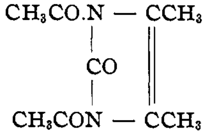
Experimental.

Diacetyldimethylglyoxalone,  $\begin{array}{l} CH_3CO.N - CCH_3 \\ \quad\; CO \quad \| \\ CH_3CON - CCH_3 \end{array}$. — This combination was prepared according to the directions given by Biltz[1] by treatment of our hydrolytic product, $C_5H_8ON_2$, with acetic anhydride. Five-tenths of a gram of the substance was digested with 5 cc. of acetic anhydride and 1 g. of anhydrous sodium acetate for 5 hrs., by heating in an oil bath. The resulting solution was then diluted with cold water, when a crystalline precipitate deposited. The compound was purified by crystallization from boiling alcohol, from which it separated on cooling, in the form of elongated prisms melting at 115–116° to a clear oil. The yield of purified material was 0.45 g. The imidazol used for comparison was made according to Kunne's method[1] and acetylated according to the directions of Biltz.[1] The diacetyl derivative obtained melted at 115–116° and we were unable to record a higher reading with the thermometers at our disposal. Biltz assigned to this compound a melting point of 117–118°. A mixture of the diacetyl derivative prepared from our hydrolytic product and Biltz's compound melted at 115–116°, showing that they were identical. A nitrogen determination gave:

Calc. for $C_9H_{12}O_3N_2$: N, 14.3. Found: N, 14.26.

NEW HAVEN, CONN.

[CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF WASHINGTON.]

REACTIONS OF PIPERIDINE WITH ORGANIC HALOGEN COMPOUNDS IN ETHER SOLUTIONS.

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In common with other bases, piperidine reacts more or less readily with halogen compounds. If these reactions are carried out in aqueous alkaline solutions, nitrogen substitution products of piperidene are formed almost invariably. If the reactions are carried out in anhydrous media, however, as for example, in ether, the end products are found to be different. In the latter case the base and the halide unite to form a molecular compound, which subsequently may or may not undergo decomposition so as to yield the halogen-acid salt of piperidine and the nitrogen substituted homologue of piperidine.

These successive reactions may be illustrated by the equations:

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[1] *Loc. cit.*

$$(1)\quad C_5H_{10}NH + R.X \longrightarrow C_5H_{10}NR.HX$$

$$(2)\quad C_5H_{10}NR.HX \longrightarrow C_5H_{10}NR + HX$$

$$(3)\quad C_5H_{10}NH + HX \longrightarrow C_5H_{10}NH.HX$$

These reactions may, of course, be grouped so as to show only the stable end products:

$$(4)\quad 2C_5H_{10}NH + RX \longrightarrow C_5H_{10}NH.HX + C_5H_{10}NR$$

With certain polyhalides,[1] piperidine gives a halogen-acid salt of piperidine and an unsaturated derivative of the halide used, as for example with tetrabromoethane:

$$(5)\quad C_5H_{10}NH + CHBr_2.CHBr_2 \longrightarrow C_5H_{10}NH.HBr + CHBr{:}CBr_2$$

To determine whether *addition* in anhydrous ether is the initial type of reaction of piperidine with these compounds is the main purpose of this investigation. Many examples of additive compounds of piperidine are given in the literature, especially with inorganic[2] halides. Additive compounds of piperidine with organic[3] halides, however, are quite rare. This paper contributes others and proves that addition, as indicated by the equations above, is the initial and main type of reaction.

When possible the pure additive compounds were prepared and analyzed thus giving direct proof of their additive nature. Owing to a variety of causes, however, pure additive compounds could not always be prepared.

The additive compounds are really halogen-acid salts of derivatives of piperidine and, like certain well-known other series of salts, possess different degrees of stability toward water, heat and free bases, hence are decomposed in accordance with the equation

$$(6)\quad C_5H_{10}NH.RX + H_2O \longrightarrow C_5H_{10}NH + H_2O.HX$$

and combinations with Reactions (2), (3) and (4). In each case, therefore, the ether-insoluble product was either the pure additive compound or a mixture of it with the halogen-acid salt of piperidine.

