Reactions of the chloroquinone and VIII were carried to completion in a mixture of 12.5 ml. of methanol and 5.0 ml. of water. In each reaction, 4.16×10^{-7} moles of VIII was used. The amounts of the dyes produced were determined spectrophotometrically. Results are shown in Table I.

TABLE I
OXIDATION OF LEUCO DYE VIII BY CHLOROQUINONE

Chloroquinone Used, Moles $\times 10^7$	Azomethine Dye Produced, Moles $\times 10^7$	Quinoxalone Dye Produced, Moles $\times 10^7$	Theoretical Chloroquinone Consumption, Moles $\times 10^7$
6.7	1.15	2.5_5	6.2_5
5.0	0.75	2.0	4.7_5
3.8	0.55	1.5_5	3.6_5
2.2	0.35	0.9	2.1_5

The last column gives the total amount of oxidant needed to produce the azomethine and quinoxalone dyes of the second and third column, on the assumption that 1 mole (two oxidation equivalents) of the oxidant is used for the formation of 1 mole of the azomethine dye and 2 moles (4 oxidation equivalents) for the formation of 1 mole of the quinoxalone dye. The correctness of these assumptions is indicated by the agreement between the figures of columns 1 and 4.

Observations on the Formation of Piperidine Hydrochloride from Chloroform and Piperidine

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The formation of piperidine hydrochloride from the reaction of chloroform and piperidine, with or without a strong base, has been reported by several workers.[2,3] The same product has also been observed in reactions that yield chloroform, when piperidine is present in the reaction mixture, but no effort has been made by previous investigators to establish the source of piperidine hydrochloride.[4,5] Since we are currently investigating similar reactions, we were interested in studying the conditions which lead to the formation of piperidine hydrochloride. Secondary amines have been shown to react with chloroform in the presence of potassium *t*-butoxide to yield amides.[6] Under these conditions, a dichlorocarbene has been shown to be an intermediate.[7]

It is the purpose of this communication to show that chloroform is sufficiently acidic to react with an organic base such as piperidine ($k = 1.2 \times 10^{-3}$)[8] to yield piperidine hydrochloride and *N*-dichloromethylpiperidine, which is instantaneously hydrolyzed to *N*-formylpiperidine. The extent to which this reaction takes place is very small in the absence of a strong base. Equimolecular amounts of piperidine and chloroform yield piperidine hydrochloride and *N*-formylpiperidine to the extent of 1%, after they are allowed to stand together for several days. The presence of *N*-formylpiperidine, as one of the products of the reaction between chloroform and piperidine in the absence of strong bases, has not been previously detected by chemical means since it is not easily identified when formed in minute amounts. We found that *N*-formylpiperidine could be easily detected when no particular attempts were made to keep the reaction mixture anhydrous. However, when precautions were taken to exclude moist air from the reaction mixture, no *N*-formylpiperidine could be detected by gas-liquid chromatography. This observation could be ascribed to the fact that if a dichlorocarbene were an intermediate in this reaction, *N*-dichloromethylpiperidine would be formed and under anhydrous conditions this compound could not be hydrolyzed to *N*-formylpiperidine. On the other hand, the observation could mean that the reaction between chloroform and piperidine proceeds *via* a free radical mechanism, as in the photolysis of diazomethane or ketone, which is believed to yield the methylene diradical.[9] To eliminate the last possibility, similar experiments were carried out, one in the absence of air and light, another in the presence of an inhibitor such as hydroquinone. These conditions did not appear to modify the course of the reaction to any great extent. The addition of hydroquinone to the reaction mixture appears to facilitate the reaction since under these conditions piperidine hydrochloride is obtained in 3% yield. This may be attributed to the increase in the polarity of the medium.

In view of these findings, it is concluded that the reaction between chloroform and piperidine proceeds *via* an ionic mechanism probably similar to that proposed by Saunders and Murray for related reaction.[10]

$$Cl_3CH + \ddot{N}C_5H_{10} \longrightarrow Cl_3C^- + \overset{+}{H_2}\ddot{N}C_5H_{10}$$

$$Cl_3C^- \longrightarrow Cl_2C: + Cl^-$$

$$Cl_2C: + \ddot{N}C_5H_{10} \longrightarrow Cl_2C\overset{-}{\ddot{N}}\overset{+}{C}C_5H_{10}$$

$$\begin{array}{c} H \\ \downarrow \\ O{=}C{-}NC_5H_{10} \xleftarrow{H_2O} Cl_2CNC_5H_{10} \end{array}$$

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These findings appear to be supported by the study of methylene derivative as intermediates in polar reactions, in which it was found that in buffered solutions the hydrolysis of chloroform is independent of pH.[11]

Experimental

Materials.—The chloroform used in this experiment was purified by successive washings with concentrated sulfuric acid and distilled water and then dried over calcium chloride overnight.[12] The drying agent was removed by filtration and the filtrate distilled through a 30-cm. column, 2 mm. in diameter, packed with glass helices, b.p. 61.0–61.5°, n^{25} 1.4457.

Piperidine was purified by allowing it to stand over potassium hydroxide pellets for 1 week. The pellets were removed by filtration and the filtrate distilled through a 30-cm. column, 2 mm. in diameter, packed with glass helices, b.p. 106°, n^{25} 1.4514.

