

carbon tetrachloride under conditions suitable for benzophenone,⁸ *p,p'*-difluorobenzophenone⁹ and *p,p'*-dibromobenzophenone⁹ liberated much free iodine and yielded no ketone. *p*-Iodobenzoyl chloride (from *p*-iodobenzoic acid⁹ and phosphorus pentachloride) and iodobenzene gave only a 1.6% of ketone.¹⁰

Ultraviolet Spectra.—The measurements were made with a model DU Beckman ultraviolet spectrophotometer using 1 cm. square quartz cells and spectroscopically pure iso-octane as the solvent.

(8) "Org. Syntheses," Coll. Vol. I, p. 95 (1941).

(9) "Org. Syntheses," Coll. Vol. I, p. 325 (1941).

(10) Montagne, *Ber.*, **51**, 1486 (1918).

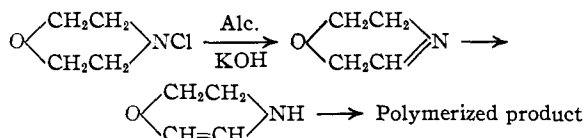
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N-Chloromorpholine and Related Compounds¹

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Morpholine reacts with aqueous solutions of sodium hypohalites to give the corresponding N-halogen substituted compounds.³ Both N-chloro- and N-bromomorpholine rapidly undergo intermolecular dehydrohalogenation on standing to yield morpholine hydrohalide and polymerized dehydro-morpholine derivatives. The dehydrohalogenation of N-chloromorpholine with alcoholic potassium hydroxide yields high-boiling, polymerized forms of dehydromorpholine rather than a monomer. This is in agreement with work done on the dehydrohalogenation of N-chloropiperidine.⁴ A rearrangement of the double bond occurs in this process since the resulting compounds still show reactions of the imino group.



N-Chloromorpholine reacts slowly with phenyl or α -naphthyl isocyanate to form chloro-substituted ureas. A mechanism involving the addition of the chloromorpholine to the double bond system of the isocyanate, followed by a rearrangement of the intermediate N-chlorourea in the same manner as N-chloroacetanilide, accounts for the products. Identical products are obtained by the action of sodium hypochlorite on the corresponding unsubstituted ureas. N-Cyano- and N-hydroxymorpholine also have been prepared.

Experimental

N-Chloromorpholine.—A quantitative yield of the chloromorpholine was obtained when 39 g. of morpholine (0.45 mole) in 50 ml. of water was added slowly with

(1) From the thesis submitted by R. A. Henry to the University of Washington in partial fulfillment of the requirements for the Ph.D. degree, December, 1942.

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(3) N-Chloromorpholine has been previously prepared in 54% yield by Myers and Wright, *Can. J. Research*, **26B**, 2681 (1948), by the action of sodium hypochlorite on an acid solution of morpholine.

(4) Lellmann, *Ber.*, **22**, 1319 (1889).

stirring to 300 ml. of 1.5 molar sodium hypochlorite (0.45 mole), maintained at 0°; pale yellow or colorless oil, b. p. 52–53° at 17 mm. Vigorous decomposition occurs if the distillation is performed at atmospheric pressure.

N-Chloromorpholine possesses a very acrid odor, has lachrymatory properties, and produces a burning sensation when applied to the skin. It does not cause the immediate evolution of nitrogen from aqueous solutions of urea although it rapidly liberates iodine from potassium iodide solution. The freshly distilled product darkens rapidly and begins to deposit crystals of morpholine hydrochloride within six to eight hours. Ten grams of N-chloromorpholine allowed to stand for three months in a sealed tube changed to a dark brown solid. All of this solid dissolved in cold water, except 0.5 g. of an amorphous residue, softening at 95–100° and decomposing at about 120°. The water soluble fraction was evaporated to dryness and treated with 50% solution of sodium hydroxide. The separated oil was taken up in ether, dried over anhydrous potassium carbonate, and distilled. Only morpholine was identified (as its naphthyl isocyanate derivative). The dark brown, viscous material remaining in the distilling flask had the characteristics of polymerized dehydromorpholine.

Reaction of N-Chloromorpholine with Amines. (A) **With Aniline.**—A mixture of 2.4 g. of N-chloromorpholine and 1.9 g. of aniline was allowed to stand for two weeks, after which it was repeatedly extracted with ether, leaving 1.8 g. of morpholine hydrochloride. On steam distilling the acidified extract, 0.3 g. of azobenzene, m. p. 64–65°, was recovered. A mixed melting point with an authentic specimen showed no depression.