Since heat and standing at room temperatures decompose the additive compounds, in accordance with Reaction 2, the element of time is of importance. Some of the precipitates were formed so slowly, by the influence of sunlight, that the kinetic decomposition of the additive

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[1] THIS JOURNAL, **34**, 286 (1912).

[2] *Jahresber.*, **1858**, 357; *Ber.*, **25**, 743 (1892); **26**, 6 (1893); **29**, 711 (1896); **31**, 914, 2841 (1898); **32**, 1409, 3220 (1899); **35**, 2420, 2770 (1902); *Ann.*, **210**, 319 (1881); **237**, 240 (1887); **247**, 55 (1888); THIS JOURNAL, **20**, 576 (1898); **21**, 946 (1899); **33**, 1594 (1911); **34**, 290, 294 (1912); *Z. anorg. Chem.*, **15**, 12 (1897); **89**, 331, 338, 351 (1914); *Gazz. chim. ital.*, **27**, 21 (1897); *Compt. rend.*, **124**, 504 (1897); *Bull. soc. chim.*, [3] **7**, 74 (1892); *J. prakt. Chem.*, **91**, 103 (1915); *Ann. chim. phys.*, [3] **38**, 76 (1853).

[3] THIS JOURNAL, **33**, 1593, 1600 (1911); **34**, 290, 294, 1407, 1413 (1912); **36**, 2100 (1914); **37**, 2129 (1915); *Arch. Pharm.*, **238**, 330 (1900); *Ber.*, **27**, 886 (1893); *J. Russ. Chem. Soc.*, **25**, 290 (1893); **41**, 1481 (1910); **42**, 1447 (1911).

compounds nearly kept pace with their formation. Other additive compounds, though formed rapidly, as in the case of phosgene, were easily decomposed at the room temperatures. Dry precipitates of the additive compounds, therefore, yielded by Reaction (2) mixtures containing *N*-homologues of piperidine. Such decompositions could be observed in the evolution of hydrohalogen acids and could be followed by making determinations of the halogen content of the mixtures. In general, the precipitates were more stable in the presence of ether than when dry.

When purification of the precipitates could not be effected by dissolving in a small volume of absolute alcohol and reprecipitating with absolute ether, they were examined by the following methods:

1. Microscopical examination of the precipitates forming in the anhydrous ether often revealed two crystalline forms.
2. Melting-point determinations of the precipitates showed that they were mixtures of the additive compound and $C_5H_{10}NH.HX$.
3. Since aqueous solutions of the salts of piperidine and halogen acids are neutral, an acid reaction of the mixture in water indirectly indicated the presence of the additive compound. An acid reaction toward litmus paper could often be obtained in the original ether solution, thus also indicating the formation of the additive compound.
4. Spinning motions produced on water by the ether-insoluble products readily indicated mixtures or the presence of the additive compound, since the pure salts of piperidine do not give such spinning motions.[1]
5. Halogen analyses of the ether-insoluble products demonstrated the ratio of the components of the mixtures. When a mixture, the percentage of halogen was always found between the percentages of the halogen in the additive compound and of the salt of piperidine. For reasons given above such precipitates must always be freshly prepared and analyzed at once.
6. Recrystallization of the precipitates by the method given above often changed both the melting point and the percentage of halogen, thus indicating that the original precipitate was a mixture.

It must be remembered in connection with the above methods that enough ether must always be used to keep in solution the unchanged original materials and the secondary product of the type $C_5H_{10}N.R$. If, owing to the decomposing effect of heat, any of the $C_5H_{10}N.R$ compound was formed in the precipitate, it could always be washed out by ether.

The piperidine used was dried for a week over sodium and was then

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[1] For other observations of these spinning motions see THIS JOURNAL, **34**, 1403, 1407 (1912); **36**, 2093 (1914); **37**, 2127 (1915).

distilled, care being taken to avoid contact with atmospheric moisture. The halides were usually dried over calcium chloride and distilled.

