Nitration of 2-Methyl-4-quinazolone.—Two and one-half grams of 2-methyl-4-quinazolone was nitrated according to the directions given for the nitration of 2,4-dimethylquinazoline. The yield of crude product was 2.8 g. The m. p. after several recrystallizations was 298–300° (dec.) Bogert and Geiger reported[13] a melting point of 299° (uncor.) for 2-methyl-6-nitro-4-quinazolone obtained by a similar nitration.

Summary

4-Mercapto-2-methylquinazoline can be used as an intermediate for synthesis of 4-(β-hydroxyethylamino)-2-methylquinazoline and 6-chloro-4-(p-methoxyanilino)-2-methylquinazoline.

The nitration of 2,4-dimethylquinazoline yields 2-methyl-6-nitro-4-quinazolone.

CORVALLIS, OREGON RECEIVED FEBRUARY 9, 1948

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(13) Bogert and Geiger, THIS JOURNAL, **34**, 529 (1912).

[CONTRIBUTION NO. 80 FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF UTAH]

The Willgerodt Reaction on α-Tetralone

BY W. J. HORTON AND J. VAN DEN BERGHE[1]

The reaction of aliphatic aromatic ketones with aqueous ammonium polysulfide to produce ω-aryl aliphatic amides, first reported by Willgerodt,[2] has been shown to be applicable to olefins, acetylenes, aldehydes, alcohols and mercaptans.[3,4] It is apparent that a rearrangement is not involved.[5] This confirms Willgerodt's experiment[6] in which isovalerophenone was converted to α-methyl-γ-phenylbutyramide rather than the β-methyl-γ-phenylbutyramide expected by rearrangement. This reaction has been successfully repeated in several laboratories.[4,7,8]

The most important suggestions as to the mechanism of the reaction[4,8] have postulated a group which migrates along the chain by reversible steps, the process being terminated by irreversible changes which yield the amide. These ideas have been supported by the fact that the proposed intermediates, olefins, acetylenes, mercaptans, will yield amides if they are submitted to the conditions of the reaction. No intermediates have been isolated from the reaction mixture.

In the hope of interrupting the progression of a functional group along the aliphatic chain, we proposed to terminate the aliphatic chain of the aliphatic aromatic ketone with a second aryl group, or to use α-tetralone in the reaction[9] so that the aryl group of the ketone would also be the terminal group on the chain. We employed for convenience the modification suggested by Schwenk and Bloch[10] which avoids the use of sealed tubes.[11] The principal product of the reaction was a tertiary aromatic amine. When this was hydrolyzed using dilute sulfuric acid in a sealed tube,[12] β-naphthol was obtained and further identified by conversion to β-naphthyl methyl ether. That the amine is 4-(2-naphthyl)-morpholine was fully confirmed by independent syntheses from β-naphthol and morpholine in the presence of aqueous sodium bisulfite, and from β-naphthylamine and β,β'-dichlorodiethyl ether.[13]

The reaction of α-tetralone, morpholine and sulfur gives, in addition to the above amine, small amounts of at least one other product which has not been fully investigated.

When α- or β-naphthol replaced α-tetralone in this reaction, no amines could be found. Thus the conversion of α-tetralone to α-naphthol by means of sulfur cannot be the initial step in the reaction.

We have also investigated the behavior of morpholine and sulfur without the addition of any other material. Several reports in which the Schwenk and Bloch modification of the Willgerodt reaction was used have appeared[14,15] but products of a reaction between morpholine and sulfur have not been noted.[16] At a temperature just above that used to produce 4-(2-naphthyl)-morpholine from α-tetralone, morpholine and sulfur, the latter two components alone gave a high melting compound which resembled that isolated in the reaction of commercial diisobutylene, two styrene homologs, or certain mercaptans with morpholine and sulfur and shown to be dithioöxalodimorpholide.[15] When our product was mixed with known dithioöxalodimorpholide, no depression of the melting point was obtained. Hydrolysis of the high melting material with aqueous hydrobromic acid produced the hydrobromide of β,β'-dibromodiethylamine. It is apparent then that sulfur attacks the morpholine molecule to give hydrogen sulfide and a dithioöxalyl fragment

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(1) In part from the Master's Dissertation of J. Van Den Berghe.