(B) **With *p*-Toluidine.**—From 0.02 molar quantities of the reactants (in benzene to moderate the initial vigorous reaction) was recovered 0.3 g. of 4,4'-azotoluene.⁵

(C) **With Morpholine.**—Only a small amount of a yellow oil, b. p. 116–118° at 28 mm., was isolated from the reaction of morpholine with N-chloromorpholine. Since the product reacted with α -naphthyl isocyanate, indicating the presence of imino groups, it was probably dehydromorpholine and not N,N'-dimorpholine.

Dehydrohalogenation of N-Chloromorpholine.—N-Chloromorpholine (31.6 g.) was added dropwise with shaking to 180 g. of a refluxing, 10% alcoholic potash solution. After heating for an additional thirty minutes, the alcohol was evaporated and the residue dissolved in a minimum of water. This aqueous solution was then continuously extracted with ether until the extractant was colorless; after desiccating the ethereal solution with anhydrous potassium carbonate, the ether was removed. Distillation of the residual oil gave no plateaus in the distillation curve between 40 and 170° at 26 mm. Material boiling below 40° at 26 mm. was morpholine; above 170° the residue in the still-pot charred. A middle cut, b. p. 75–120°, was a yellow viscous oil which slowly crystallized to white masses, m. p. 105–106°.⁶

Anal. Calcd. for (C₄H₇ON)_x: N, 16.48. Found: N, 16.22.

This material was readily soluble in water, acids, and alcohol; difficultly soluble in ether. The α -naphthyl isocyanate derivative crystallized from a mixture of ethyl ether and petroleum ether as a white amorphous powder, m. p. 175–180°, after forming a sticky foam at 134–135°. The acetyl derivative boiled at 230–232° at 760 mm.

Anal. Calcd. for C₆H₁₁O₂N: N, 10.83. Found: N, 10.73.

Reaction of N-Chloromorpholine with Isocyanates. (A) **With Phenyl Isocyanate.**—A solution of 1.2 g. of phenyl isocyanate and 2.4 g. of N-chloromorpholine in 10 ml. of absolute ethyl ether was allowed to stand three days. The solid that separated was removed by filtration and washed with ether to remove excess reactants; yield 1.0 g. One recrystallization from alcohol gave needles melting at 196°.

(5) Pierson and Heumann, *Ber.*, **16**, 1048 (1883), prepared 4,4'-azotoluene by treating *p*-toluidine with ethyldichloramine.

(6) The melting points are corrected.

Anal. Calcd. for $C_{11}H_{13}O_2N_2Cl$: N, 11.64. Found: N, 11.66.

(B) With α -Naphthyl Isocyanate.—The above procedure was used; yield 1.5 g. after four days; m. p. 195–196°; a mixed melting point with the product of reaction (A) was 165–170°. A mixed melting point with the product prepared by the following method showed no depression.

Anal. Calcd. for $C_{16}H_{15}O_2N_2Cl$: N, 9.64. Found: N, 9.74.

One gram of the urea derivative from α -naphthyl isocyanate and morpholine⁷ was dissolved in 25 ml. of glacial acetic acid and 5 ml. of water, and cooled to 0°. With stirring, 6 g. of commercial bleaching solution was added dropwise over a period of one-half hour. The solution was then warmed slowly to room temperature and finally heated to 60°. The crude product was precipitated by the addition of 60 ml. of water, filtered, and washed with water until free of acid. Recrystallization from aqueous alcohol gave a product melting at 195°.

N-Bromomorpholine.—The reaction of equivalent quantities of sodium hypobromite solution and morpholine at 0° yielded a bright yellow solid with a very pungent odor. This compound decomposed completely within ten hours to a red, paste-like mixture, containing both needles of morpholine hydrobromide (m. p. 204°), and orange prisms of an unidentified material (m. p. 117–119°). Attempted recrystallization of the latter resulted in its decomposition. This viscous mass gradually became dark brown and very hard.

Anal. Calcd. for C_4H_8ONBr : N, 8.44. Found: N, 8.29.

N-Cyanomorpholine.—The method of Slosson⁸ was employed. The yield from 9.8 g. of potassium cyanide and 18.1 g. of N-chloromorpholine was 6.2 g. of a colorless oil, b. p. 123–124° at 18 mm.

Anal. Calcd. for $C_4H_8ON_2$: N, 24.99. Found: N, 24.38.