A 1–2% stock solution of piperidene in anhydrous ether was prepared and was run into convenient sized bottles, whcih had previously been freed as far as possible from atmospheric moisture. These bottles were stoppered quickly and, when needed, were treated with the *equimolecular* quantities of the respective halogen compounds. The solutions thus prepared were allowed to stand in direct sunlight for a time to complete the reactions.

As soon as sufficient precipitate for analysis had formed, it was removed by rapid filtering and washing with dry ether. Traces of ether were removed by standing for a short time in desiccators over sulfuric acid. Since many of the precipitates thus obtained were mixtures difficult to separate, they were analyzed as a whole for halogen, in the manner indicated above, and their composition was calculated from their halogen content. Pure substances, such as the halide salts of piperidine, when previously known, were identified by their melting points.

The formation of the additive compounds is difficult, and indeed impossible, to explain on the basis of a preliminary ionic dissociation of the reacting molecules.

1. The reactions are brought about in anhydrous ether, a non-ionizing solvent.

2. In the absence of water, the ions of piperidine must be either $C_5H_{10}N^-$ and H^+, or $C_5H_{10}N^+$ and H^-. The former dissociation classifies piperidine as an acid; the latter dissociation classifies hydrogen as electro *negative.* Both of these assumptions are improbable.

3. The speeds of reactions differ so widely that constant concentrations of the ions of piperidine in the ether, if such ions exist, cannot be imagined. Some of the reactions take place immediately; others fail absolutely for months and until promoted by heat or by sunlight. If some ions of piperidine were present, the reactions should progress constantly though slowly; however, some reactions fail absolutely until promoted by sunlight or by heat. On the other hand, if the ionizations of the halide alone are considered responsible for the reactions, then the same difficulties are met with. Some halides react and others do not. The absence of light slows down or totally prevents reactions already in progress and the presence of direct sunlight promotes reactions that could not be started in diffused sunlight or in darkness.

Methyliodide.—When equimolecular quantities of piperidine and methyliodide were brought together in anhydrous ether, pure *methylpiperidinehydroiodide* was formed at once.

Calc. for $C_5H_{10}NCH_3.HI$: I, 55.89%. Found: I, 55.67%.

Isopropylbromide.—After long standing, only crystals of piperidinehydrobromide,[1] prisms melting[2] at 234° and containing 48.32% Br, were obtained. The ether solution contained isopropylpiperidine.[3]

Isobutyliodide.—Thick prismatic needles, melting at 131°, were slowly formed. They analyzed as nearly pure *isobutylpiperidinehydroiodide.*

Calc. for $C_5H_{10}NC_4H_9.HI$: I, 47.17%. Found: I, 45.36%.

Isoamylchloride.—Slow-forming, long, prismatic crystals, melting at 230°, were obtained. Treatment of the ether solution with hydrogen-chloride gave pure *isoamylpiperidinehydrogenchloride*, melting at 233° and containing 18.83% Cl.[4]

Calc. for $C_5H_{10}NC_5H_{11}.HCl$: Cl, 18.53%. Found: Cl, 20.23% (AC, 84%).

Isoamylbromide.—Short, prismatic needles, melting 235°, were obtained.

Calc. for $C_5H_{19}NC_5H_{11}.HBr$: Br, 33.85%. Found: Br, 47.98% (AC, 0.8%).

Isoamyliodide.—Long needles and thin plates,[5] melting at 136°, were formed.

Calc. for $C_5H_{10}NC_5H_{11}.HI$: I, 44.83%. Found: I, 50.50% (AC, 61.5%).

Cetyliodide.—Thick, prismatic needles, melting at 128°, were obtained.

Calc. for $C_5H_{10}NC_{16}H_{33}.HI$: I, 29.03%. Found: I, 41.70% (AC, 58.5%).

Benzylchloride.—Fine needles, melting at 230°. The ether solution contained benzylpiperidine.[6]

Calc. for $C_5H_{10}NC_7H_7.HCl$: Cl, 16.76%. Found: Cl, 20.20% (AC, 66.8%).

Epichlorohydrine.—After three weeks, long needles melting at 149° were obtained.

Calc. for $C_5H_{10}N.C_3H_5O.HCl$: Cl, 19.97%. Found: Cl, 22.33% (AC, 74.3%).

