded in the literature.

p-Methylmercaptoacetophenone.—To a mixture of 0.5 mole of phenyl methyl sulfide[8] and 1.0 mole of anhydrous aluminum chloride in carbon disulfide, 0.5 mole of acetyl chloride was added. After one hour the reaction mixture was decomposed by addition to a mixture of ice and hydrochloric acid and the water-insoluble product was crystallized from Skellysolve C; yield 70%, m. p. 79–80°.

Anal. Calcd. for $C_9H_{10}OS$: C, 65.03; H, 6.06. Found: C, 65.20; H, 6.26.

2,4-Dinitrophenylhydrazone m. p. 231–232°; crystallized from chloroform.

Anal. Calcd. for $C_{15}H_{14}O_4N_4S$: N, 16.18. Found: N, 16.14.

The para position for the methylmercapto group is indicated by conversion to the quaternary salt and subsequent alkaline cleavage to the known p-methylmercaptobenzoic acid.

Preparation of Quaternary Iodides.—The experimental procedure was identical with that previously reported.[1] The product from the reaction of 0.1 mole of ketone with 0.1 mole of iodine and excess pyridine was washed with ether and then with water. The residue was then crystallized from a suitable solvent. The solvents used for crystallization, the melting points, analyses, and percentage yields are listed in Table I.

Slight variations in the procedure were required for reactions of n-butyl phenyl ketone and n-amyl-phenyl ketone with iodine and pyridine. The following procedure facilitated the isolation of analytically pure products from these substances. The reaction mixtures were washed with ether and then extracted with acetone. Addition of water or ether to the acetone extracts resulted in the separation of an oil. This oil was crystallized twice from an acetone–ether mixture by cooling in a Dry Ice–acetone-bath. The crystals, which were collected by filtration, melted upon warming to room temperature. By drying this product *in vacuo*, an amber-colored glass with the proper carbon, hydrogen and iodine analyses was obtained from the reaction using n-butyl phenyl ketone. The liquid obtained by this method from the reaction of n-amyl phenyl ketone crystallized after two days.

Preparation of Quaternary Perchlorates.—The perchlorates were prepared in a manner similar to that reported in other papers.[1]

It is not possible by this method to prepare crystalline perchlorate salts from 1-(1-benzoylbutyl)-pyridinium iodide or from 1-(1-benzoylamyl)-pyridinium iodide. Attempts to prepare picrates from these two iodides also failed.

Alkaline Hydrolysis of Quaternary Iodides.—This was effected in a manner similar to that previously reported.[1] The data on yield and identity of the acids are reported in Table II.

Reaction of Dibenzoylmethane with Iodine and Pyridine.—This reaction was carried out in a manner similar to the general procedure described above with the exception that, during the reaction and in the process of purification, care was taken to exclude water. Nevertheless, no product possessing the characteristics of dibenzoylmethyl pyridinium betaine or the characteristics expected of 1-(dibenzoylmethyl)-pyridinium iodide was isolated. Instead, the only crystalline product was a solid, obtained in 20–25% yield, which was presumed to be 1-phenacylpyridinium iodide on the basis of the following properties; m. p. 213°,

Anal. Calcd. for $C_{13}H_{12}ONI$: N, 4.31; I, 39.0. Found: N, 4.05; I, 39.2.

1-Keto-2-tetrahydronaphthylpyridinium Iodide (IV).—One-tenth mole of α-tetralone was allowed to react with 0.1 mole of iodine and 0.2 mole of pyridine. The product was isolated as indicated in a previous paper,[1] and crystallized from water–alcohol; yield 55%, m. p. 218–220°.

Anal. Calcd. for $C_{15}H_{14}ONI$: C, 51.32; H, 4.02; I, 36.14. Found: C, 51.59; H, 4.25; I, 36.16.

The perchlorate m. p. 180–181°.

Anal. Calcd. for $C_{15}H_{14}O_5NCl$: C, 55.65; H, 4.36. Found: C, 55.46; H, 4.57.

The above iodide, by chromic acid oxidation, was converted to phthalic acid (identified as the anhydride).

1-Keto-2-tetrahydronaphthylpyridinium Betaine (V).—An excess of cold sodium hydroxide solution was added to a suspension of (IV) in water. A golden-red solid precipitated at once. The material which was collected by filtration was unstable on standing and was found to darken at about 65°. A sample of (V) when suspended in water and treated with perchloric acid was converted to the perchlorate of (IV); m. p. 179–180°. The filtrate from which (V) was isolated contained 93% of the iodine originally associated with the salt.

3-(2-Carboxyphenyl)-propylpyridinium Iodide (VI).—A suspension of 11.0 g. of (V) was warmed for one hour with dilute sodium hydroxide containing potassium iodide. The solution was then acidified with hydrogen iodide and the insoluble material separated by filtration. The filtrate was evaporated to a volume of 50–100 cc. and cooled. The light colored precipitate was taken up in absolute alcohol and precipitated with ether. The product weighed 4.0 g.; m. p. 180–182°.

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[8] Knapp, *Monatsh.*, **56**, 66 (1930).

Anal. Calcd. for $C_{15}H_{16}O_2NI$: N, 3.80. Found: N, 3.68.

Summary

1. A series of quaternary salts, of interest in chemotherapy studies of cancer, has been prepared by treating iodine and pyridine with substituted methyl aryl ketones, with α-substituted acetophenones, and with α-tetralone.

2. The products obtained from the α-substituted acetophenones became increasingly difficult to purify as the length of the side chain increased, and no pure quaternary salt was obtained from isobutyrophenone.