(2) Willgerodt, *Ber.*, **20**, 2467 (1887).

(3) For a recent review of this reaction, see Carmack and Spielman, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 83.

(4) King and McMillan, THIS JOURNAL, **68**, 525, 632 (1946).

(5) Shantz and Rittenberg, *ibid.*, **68**, 2109 (1946). Calvin, *et al.*, *ibid.*, **68**, 2117 (1946), have shown that the acid produced is not formed by the same mechanism as the amide.

(6) Willgerodt and Merck, *J. prakt. Chem.*, **80**, 192 (1909).

(7) Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940).

(8) Carmack and De Tar, *ibid.*, **68**, 2029 (1946).

(9) This is the first recorded example of a cyclic ketone in the Willgerodt reaction.

(10) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(11) Preliminary work by one of us on α-tetralone and aqueous ammonium polysulfide in a sealed tube gave crystals melting at 139–140° which contain sulfur but no nitrogen.

(12) *Cf.* Arnold, Buckley and Richter, THIS JOURNAL, **69**, 2322 (1947), who treated 1-acetamido-3,4-dimethylnaphthalene in this manner.

(13) Cretcher and Pittenger, *ibid.*, **47**, 163 (1925).

(14) Campaigne and Rutan, *ibid.*, **69**, 1211 (1947); Arnold and Rondestvedt, *ibid.*, **67**, 1265 (1945).

(15) McMillan and King, *ibid.*, **69**, 1207 (1947).

(16) Carmack has reported (ref. 8) a high melting material in the reaction of phenylacetylene with morpholine and sulfur.

which is stable when converted to dithioöxalodimorpholide.

This work is being continued in an attempt to explain the appearance of the morpholinyl group at the 2-position of the naphthalene ring when α-tetralone is used.

We are indebted to assistance from the University of Utah Research Committee. The help of Mr. C. H. Arrington is gratefully acknowledged.

Experimental[17]

4-(2-Naphthyl)-morpholine.—(a) Morpholine from Commercial Solvents Corp. was redistilled and the colorless fraction, b. p. 121.5–122° at 644 mm., was used. The α-tetralone was prepared by the methods described[18] and had a b. p. 127–137° at 13 mm. α-Tetralone prepared by air oxidation of tetralin gave similar results. A mixture of 4.0 g. (0.027 mole) of α-tetralone, 2.48 g. (0.028 mole) of morpholine and 0.86 g. (0.027 mole) of powdered sulfur was refluxed by heating the flask in an oil-bath at 128–135° for eight hours. Within the first hour, the sulfur dissolved, an odor of hydrogen sulfide was noted and the color of the solution lightened. The reaction mixture was allowed to cool to room temperature and stand overnight, whereupon it solidified. The solid was treated with a warm solution of 5 cc. of concentrated hydrochloric acid in 10 cc. of water and decanted to a filter. This treatment was repeated twice. The oil remaining undissolved was washed with water and the washings added to the acidic filtrate. The cooled filtrate was made basic with ammonia, the suspension of dark precipitate was cooled, filtered and washed with water. The dried crude amine weighed 2.87 g. Steam distillation and three recrystallizations from aqueous ethanol gave thin rods, m. p. 87–90°, reported 90°.[13]

Anal. Calcd. for $C_{14}H_{15}NO$: N, 6.57. Found: N, 6.55.

The amine was dissolved in dilute hydrochloric acid with warming and the acidity was increased to 10% by addition of concentrated hydrochloric acid. On cooling, the hydrochloride of 4-(2-naphthyl)-morpholine appeared as colorless crystals. Recrystallization first from a small volume of water and then from absolute alcohol, produced large granular crystals which melted at 211.5–215° with sudden evolution of gas at 215°.