Commercial anhydrous ether was dried more completely by allowing it to stand over calcium hydride for one week.

Reaction of Piperidine and Chloroform.—Chloroform (11.9 g., 0.1 mole) was added to piperidine (8.5 g., 0.1 mole). The reaction was exothermic. Piperidine hydrochloride was isolated by the addition of anhydrous ether to the reaction mixture after 24 hr., yield 1%. Piperidine hydrochloride was identified by its melting point, 244°, and infrared spectrum. The presence of *N*-formylpiperidine was verified by gas-liquid chromatography using a 3-ft. column of 25% carbowax 20-M on chromosorb 30–60 regular mesh packing, or a 6-ft. column of 25% silicone grease on chromosorb 30–60 regular mesh packing on fluoropak, all at 200° and 145 ml. of helium per min. *N*-Formylpiperidine cannot be obtained by distillation when present in small quantities because of its polar nature and its tendency to decompose when distilled under atmospheric pressure. It may be isolated as its mercuric chloride derivative. This derivative is easily prepared by adding small amounts of solutions believed to contain *N*-formylpiperidine to an aqueous solution of mercuric chloride (5 g. of mercuric chloride in 100 ml. of water). A solid forms immediately, m.p. 145°. The identity of this solid was established by comparing its infrared spectrum to that of an authentic sample of the mercuric chloride derivative of *N*-formylpiperidine. A mixture of the two compounds showed no depression in melting point. The authentic sample of the mercury derivative was prepared according to the directions of Farlow and Adkins[13] from *N*-formylpiperidine which had been obtained from the reaction of chloral and piperidine.[14]

Reaction of Piperidine and Chloroform in the Absence of Air and Light.—In a darkroom, nitrogen was bubbled through chloroform (11.9 g., 0.1 mole) and piperidine (8.5 g., 0.1 mole). Chloroform was added to piperidine and the reaction was exothermic. The mixture was allowed to stand in a pressure bottle, under nitrogen, in the darkroom overnight. To a 10-ml. aliquot of this reaction mixture, 200 ml. of *n*-hexane was added, still in the darkroom. A white solid precipitated, m.p. 242°, yield 1%. The infrared spectrum of this compound agreed with an authentic sample of piperidine hydrochloride. The rest of the reaction mixture was analyzed by gas-liquid chromatography using a 3-ft. column containing 25% carbowax 20-M on chromosorb 30–60 regular mesh packing, at 200° and 145 ml. of helium per minute. Three peaks were obtained. They were attributed to chloroform, piperidine, and *N*-dichloromethylpiperidine, respectively. The last peak had a retention time of 0.78 min. under the above conditions. This peak disappeared upon subsequent hydrolysis of the reaction mixture and a new peak corresponding to *N*-formylpiperidine was observed. The presence of *N*-formylpiperidine was verified by addition of an authentic sample of *N*-formylpiperidine in various amounts to the hydrolyzed reaction mixture.

Reaction of Piperidine and Chloroform in the Presence of Hydroquinone.—Chloroform (11.9 g., 0.1 mole) was added to a piperidine solution (8.5 g., 0.1 mole) containing hydroquinone (1.1 g., 0.01 mole). The reaction was exothermic and the solution turned red within 0.5 hr. The reaction mixture was allowed to stand in a pressure bottle overnight, without attempting to exclude light. The solid which formed was removed by filtration. *n*-Hexane (400 ml.) was added to a 10-ml. aliquot of the reaction mixture and the solid which formed was collected by filtration. The solids were combined and washed with chloroform. The chloroform solution was treated with 400 ml. of *n*-hexane. A solid precipitated and was removed by filtration. This solid was recrystallized from absolute ethanol and anhydrous ether, m.p. 242°, yield 3%.

The remaining reaction mixture was analyzed by gas-liquid chromatography using a 3-ft column of 25% carbowax 20-M on chromosorb 30–60 regular mesh, at 200° and 145 ml. of helium per min. Three peaks were observed which were attributed to chloroform, piperidine, and *N*-dichloromethylpiperidine, the last peak having a retention time of 0.78 min. under the above conditions. After subsequent hydrolysis, the peak occurring at 0.78 min. disappeared and the peak corresponding to *N*-formylpiperidine, having a retention time of 7.38 min., was observed. The proof of the presence of *N*-formylpiperidine was carried out in the same manner as described in the previous experiment.

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The Synthesis of Certain 7α- and 21-Methylsulfinyl and Methylsulfonyl Steroid Derivatives

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Our interest in the synthesis of steroid hormone analogs and the availability in our laboratory of a number of steroids substituted at C-7[1] or at C-21[2] with a methylthio group prompted us to investigate the preparation of the corresponding sulfoxide and sulfone derivatives. Several attempts to effect the oxidation of 7α-methylthiocortisone acetate with hydrogen peroxide were unsuccessful and crystalline material could not be isolated.[3] However, treatment of this compound with 1.1 molar equivalents of monoperphthalic acid (MPA) smoothly afforded a 65% yield of the desired sulfoxide. The 7α-methylsulfinyl derivatives of testosterone ace-

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(3) These experiments utilized a modification of the procedure reported by Ralls, Dodson, and Riegel [*J. Am. Chem. Soc.*, **71**, 3320 (1949)] for the oxidation of 3β-ethylthio-5-cholestenone to the corresponding sulfone.