3. Each of the quaternary salts, except that prepared from acetomesitylene, was converted into a characteristic carboxylic acid by the action of aqueous alkali.

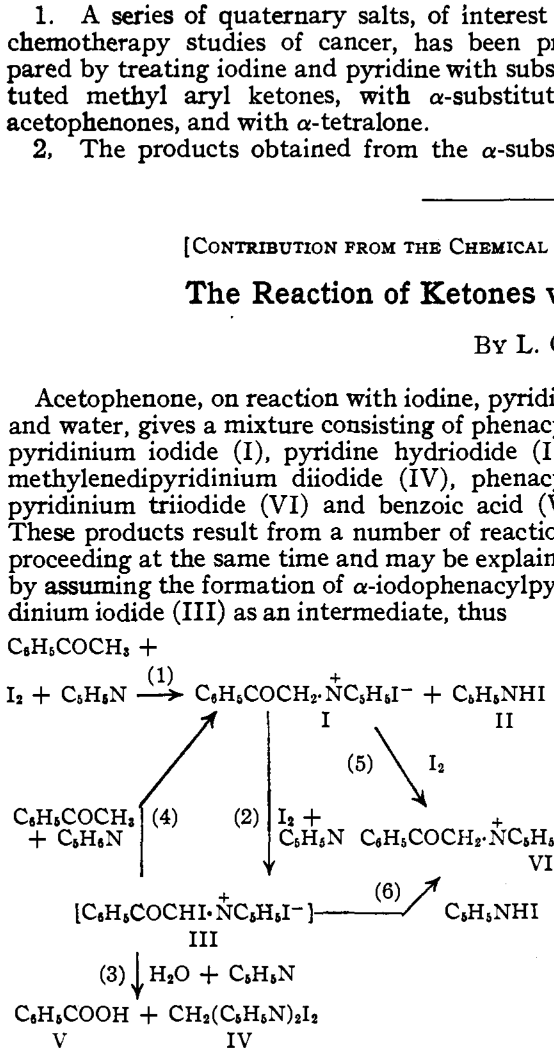
EVANSTON, ILLINOIS RECEIVED JULY 21, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Iodine, Pyridine and Water[1]

BY L. CARROLL KING

Acetophenone, on reaction with iodine, pyridine and water, gives a mixture consisting of phenacylpyridinium iodide (I), pyridine hydriodide (II), methylenedipyridinium diiodide (IV), phenacylpyridinium triiodide (VI) and benzoic acid (V). These products result from a number of reactions proceeding at the same time and may be explained by assuming the formation of α-iodophenacylpyridinium iodide (III) as an intermediate, thus



The salt (I) is first formed (reaction 1) and this may then react with iodine and pyridine to form III (reaction 2). Compound III may then react irreversibly with water and pyridine to form IV and V (reaction 3), or it may react with unchanged ketone and pyridine to regenerate I (reaction 4). Reaction 3 is the favored one in very dilute or homogeneous solution even if the ketone is present in excess (see example 4 of the experimental). Reaction 4 is favored in heterogeneous reaction mixtures or when the ketone concentration is high (see example 2 of the experimental). Reactions which produce phenacylpyridinium triiodide (VI) (reactions 5 and 6) are favored in heterogeneous reaction mixtures by an excess of iodine, whereas, in dilute or homogeneous solution, Reaction 3 is favored by excess iodine (see example 1 of the experimental).

Phenacylpyridinium iodide (I), when it reacted with iodine, pyridine and water, gave IV and V in somewhat better yields than those obtained when starting with the corresponding ketone. With a limited amount of water compound VI also was observed.

In experiments where both yields were measured, the mole yield of benzoic acid (V) was always in excess of the mole yield of methylenedipyridinium diiodide (IV) (see example 1 of the experimental). This discrepancy may be due to isolation difficulties, or it may be due to a reaction where iodine in water solution causes oxidation of I to benzoic acid and carbon dioxide.[2]

An attempt to isolate α-iodophenacylpyridinium iodide (III) from the reaction mixture failed. An attempt to prepare III by a method found satisfactory for preparation of the corresponding α-bromophenacylpyridinium bromide[3] (VII) gave none of the expected III but gave phenacylpyridinium triiodide (VI) in almost quantitative yield.

$$C_6H_5COCHBr\cdot\overset{+}{N}C_5H_5\ Br^- \qquad \text{VII}$$

Some reactions of the analogous α-bromophenacylpyridinium bromide (VII) would indicate that the intermediate (III) can enter into the reactions suggested but that III should not be isolable from these reactions. Thus, VII reacted with acetophenone and then with pyridine to give phenacylpyridinium bromide (analogous to reaction 4), with pyridine hydroiodide to give VI (analogous to reaction 6), and with water and pyridine to give methylenedipyridinium dibromide[3] (analogous to reaction 3).

The methylenedipyridinium diiodide (IV) isolated in the reaction studies was in each case compared in detail with an authentic specimen prepared by action of pyridine on methylene iodide.

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[1] Paper no. 6 on the Reaction of Ketones with Halogens and Nitrogeneous Bases. For other papers in this series see King and co-workers, THIS JOURNAL, **66**, 894, 1612 (1944); **67**, 2089 (1945); **68**, 717 (1946); **70**, 239 (1948).

[2] Such a reaction was observed[3] when bromine water reacted with phenacylpyridinium bromide.

[3] Kröhnke, *Ber.*, **66**, 1386 (1933).