Anal. Calcd. for $C_{14}H_{16}NOCl$: N, 5.61; neut. equiv., 250. Found: N, 5.64; neut. equiv., 250.

A solution of 0.5 g. of amine and 0.5 g. of picric acid in 25 cc. of warm ethanol gave 0.77 g. of picrate on cooling. Recrystallization from alcohol gave fine, rectangular, canary-yellow rods which melted at 152–155° (dec.).

Anal. Calcd. for $C_{20}H_{18}N_4O_8$: neut. equiv., 442. Found: neut. equiv., 438.

When α-naphthol or β-naphthol (0.027 mole) replaced α-tetralone in the above procedure, no detectable amounts of amines could be obtained from the hydrochloric acid extracts of the reaction mixture.

(b) A sample of 4-(2-naphthyl)-morpholine prepared by the reported procedure[13] melted at 84.5–87° and a mixture with the amine from (a) melted at 87–89°. A picrate was prepared which melted at 152–155° (dec.). No change in m. p. was observed when this was mixed with the picrate obtained in (a).

(c) A sealed glass tube containing 1.0 g. of β-naphthol (0.0069 mole), 1.2 g. of morpholine (0.014 mole), 0.73 g. of sodium bisulfite (0.007 mole) and 1.5 cc. of water was heated for twenty-four hours at 190–200°. Extraction of the tube contents three times with a solution of 1 cc. of alcohol in 9 cc. of 6 *N* hydrochloric acid, filtration and neutralization of the filtrate gave 1.06 g. of crude amine. On solution in dilute hydrochloric acid, filtration and neutralization, 1.03 g. of nearly colorless amine, m. p. 84–87°, was obtained. A mixture with the amine produced in (a) melted at 87–89°. Similarly, a mixture of the picrates melted without depression.

Hydrolysis of 4-(2-Naphthyl)-morpholine.—Two hundred milligrams of the amine from α-tetralone, morpholine and sulfur was sealed in a glass tube with 10 cc. of 15% sulfuric acid.[12] The tube was heated in a metal-bath at 220–240° for three hours. The crystalline contents of the tube were filtered and washed with water. The solid, dissolved in warm benzene, was washed with a solution of 0.5 cc. of hydrochloric acid in 20 cc. of water. The separated benzene solution was washed with water until neutral and the benzene evaporated. The residue partially dissolved in 10% sodium hydroxide. The filtered solution was acidified to yield a gelatinous precipitate which dissolved on warming and reappeared as colorless crystals on cooling. These melted at 114–120° and a mixture with authentic β-naphthol melted at 117–120°. A solution of 10 mg. of the crystals in 0.5 cc. of 10% sodium hydroxide and 2 cc. of water was treated with two 0.1-cc. portions of dimethyl sulfate to yield 5 mg. of β-naphthyl methyl ether, conveniently recovered by steam distillation of the reaction mixture. The β-naphthyl methyl ether was recognized by its distinctive odor, m. p. 71.5–74° alone, and when mixed with known β-naphthyl methyl ether, m. p. 71.5–73.5°.

Reaction of Morpholine and Sulfur.—A mixture of 4.3 g. (0.13 mole) of powdered sulfur and 12.4 g. of redistilled morpholine (0.14 mole) was heated in an oil-bath held at 150–158° for four hours. Use of a Hopkins-type condenser permitted gentle refluxing with only a small portion of the material becoming solid in the condenser. The warm reaction product was mixed with 50 cc. of 95% ethanol and allowed to stand at room temperature overnight. The crystals so obtained were washed with cold alcohol and weighed 1.16 g., m. p. 217–227°. A filtered solution of the compound in hot water deposited 0.45 g. of colorless flat prisms on cooling, m. p. 253.5–255°. The m. p. was not raised by subsequent recrystallization from alcohol.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S_2$: N, 10.76. Found: N, 10.76.

