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.

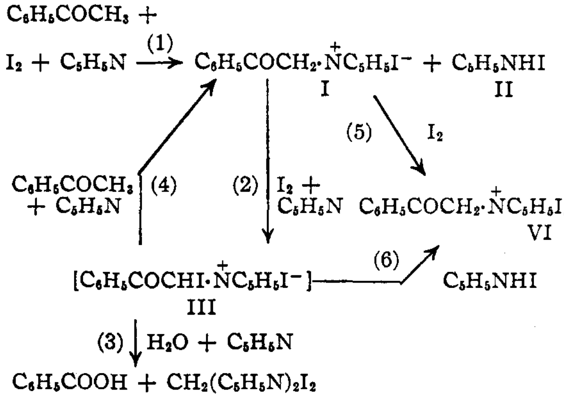
EVANSTON, ILLINOIS RECEIVED JULY 21, 1947

[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).

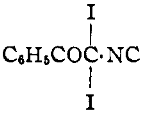
(2) Such a reaction was observed[3] when bromine water reacted with phenacylpyridinium bromide.

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

The compound described as phenacylpyridinium triiodide is new. The structure is based on two lines of evidence: (a) it is produced in nearly quantitative yield by reaction of iodine and phenacylpyridinium iodide (I) in glacial acetic acid, and (b) it was found to react with pyridine and acetophenone to give pyridine hydroiodide (II) and phenacylpyridinium iodide (I). This latter compound was present at the end of the reaction in mole quantity about twice that of the starting triiodide. The appearance of pyridine hydroiodide and this extra phenacylpyridinium iodide is evidence that iodine reacted with acetophenone and pyridine.[1] This may be represented as

$$C_6H_5COCH_2\overset{+}{N}C_5H_5I_3^- + C_6H_5COCH_3 \quad 2C_5H_5N \longrightarrow 2C_6H_5COCH_2\cdot\overset{+}{N}C_5H_5I^- + C_5H_5NHI$$

Had the compound VI been an iodinated substance such as VIII no pyridine hydroiodide



$$C_6H_5CO\overset{I}{\underset{I}{C}}\cdot NC_5H_5I$$

VIII

would have been produced in this reaction. Furthermore, since α-halogenated salts of this type (for example, VII) were shown to react readily with acetophenone and pyridine, three moles of I would have been produced for each mole of the starting substance had the starting substance been VIII.

Experimental

Reaction of Acetophenone with Iodine, Pyridine and Water.—These reactions were studied by determination of the amount of some of the isolable reaction products under a variety of conditions. A summary of the general procedure and typical results is illustrated by the following examples.

Example 1.—A mixture consisting of 0.025 mole of acetophenone, 0.05 mole of iodine, 20 cc. of pyridine and 2.5 moles of water[4] in an open flask was heated to dryness on the steam-bath. The residue was leached with ether (1.6 g., 55%[5] of benzoic acid was isolated from the ether extract). The solid remaining was leached with acetone (25 mg. of phenacylpyridinium triiodide[6] (VI) was isolated from the acetone extract). The solid remaining after the acetone extraction was then leached with hot absolute alcohol. (From the alcohol extract 1.2 g., 14%,[5] of phenacylpyridinium iodide (I) and a quantity of pyridine hydroiodide[7] was obtained.) The residue left after alcohol extraction was methylenedipyridinium diiodide[6] (IV); yield 2.5 g. or 24%.[5]

A duplicate experiment gave 1.7 g. of I and 1.7 g. of IV.

Example 2.—A mixture consisting of 0.1 mole of acetophenone, 0.1 mole of iodine, 20 cc. of pyridine and 45 g. (2.5 moles) of water[8] in an open flask was heated for fifteen hours on the steam-bath. From the residue 18.5 g., 57%,[5] of I, pyridine hydroiodide in quantity and a trace of IV were obtained.

Example 3.—A mixture consisting of 0.025 mole of acetophenone, 0.025 mole of iodine, 20 cc. of pyridine and 45 g. (2.5 moles) of water,[4] when heated as in Example 1, gave 0.7 g., 14%,[9] of IV, a quantity of pyridine hydroiodide, a trace of phenacylpyridinium iodide (I) and benzoic acid.

Example 4.—A solution consisting of 5.0 g. (0.041 mole) of acetophenone, 100 cc. of pyridine, 300 cc. of water and 1.0 g. (0.004 mole) of iodine[4] was evaporated to dryness on the steam-bath. The residue consisted of pyridine hydroiodide, benzoic acid and 0.30 g. of IV, 36%.[9] No phenacylpyridinium iodide could be detected.