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[1] Piperidinehydrobromide contains 48.14% Br; piperidinehydrochloride contains 29.17% Cl; piperidinehydroiodide contains 59.57% I. These calculated values are not given in the above text, hence reference to these values must be made to this footnote, when the found values for the respective halides are to be compared or when the percentage of the *additive compound* is to be calculated. The percentage of the additive compound, indicated by (AC) in the text, is found by subtracting from the above respective percentage, first the percentage of the additive compound, then the percentage of halogen found by analysis. The latter difference, multiplied by 100 and divided by the former difference, gives the percentage of the additive compound. For example, in the case of isoamylchloride, 29.17—18.53 = 10.64 and 29.17—20.23 = 8.94. Multiply 8.94 by 100 and divide by 10.64 and we obtain 84% of AC.

[2] Piperidinehydrobromide melts at 235–239°. Bischoff, *Ber.*, **31**, 2841 (1898); Fock, *Ibid.*, **32**, 1409 (1899); THIS JOURNAL, **33**, 1594 (1911).

[3] Ladenburg, *Ber.*, **14**, 1348 (1881); *Z. Electrochem.*, **7**, 816 (1901); Hjortdahl, *Jahresb.*, **1882**, 1085.

[4] Piperidinehydrochloride melts at 237°. Ladenburg, *Ann.*, **247**, 55 (1888).

[5] Isoamylpiperidinehydroiodide is described as forming plates. Schotten, *Ber.*, **15**, 421 (1882).

[6] Schotten, *Ber.*, **15**, 423 (1882); Baillie and Tafel, *Ibid.*, **32**, 74 (1899); Auerbach and Wolffenstein, *Ibid.*, **32**, 2517 (1899).

Ethylchlorocarbonate.—An immediate precipitate, melting at 227°, was obtained. The ether solution contained piperidylurethane.[1]

Calc. for $C_5H_{10}N.C_3H_5O_2.HCl$: Cl, 18.31%. Found: Cl, 28.32% (AC, 8%).

Acetonechloride.—An immediate precipitate of nearly pure piperidinehydrochloride, melting at 235° and containing 28.58% Cl, was obtained. The probable reaction[2] is:

$$C_5H_{10}NH + CH_3CCl_2CH_3 \longrightarrow C_5H_{10}NH.HCl + CH_2{=}CClCH_3$$

Tetrachloroethane.—An immediate precipitate of nearly pure piperidinehydrochloride, melting at 237°, and containing 29.00% Cl, was obtained. The ether solution yielded an oil boiling at 85°; trichloroethylene[3] boils at 88°. The reaction here is:

$$C_5H_{10}NH + C_2H_2Cl_4 \longrightarrow C_5H_{10}NH.HCl + CHCl{=}CCl_2$$

Phosgene.—An immediate amorphous precipitate, melting at 160°, was obtained. Though washed repeatedly with ether it continued to give off hydrogenchloride, thus indicating decomposition of the additive compound.

Calc. for $(C_5H_{10}NH)_2COCl_2$: Cl, 26.35%. Found: Cl, 25.20%.

The reactions here are probably:

$$2C_5H_{10}NH + COCl_2 \longrightarrow (C_5H_{10}N)_2CO.2HCl$$

$$(C_5H_{10}N)_2CO.2HCl \longrightarrow (C_5H_{10}N)_2CO.HCl + HCl \longrightarrow (C_5H_{10}N)_2CO + HCl$$

Acetylthiocyanate.—An oily precipitate, which solidified to a crystalline mass melting at 83–85°, was obtained. This was nearly pure *acetylpiperidinethiocyanate.*

Calc. for $C_5H_{10}N.C_2H_3O.HSCN$: SCN, 31.20%.
Calc. for $C_5H_{10}N.HSCN$: SCN, 40.56%. Found: SCN, 32.00% (AC, 91.4%).

Phenylpropionylchloride.—An immediate precipitate, melting at 237°, was obtained.

Calc. for $C_5H_{10}NC_9H_9O.HCl$: Cl, 13.98%. Found: Cl, 27.45% (AC, 11%).