When mixed with dithioöxalodimorpholide prepared by the described method,[15] m. p. 254.5–256°, reported m. p. 252–253°, the mixture melted at 252.5–255°.

Hydrolysis with Hydrobromic Acid.—To 0.28 g. of the compound from morpholine and sulfur was added 10 cc. of 48% hydrobromic acid and the solution was refluxed for twelve hours. Removal of the acid at reduced pressure by warming on the water-bath left a residue which crystallized on cooling. The crystals were dissolved in 10 cc. of warm absolute alcohol, filtered and the solution concentrated. On cooling, crystals appeared which were filtered and washed with ice-cold alcohol. The material weighed 100 mg. and melted at 195–201°. Reported[19] for β,β′-dibromodiethylamine hydrobromide, m. p. 199–200°. A hot water solution of 70 mg. of the hydrobromide and 50 mg. of picric acid deposited 50 mg. of canary-yellow crystals, m. p. 125–134°. Recrystallization from a few cc. of hot water gave crystals, m. p. 132–134° with shrinking at 129°. Reported[19] for the picrate of β,β′-dibromodiethylamine, m. p. 128°.

Oxalodimorpholide.—A solution of 14.4 g. of morpholine in 50 cc. of anhydrous reagent benzene was treated with a solution of 4.2 g. of oxalyl chloride in 50 cc. of benzene. The oxalyl chloride solution was added slowly with swirling and cooling in cold water. After standing at room temperature for thirty minutes, followed by warming on the steam-bath, the cooled mixture was filtered and the filter washed with benzene. After removal of the benzene from the filtrate, the residue and the colorless salt insoluble in benzene were thoroughly extracted with warm acetone. On concentration of the acetone and cooling, 5.32 g. of short, rectangular prisms was obtained, m. p. 173–182.5°, reported 184–185°.[15] By concentration of the filtrate and addition of petroleum ether (b. p. 70–90°), 1.2 g.

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[17] Melting points and boiling points are uncorrected.

[18] Martin and Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 569; Thompson, *ibid.*, Vol 20, p. 94.

[19] Gabriel and Eschenbach, *Ber.*, **30**, 809 (1897).

was obtained, m. p. 138–176°. The first crop material was suitable for the preparation of dithioöxalodimorpholide.[16]

Summary

The reaction of α-tetralone with morpholine and sulfur yields 4-(2-naphthyl)-morpholine.

Dithioöxalodimorpholide has been isolated as a reaction product of sulfur and morpholine.

SALT LAKE CITY, UTAH RECEIVED MARCH 9, 1948

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

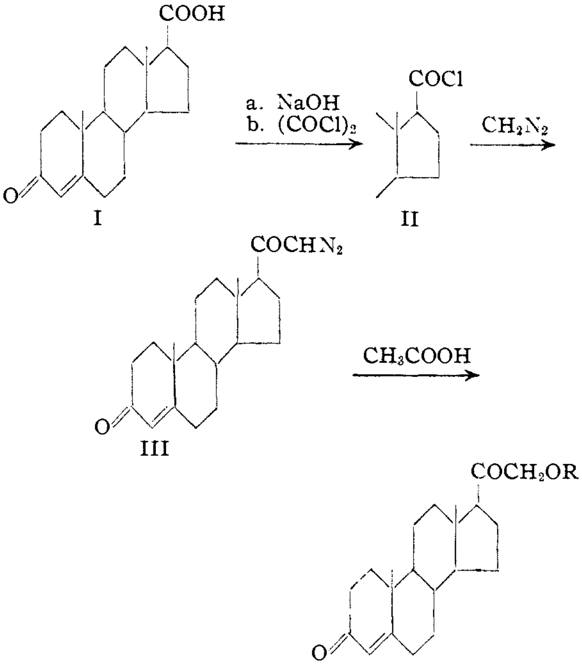
The Preparation of Desoxycorticosterone Acetate from 3-Keto-Δ4-etiocholenic Acid