The same compound was formed in essentially quantitative yield by treating two moles of morpholine with one of cyanogen bromide in ethereal solution.⁹

N,N',N''-Bis-(oxydiethylene)-guanidine, O(C₄H₈)₃NC(NH)N(C₄H₈)O.—Three grams of N-cyanomorpholine and 9 g. of morpholine hydrobromide were heated for thirty minutes in an oil-bath at 155–165° (method of v. Braun¹⁰). The cold melt was treated with 2.2 g. of sodium hydroxide in 30 ml. of water and steam distilled to remove unreacted morpholine. The residue in the still-pot was cooled to 0°, made strongly alkaline, and extracted immediately with three 25-ml. portions of ethyl ether. Removal of the ether, after desiccation over anhydrous potassium carbonate, left an oil that soon solidified. Fractional crystallization from commercial ethyl ether gave colorless plates containing one molecule of ethyl alcohol; m. p. 116–117°.

Anal. Calcd. for $C_9H_{17}O_2N_3 \cdot C_2H_5OH$: N, 17.13. Found: N, 17.17, 17.23.

N-Hydroxymorpholine.—A 30% solution of hydrogen peroxide (22.7 g.) was added slowly to 17.4 g. of morpholine. Initially, only a small amount of heat was evolved, but if the mixture was permitted to stand at room temperature for about thirty minutes a very vigorous reaction took place. Considerable gas was evolved and an undesirable darkening occurred. To avoid this, the solution was cooled in an ice-bath for five to six hours, the oxidation then proceeding smoothly. Vacuum distillation of the reaction mixture yielded 1.1 g. of a colorless, viscous oil, b. p. 100–102° at 16 mm. The major portion of the product remained as a brown residue in the distilling flask.

(7) Henry and Dehn, *THIS JOURNAL*, **71**, 2298 (1949).

(8) Slosson, *Am. Chem. J.*, **29**, 302 (1903).

(9) D'Alelio and Pyle, U. S. Patent 2,375,628, May 8, 1945.

(10) v. Braun, *Ber.*, **42**, 2039 (1909).

Anal. Calcd. for $C_4H_7O_2N$: N, 13.59. Found: N, 13.56.

N-Hydroxymorpholine is readily soluble in water and in ether. It rapidly reduces silver nitrate solution.

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Desulfuration of the 20-Thioenol Ether of Pregnenolone

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A recent report of the desulfuration of the 3-thioenol ether of a Δ^4 -3-ketosteroid¹ to give a sulfur-free product in which the double bond is reduced prompts us to publish similar findings for the 20-thioenol ether of pregnenolone.

Reaction between 5-pregnen-3 β -ol-20-one acetate and ethyl mercaptan in the presence of zinc chloride and anhydrous sodium sulfate leads to a crystalline mixture which cannot be purified by crystallization or chromatography. Analysis indicates the presence of approximately 35% of the 20-diethyl mercaptol (I) and 65% of a 20-thioenol ether (II). The location of the double bond can be assumed to be in position 17,20 by analogy with the Δ^{17} -enol-20-acetate.²

Hydrogenolytic-desulfuration of the crystalline mixture of I and II with a fully active Raney nickel, prepared according to the method of Mozingo,³ affords in yield of 82% 5-pregnen-3 β -ol acetate, recently prepared by Huang-Minlon.⁴ This compound was characterized by saponification and Oppenauer oxidation to 4-pregnen-3-one.⁵



Experimental^{6,7,8}

Mixture of 20-Thioenol Ethyl Ether and 20-Diethylmercaptol of 5-Pregnen-3 β -ol-20-one Acetate (I and II).—To a solution of 200 mg. of 5-pregnen-3 β -ol-20-one acetate in 12 ml. of ethyl mercaptan was added 600 mg. of freshly fused zinc chloride and 600 mg. of anhydrous sodium sulfate. The mixture was kept overnight at 5°. The ethyl mercaptan was removed *in vacuo*, water added, and the mixture extracted with ether. The ethereal solution was washed twice with 2 N sodium hydroxide, three times with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was crystallized from meth-

(1) Rosenkranz, Kaufmann and Romo, *THIS JOURNAL*, **71**, 3689 (1949).

(2) Fieser and Huang-Minlon, *ibid.*, **71**, 1840 (1949).

(3) Mozingo, Wolf, Harris and Folkers, *ibid.*, **65**, 1013 (1943); "Organic Syntheses," **21**, 15 (1949).

(4) Huang-Minlon, *ibid.*, **71**, 3301 (1949).

(5) Marker and Lawson, *ibid.*, **61**, 586 (1939).

(6) All the melting points were determined on the Kofler micro melting point apparatus.

(7) The rotations were observed in a 2-dm. tube of 2.5 ml. capacity.

(8) The microanalyses were carried out by Dr. K. Ritter, Basle, Switzerland.