Benzenesulfonechloride.[4]—An immediate voluminous precipitate of piperidinehydrochloride (28.90%) was obtained. The ether yielded benzenesulfonpiperidide,[5] melting at 92°.

Arsenic Trichloride, Antimony Trichloride and Chromyl Chloride.—Each gave immediately crystals, melting at 236–237° and containing 29.00–29.19% Cl, hence were nearly pure piperidinehydrochloride.

Pentachloroethane.—An immediate, though not voluminous precipitate,

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[1] Schotten, *Ber.*, 15, 421 (1882).

[2] Friedel, *Ann.*, 134, 263 (1865).

[3] Berthelot and Jungfleisch, *Ann. Supl.*, 7, 255 (1870).

[4] For the reaction with benzoyl chloride, see THIS JOURNAL, 36, 2100 (1914).

[5] Hinsberg, *Ann.*, 265, 182 (1891).

was formed at once. It melted at 239° and contained 28.50% Cl, hence was nearly pure piperidinehydrochloride. The reaction here is:

$$C_5H_{10}NH + CCl_3CHCl_2 \longrightarrow C_5H_{10}NH.HCl + CCl_2{=}CCl_2$$

Hexachloroethane.—Long, prismatic needles were deposited after many weeks' standing in direct sunlight. The crystals melted at 237° and contained 29.00% Cl, hence were pure piperidinehydrochloride. The reaction is probably:

$$2C_5H_{10}NH + CCl_3CCl_3 \longrightarrow C_5H_{10}NH.HCl + C_5H_{10}NC_2Cl_5$$

s-**Dibromoethane.**—Crystals melting at 233° and containing 48.19% Br were obtained, hence piperidinehydrobromide was formed.

Bromoform.[1]—After one week needles and prisms, melting at 191°.

Calc. for $C_5H_{10}NH.CHBr_3$: Br, 23.60%. Found: Br, 38.10% (AC, 41%).

Carbontetrachloride.[2]—After one month nearly pure crystals of piperidinehydrochloride were obtained; they melted at 230° and contained 28.10% Cl.

Trichloroaceticester.—After two days large prismatic needles, melting at 237° and containing 30.00% Cl, were obtained.

Acetylbromide.[3] — Slow-forming, transparent, deliquescent needles, melting[4] at 127°, were obtained.

Calc. for $C_5H_{10}N.C_2H_3O.HBr$: Br, 38.41%. Found: Br, 41.14% (AC, 72%).

Isobutyrylbromide.—Slow-forming, prismatic needles, melting at first at 130–138° and after recrystallization at 134–135°, were obtained.

Calc. for $C_5H_{10}N.C_4H_7O.HBr$: Br, 33.90%. Found: Br, 35.80% (AC, 86.7%).

Summary.

1. The lower alkyl monohalides react with piperidine with ease, precipitates forming immediately and continuing to form even in the dark. The chlorides react least readily; the bromides, more readily; the iodides, most readily. Retardation of reaction increases with the carbon content of the alkyl and with the presence of aryl groups. The latter gave little or no precipitates even after months of standing in sunlight. The alkyl polyhalides gave a variety of end products. Acyl halides and inorganic halides reacted with great ease.

2. Additive compounds were obtained either pure or in mixtures. Their formation is the main and the preliminary type of reaction with the materials studied.

3. Preliminary ionization of the compounds reacting is an improbable assumption to account for the end products.

SEATTLE, WASH.

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[1] With iodoform, $C_5H_{11}N.CHI_3$ was formed. THIS JOURNAL, **34**, 1413 (1912).

[2] With carbon tetrabromide, $C_5H_{11}N.(CBr_4)_2$ was formed. *Ibid.*, **33**, 1593 (1911).

[3] With acetylchloride, see *Ibid.*, **34**, 1407 (1912).

[4] Acetylpiperidinehydrobromide melts at 131–133°. Arnes, *Ber.*, **27**, 2088 (1894). For the action of acetylchloride on piperidine, see *Ibid.*, **34**, 1407 (1912).