[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

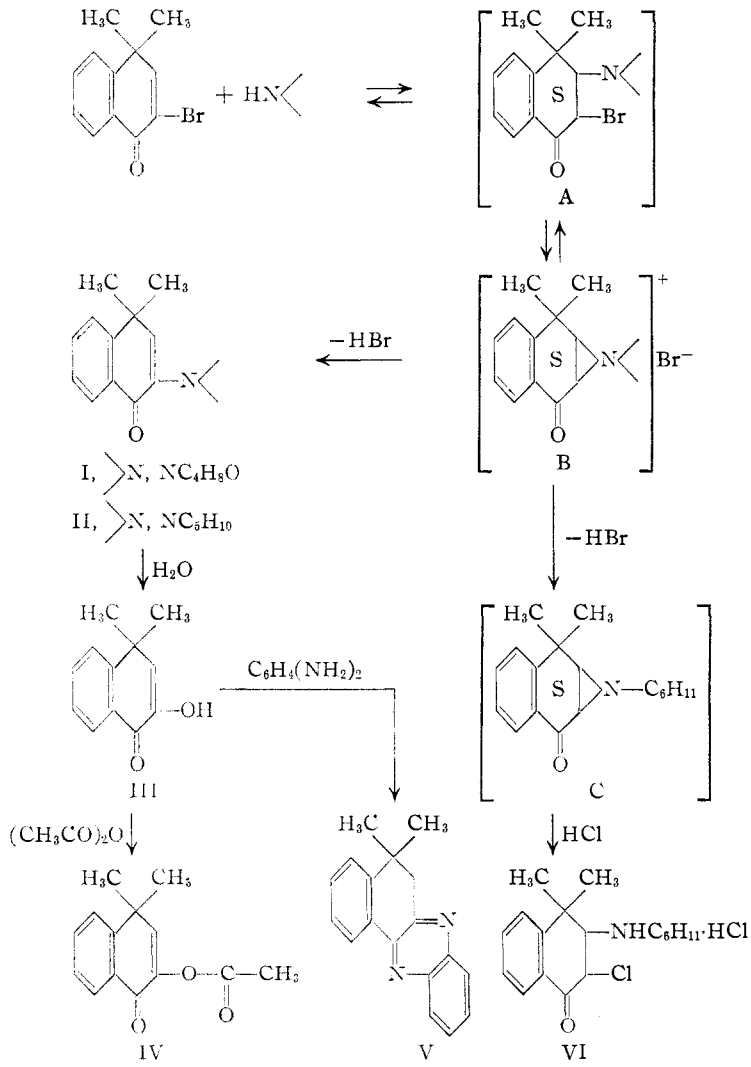
Endocyclic α,β-Unsaturated Ketones. III.[1] Reaction of 2-Bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene with Amines[2]

BY NORMAN H. CROMWELL, HAROLD H. EBY AND DAVID B. CAPPS

The purpose of this investigation was to extend our knowledge of the behavior of endocyclic α-bromo-α,β-unsaturated ketones with amines. 2-Bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene has been found to react with morpholine and piperidine to produce α-amino-α,β-unsaturated ketones. These reactions are contrasted with those previously reported in the perinaphthenone-7 series and for the open chain α-bromo-α,β-unsaturated ketones. It was surprising to find that the same α-amino-α,β-unsaturated ketones also resulted in low yields from the reactions of the amines with the corresponding saturated ketone, 2-bromo-4,4-dimethyltetralone-1. The unsaturated bromide reacted with cyclohexylamine to produce an ethylene imine ketone which was converted to the corresponding α-chloro-β-amino ketone hydrochloride.

In the previous paper[1] in this series the reactions of the endocyclic α-bromo-α,β-unsaturated ketone, 8-bromoperinaphthenone-7 with amines were discussed. Recently Arnold and his co-workers[3] have reported the synthesis of another interesting bromide of this type, namely, 2-bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene. This α-bromo-α,β- unsaturated ketone has been found to react readily at room temperature in the presence of an excess of morpholine or piperidine to give excellent yields of 2-morpholino (I) and 2-piperidino (II) 4,4-dimethyl-1-keto-1,4-dihydronaphthalene, respectively. With two or three equivalents of the amine to one equivalent of the bromide, the reactions were quite slow especially in b enzene. These results are somewhat in line with the previous findings with 8-bromoperinaphthenone-7[1] and vary sharply with the behavior of the open chain α-bromo-α,β-unsaturated ketones.[4]