Reaction of Phenacylpyridinium Iodide with Iodine, Pyridine and Water.—A solution of 0.025 mole of I in 50 cc. of water was treated with 10 cc. of pyridine and 0.025 mole of iodine. The solution was placed in an open flask and heated to dryness on the steam-bath. Benzoic acid was present as a sublimate. The residue was successively leached with ether, acetone and absolute alcohol, and finally crystallized from alcohol containing a small amount of water; yield 4.4 g. (42%) of methylenedipyridinium iodide.[6] When a similar experiment was carried out using a limited amount of water, a mixture similar to that described in example 1 was obtained.

α-Bromophenacylpyridinium Bromide (VII).—This substance was prepared according to the directions of Kröhnke.[3] It was crystallized twice from glacial acetic acid; m. p. 219°.[10]

Anal. Calcd. for $C_{13}H_{11}ONBr_2$: Br, 44.8. Found: Br, 45.5.

Reaction of VII with Pyridine and Acetophenone.—A mixture of 5.0 g. of VII, 7 cc. of acetophenone and 10 cc. of pyridine was heated for three hours on the steam-bath. The mixture was diluted with ether and filtered. The product was phenacylpyridinium bromide; yield 7.8 g.; m. p. 219°.

Anal. Calcd. for $C_{13}H_{12}ONBr\cdot H_2O$: Br, 27.0. Found: Br, 26.2. The perchlorate had m. p. 189.°

Reaction of VII with Pyridine Hydroiodide.—A mixture of 0.01 mole of VII and 10 g. of pyridine hydroiodide was dissolved in boiling glacial acetic acid. An intense iodine color developed. The solution was cooled, filtered, and the solid leached with acetone. Phenacylpyridinium triiodide (VI) was recovered from the acetone extract; yield 1 g.; m. p. 111–112°.

Methylenedipyridinium Diiodide (IV).—A mixture consisting of 3 cc. of methylene iodide and 10 cc. of pyridine was heated for one hour on the steam-bath. The crystalline product which separated was washed with ether and crystallized four times from alcohol containing a little water; m. p. 223–224°. This substance is insoluble in absolute alcohol, and very soluble in water.

Anal. Calcd. for $C_{11}H_{12}N_2I_2$: I, 59.7; N, 6.42. Found: I, 59.0; N, 6.72.

The diperchlorate showed m. p. 232–235°.

Anal. Calcd. for $C_{11}H_{12}N_2Cl_2O_8$: N, 7.57. Found: N, 7.63.

The picrate gave m. p. 245–249°.[11]

Phenacylpyridinium Triiodide (VI): Method I.—A solution of 5 g. of phenacylpyridinium iodide (I) in 40 cc. of hot water-alcohol was added to a solution of 10 g. of potassium iodide and 5 g. of iodine in 40 cc. of water. A red oil precipitated; it was separated by decantation, dissolved in hot absolute alcohol, and the solution cooled. The red-brown flaky crystals obtained were crystallized four times from absolute alcohol; yield 5 g.; m. p. 114–115°.

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(4) This mixture was homogeneous after heating for a few minutes on the steam-bath.

(5) Based on the ketone.

(6) Characterized by detailed comparison with the authentic material as described elsewhere in this paper.

(7) The amount of this substance was not determined. It was present in considerable quantity in all reaction mixtures.

(8) This mixture was not homogeneous.

(9) Based on iodine assuming all iodine was used according to reactions 1, 2 and 3.

(10) Kröhnke[3] reported the melting point of this compound as 219° after crystallizing from water or alcohol. The substance prepared in this Laboratory shows marked decomposition in the range 120–150°, but most of it persists until 219–220°.

(11) The melting point of this substance was reported as 230° by Schmidt, *Arch. Pharm.*, **251**, 186 (1913). In several preparations we have never observed this value.

Anal. Calcd. for $C_{13}H_{12}NOI_3$: I, 65.8; N, 2.42. Found: I, 63.0; N, 2.48.

This substance is very slightly soluble in water, benzene and ether, moderately soluble in absolute alcohol, and very soluble in acetone. A suspension of it in water slowly turns starch to a blue color.

Method II.—A solution of 0.05 mole of phenacylpyridinium iodide in 75 cc. of boiling glacial acetic acid was treated with 0.05 mole of iodine. On cooling, the triiodide (VI) separated; yield, 95%; m. p. 111–113°.

Reaction of Phenacylpyridinium Triiodide (VI) with Acetophenone and Pyridine.—A solution consisting of 2.57 g. (0.0044 mole) of VI in 5 g. of acetophenone and 5 g. of pyridine was heated for two hours on the steam-bath. At the end of this time most of the color had disappeared and a light brown crystalline solid was present in the reaction flask. This solid was separated and thoroughly washed with ether; yield 3.6 g. of crude solids. The material was then digested with 10 cc. of warm water, the suspension cooled in an ice-bath and filtered. The solid, weight 2.54 g. (0.0078 mole), was phenacylpyridinium iodide (I). The water-soluble portion was concentrated and treated with perchloric acid. Pyridine perchlorate, 0.9 g. (0.0044 mole), m. p. 285°, separated. This was considered proof that pyridine hydroiodide was present in the reaction mixture as an ether insoluble salt and hence had been formed in the original reaction.