BY A. L. WILDS AND CLIFFORD H. SHUNK[1]

Desoxycorticosterone acetate (IVa) has been prepared by Reichstein and co-workers[2] from 3-acetoxy-Δ5-etiocholenic acid by treating the acid chloride with diazomethane to form the diazoketone, followed by hydrolysis, Oppenauer oxidation of the remarkably stable diazoketone to 21-diazoprogesterone (III) and finally reaction with acetic acid. Attempts to prepare this adrenal cortical hormone from 3-keto-Δ4-etiocholenic acid (I), thus avoiding the selective hydrolysis and oxidation of the diazoketone, have been unsatisfactory because of difficulties in preparing the acid chloride.[3,4] The α,β-unsaturated ketone grouping seems to be sensitive to reagents, such as thionyl chloride, normally used to prepare the acid chlorides. Apparently because of these difficulties, Reich and Lardon[5] developed a six-step procedure for converting 3-keto-Δ4-steroids into the 3-acetoxy-Δ5-derivative. This procedure was employed by von Euw and Reichstein[6] in a partial synthesis of 11-dehydrocorticosterone which necessitated reoxidation to the 3-keto-Δ4 derivative at a later stage.

In connection with the synthesis of certain analogs of desoxycorticosterone and progesterone lacking ring C, we have developed an improved procedure for converting unsaturated keto acids of this type into the acid chlorides and diazoketones. This procedure has proved to be quite successful with 3-keto-Δ4-etiocholenic acid (I). The critical step is the formation of the acid chloride at low temperatures (below 15°) by reaction of the sodium salt of the acid with oxalyl chloride.[7,8] After reaction with diazomethane the diazoketone III was obtained in 81% over-all yield from the acid I. By adding the diazoketone to boiling acetic acid,[9] desoxycorticosterone acetate (IVa) was obtained in 73% yield. The over-all yield is considerably higher than those reported for the earlier syntheses.

These procedures should prove of value for similar reactions with the 11-oxygenated derivatives of I.



IVa, R = CH$_3$CO
IVb, R = H

Experimental[10]

21-Diazoprogesterone (III).—A solution of 506 mg. of 3-keto-Δ4-etiocholenic acid[11] in 19 ml. of 0.091 *N* sodium hydroxide was frozen and evaporated to dryness (lyophilized) under reduced pressure and the residue dried at 110° (0.1 mm.) for eight hours. After cooling, 10 ml. of dry, thiophene-free benzene and 3 drops of pyridine were added; the salt was scraped from the sides of the flask, mixed thoroughly and cooled in an ice-bath before adding 2 ml. of redistilled oxalyl chloride (b. p. 60–60.5°). There was an immediate evolution of gas which stopped after a few

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(1) National Research Council Predoctoral Fellow, 1946–1948.

(2) Reichstein and v. Euw, *Helv. Chim. Acta*, **23**, 136 (1940); see also Steiger and Reichstein, *ibid.*, **20**, 1164 (1937).

(3) Private communication from Dr. Lewis H. Sarett of Merck and Co., Inc., Rahway, New Jersey.

(4) Dr. Wayne Cole of The Glidden Co., Soya Products Division, Chicago, Ill., has informed us that they have obtained this acid chloride in impure form using thionyl chloride in cold ether containing a trace of pyridine.

(5) Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).

(6) v. Euw and Reichstein, *ibid.*, **29**, 1913 (1946).

(7) Adams and Ulich, THIS JOURNAL, **42**, 599 (1920).

(8) Dr. Thomas L. Johnson found this to be a superior method for preparing the acid chloride of a different type of keto acid; see Wilds and T. L. Johnson, THIS JOURNAL, **70**, 1166 (1948).

(9) Dr. Warren R. Biggerstaff has found that this procedure is superior to dissolving in acetic acid before heating.

(10) All melting points are corrected.

(11) We are indebted to the Research Dept. of The Glidden Co., Soya Products Division, for this material.