With the present α-bromo-α,β-unsaturated ketone, no tendency to form β-amino-α,β-unsaturated ketones was observed. This is in contrast to the behavior of 8-bromoperinaphthenone-7 which produced both α-amino- and β-amino-α,β-unsaturated ketones in such reactions. The steric effect of the two methyl groups in the 4-position of the present α-bromo-α,β-unsaturated ketone promotes the rearrangement of the primary product, 2-bromo-3-amino-4,4-dimethyltetralone-1 (A), to the intermediate quaternary ethyleneimmonium salt (B). The salt (B) preferentially loses hydrogen bromide to form the α-amino ketones. The mechanisms of such reactions have been discussed in more detail previously.[1,4]



The structures of the amino ketones (I) and (II) were established by acid hydrolysis and from a study of their absorption spectra. The hydrolysis produced a new 1,2-diketone (III) which readily gave the expected acetoxy derivative (IV), and *o*-phenylenediamine produced the phenazine derivative (V). The maxima of the ultraviolet absorption spectra curves shown in Fig. 1 point to an α-amino-α,β-unsaturated ketone structure for (I) and (II). The low, broad band nearest the red end of the spectrum is the most characteristic feature of the spectra of such compounds.[1,5]

Cyclohexylamine reacted with 2-bromo-4,4-di-

(1) For paper II in this series, see Cromwell, Capps and Palmer, THIS JOURNAL, **73**, 1226 (1951).

(2) A part of this material is abstracted from the Ph.D. thesis of Harold H. Eby, Eastman Kodak Fellow, University of Nebraska, 1947–1948.

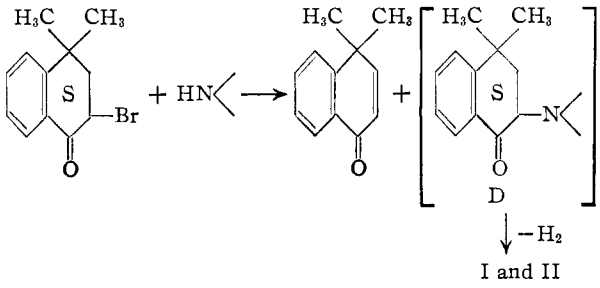
(3) Arnold, Buckley and Richter, THIS JOURNAL, **69**, 2322 (1947).

(4) For example the reactions of α-bromobenzalacetone and α-bromobenzalacetophenone with only one equivalent of morpholine or piperidine at 0° in ether solution is quite rapid; see Cromwell, *Chem. Revs.*, **38**, 83 (1946), and original papers referred to therein.

(5) Cromwell and Watson, *J. Org. Chem.*, **14**, 411 (1949).

methyl-1-keto-1,4-dihydronaphthalene apparently to produce an ethylene imine ketone (C) which was an oil and could not be identified as such. This product (C), however, reacted with hydrogen chloride in a manner characteristic of ethylene imine ketones[6] to produce 2-chloro-3-cyclohexylamino-4,4-dimethyltetralone-1-hydrochloride (VI) in an excellent yield. The structure of this product (VI) is indicated by its analysis and by the fact that it readily releases iodine from an acidified potassium iodide solution at 65°.[7]

It was surprising to find that the saturated ketone, 2-bromo-4,4-dimethyltetralone-1, reacted slowly with morpholine or piperidine under various conditions to produce the α-amino-α,β-unsaturated ketones (I) and (II) along with large amounts of the dehydrobrominated product, 4,4-dimethyl-1-keto-1,4-dihydronaphthalene. Although the dehydrobromination is not too unexpected[8] the formation of the α-amino-α,β-unsaturated ketones (I) and (II) instead of the expected α-amino saturated ketones (D) is unique. The dehydrogenation of the expected product (D), which must have taken place to produce (I) and (II), is unusual.



We were unable to isolate any of the saturated ketone, 4,4-dimethyltetralone-1. Had this substance been found in quantity it would have indicated that the dehydrobrominated product 4,4-dimethyl-1-keto-1,4-dihydronaphthalene had functioned as a dehydrogenation agent during the reaction.

Numerous attempts, using the usual conditions and such amines as piperidine, morpholine and tetrahydroisoquinoline, were made to add amines to 4,4-dimethyl-1-keto-1,4-dihydronaphthalene.[3] There was no evidence of any reaction having taken place. Such addition reactions go readily with various open chain α,β-unsaturated ketones[8] but have failed with another endocyclic α,β-unsaturated ketone, perinaphthenone-7.[1]

Experimental[9]

Reaction of 2-Bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene with Morpholine and Piperidine.—Four-gram samples of the unsaturated bromoketone[3] were dissolved in 14 ml. each of morpholine and piperidine at room temperature and allowed to stand for two days. The addition of 250 ml. of dry ether to the reaction mixtures precipitated near theoretical amounts of the starting amine hydrobromides. The excess starting amine was washed away with water and the ether solutions extracted with dilute hydrochloric acid. Nearly pure solid products resulted on neutralization of the acid solutions with sodium carbonate.