Summary

1. The reaction of acetophenone with iodine, pyridine and water was studied and five products separated and identified. A reaction scheme to explain these products is given and independent experiments were carried out to establish each of the postulated reactions.

2. Phenacylpyridinium triiodide was prepared and it was demonstrated that it contains the triiodide ion.

EVANSTON, ILLINOIS RECEIVED AUGUST 11, 1947

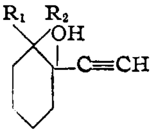
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

The Action of Formic Acid on Ethynylcarbinols[1]

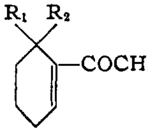
BY J. D. CHANLEY

Ethynylcarbinols on treatment with formic acid yield isomeric unsaturated carbonyl compounds. Rupe,[2] in the years 1926–1929, studied this isomerization in a number of instances and originally concluded that the reaction products were unsaturated aldehydes. Fischer and Löwenberg,[3] however, showed that the interaction of 1-ethynyl-1-cyclohexanol (IA) and formic acid yielded the isomeric ketone, 1-acetyl-1-cyclohexene (IIA) and not cyclohexylideneacetaldehyde (IIIA), as postulated by Rupe; they suggested that ketones always were the main products of this type of reaction and that aldehydes, if formed, were present in small quantities. Rupe,[4] accepted their evidence and suggestion, but insisted that some aldehyde was present in each reaction product he had previously described.[5] Hurd and Christ[6a] also repeated Rupe's work on 1-ethynyl-1-cyclohexanol and phenylmethylethynylcarbinol and chose for further study the action of formic acid on ethynylbornyl alcohol. They reported that only the corresponding ketones 1-acetyl-1-cyclohexene, acetophenone and 2-acetyl-6-hydroxycamphane were formed and went beyond Rupe's modified concept by doubting the presence of any aldehydes in Rupe's reaction products. However, their products must have contained some aldehydes, since their ketones, like Rupe's, gave a positive test for aldehydes with Schiff reagent. However, they discounted the significance of this test.[6b]

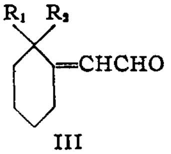
In the present paper evidence will be offered to show that 1-ethynyl-1-cyclohexanol (IA) on treatment with formic acid and after careful fractionation gives, in addition to the main product, 1-acetyl-1-cyclohexene (IIA) (50% yield), a small but significant quantity of cyclohexylideneacetaldehyde (0.8% yield). As a second example we prepared the new 1-ethynyl-2,2-dimethyl-1-cyclohexanol (IB) which on similar treatment gave the new ketone 2,2-dimethyl-1-acetyl-1-cyclohexene (IIB) (56% yield) and the new aldehyde 2,2-dimethylcyclohexylideneacetaldehyde (IIIB) (6% yield). Neither of the above mentioned pure ketones gave a positive test for aldehydes with Schiff reagent.



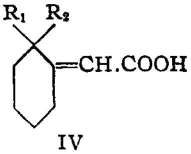
I



II



III



IV

For formulas IA-IVA, $R_1 = R_2 = H$; for IB-IVB, $R_1 = R_2 = CH_3$

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[1] This investigation was supported in part by a grant in aid from the United Hospital Fund, New York City, to Dr. Harry Sobotka. It grew out of a project, conducted by Dr. Harry Sobotka and coworkers, dealing with syntheses in the carotenoid group.

[2] Rupe and co workers, *Helv. Chim. Acta*, **9**, 672 (1926); **11**, 449, 656, 965 (1928).

[3] Fischer and Löwenberg, *Ann.*, **475**, 203 (1929).

[4] Rupe and Hirschmann, *Helv. Chim. Acta*, **14**, 688 footnote (1931).

[5] Subsequently Rupe claimed that 1-ethynyl-2-isopropyl-5-methyl-1-cyclohexanol, 1-ethynyl-3-isopropyl-6-methyl-1-cyclohexanol and ethynylfenchyl alcohol were rearranged exclusively to unsaturated aldehydes of type III (see Rupe and Kuenzy, *Helv. Chim. Acta*, **14**, 708 (1931); **17**, 283 (1934)).

[6a] Hurd and Christ, THIS JOURNAL, **59**, 118 (1937).

[6b] *Cf.* also Price and Meisel, *ibid.*, **69**, 1497 (1947).