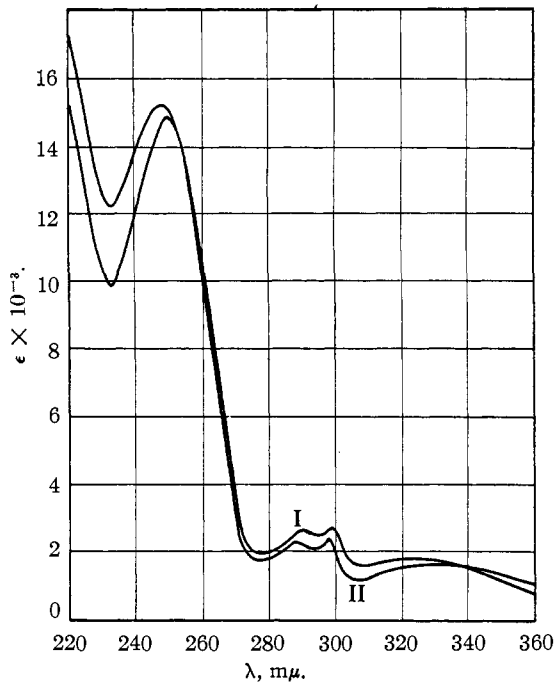


Fig. 1.—Ultraviolet absorption spectra of α-amino-α,β-unsaturated ketones (I) and (II) in heptane solutions.

The reaction with morpholine gave a 98% yield of colorless crystals (I); recrystallized from aqueous ethanol or petroleum ether, m.p. 124–125°.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.69; H, 7.44; N, 5.44. Found: C, 74.38; H, 7.04; N, 5.62.

The reaction with piperidine produced a 99% yield of pale yellow crystals (II); recrystallized as for (I), m.p. 69–70°.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.81; H, 8.36; N, 5.57.

A reaction between 2.9 g. (0.0115 mole) of the bromide and 3.1 ml. (0.0356 mole) of morpholine in 25 ml. of methanol after refluxing for eight hours gave only a 53% yield of (I). Using three molar equivalents of morpholine and piperidine, respectively, to one equivalent of the bromide in benzene solution, reflux times of 71 and 48 hours were required to obtain a 68.5% yield of (I) and a 67% yield of (II).

Acid Hydrolysis of (I) and (II) to 4,4-Dimethyl-1,2-diketotetralin (III).—A 2.15-g. sample of (I) and (II) were each heated on the steam-bath with 25 ml. of 30% sulfuric acid for 1.5 hours. The oil which separated was recrystallized from petroleum ether. Compound (I) gave a 95.5% yield while (II) gave an 80% yield of (III); colorless crystals, m.p. 70–71°.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.49; H, 6.23.

This diketone (III) gave muddy, violet-brown color with ferric chloride and readily dissolved in dilute sodium hydroxide to give a yellow solution. Acidification of the alkaline solution precipitated (III).

2-Acetoxy-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (IV).—A mixture of 0.30 g. of (III), 0.15 g. of sodium acetate and 3.0 ml. of acetic anhydride was heated on the steam-bath for two hours. An 81% yield of (IV), colorless crystals from aqueous ethanol, resulted, m.p. 66–67°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.88; H, 6.01.

2,2-Dimethyl-3,4-benzo-1,2-dihydrophenazine (V).—The diketone (III) reacted with *o*-phenylenediamine in 95% ethanol in five minutes to give a 71% yield of (V); colorless crystals from aqueous ethanol, m.p. 114.5–116°.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.21; N, 10.75. Found: C, 83.14; H, 6.64; N, 10.45.

(6) See, for example, Cromwell and Wankel, THIS JOURNAL, **71**, 711 (1949).

(7) Cromwell and Wankel, *ibid.*, **70**, 1320 (1948).

(8) (a) Cromwell, Wiles and Schroeder, *ibid.*, **64**, 2432 (1942); (b) Cromwell and Burch, *ibid.*, **66**, 872 (1944).

(9) Most of the micro analyses for carbon, hydrogen and nitrogen are by the Clark Microanalytical Laboratory, Urbana, Illinois, arranged for through the courtesy of the Smith, Kline and French Laboratories, Philadelphia, Pa.

Reaction of 2-Bromo-4,4-dimethyltetralone-1 with Morpholine and Piperidine.—The reaction of this saturated α-bromoketone[3] with morpholine was carried out under four different sets of conditions. (a) A 1.27-g. (0.005 mole) sample of bromide and 1.3 g. (0.015 mole) of morpholine were allowed to stand for 11 days in 13 ml. of methanol in the dark at room temperature. Only 27% of the bromide had reacted after this time. Based upon the amount of bromide reacting, a 55% yield of the α-amino-α,β-unsaturated ketone (I) resulted. The unreacted bromide was largely recovered. (b) Using the same amounts of reagents at 65° for 28 hours, 80% of the starting bromide reacted. An 18% yield of (I) and a 20% yield of 4,4-dimethyl 1-keto-1,4-dihydronaphthalene were isolated from the reaction mixture. (c) A 1.26-g. sample of the saturated α-bromoketone was allowed to stand in the ice-chest for 27 days in 4 ml. of morpholine. The calculated amount of morpholine hydrobromide was obtained along with a 22% yield of (I) and a 72% yield of 4,4-dimethyl-1-keto-1,4-dihydronaphthalene from the reaction mixture. (d) Experiment (c) was repeated except that the reaction mixture stood for three days at room temperature. The calculated amount of morpholine hydrobromide, as well as a 31% yield of (I) and a 20% yield 4,4-dimethyl-1-keto-1,4-dihydronaphthalene were isolated.

Using piperidine in place of morpholine, experiment (d) was repeated giving the theoretical yield of piperidine hydrobromide, a 35% yield of (II), and a 47% yield of 4,4-dimethyl-1-keto-1,4-dihydronaphthalene.

Reaction of 2-Bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene with Cyclohexylamine.—A mixture of 1.26 g. (0.005 mole) of the unsaturated α-bromoketone, 1.15 ml. (0.01 mole) of cyclohexylamine and 0.5 ml. of absolute ethanol was allowed to stand at room temperature in the dark for three days. The colorless oily product which could not be induced to crystallize was treated with dry hydrogen chloride gas in dry ether to produce 1.62 g. (95%) of a colorless solid; recrystallized from methanol and ether, m.p. 176–177° (VI).

Anal. Calcd. for $C_{18}H_{25}NOCl_2$: C, 63.16; H, 7.36; N, 4.09. Found: C, 63.12; H, 7.15; N, 3.96.

Using the technique described previously[7] the aminochloroketone hydrochloride (VI) reacted with acidic potassium iodide solution at 65° to release 32.8% of one equivalent of iodine in 15 minutes, 74.4% in 30 minutes and 85% in 45 minutes. Under these conditions 2-bromo-4,4-dimethyltetralone-1 released 100% in five minutes while 2-bromo-4,4-dimethyl-1-keto-1,4-dihydronaphthalene released no iodine in 30 minutes.

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[CONTRIBUTION FROM THE GIBBS CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Inhibition of Urease by Silver Ions

BY JOHN F. AMBROSE,[1a] G. B. KISTIAKOWSKY AND ANDREW G. KRIDL[1b]

The inhibition of urease by silver ions has been studied in a citrate buffer at *p*H 5.6 and 20°. The results indicate that the inhibition is produced by a reversible reaction of one silver ion with an active site in the enzyme molecule. Silver ions react also with inactive protein which was present in the repeatedly recrystallized samples of urease. The affinity for silver and the specific binding capacity of active urease and of the inactive protein were found to be the same, which suggests that the inactive protein was urease deactivated in the process of purification. Extrapolation to pure active enzyme shows that one mole of it is totally inhibited by reaction with three to four moles of silver ions. The significance of these findings is discussed.

Marked inhibitory effects of metal ions on the activity of urease have been reported.[2a,b,3] The action of silver ions has been the subject of a detailed study by Sumner and Myrback.[4] They concluded that seven ions suffice to inactivate one molecule of urease, from their measurements of the total concentration of silver ions required for half inactivation of the enzyme. The reversible nature of the inhibition as well as the uncertainty in the extrapolation of the half inactivation concentration to total inactivation was realized and emphasized by these writers.

Sumner and Myrback have shown also that the quantity of silver which is bound by the enzyme at higher concentrations of silver ions exceeds by at least a factor of ten the minimal amount necessary for total inhibition.

The inhibition of urease by *p*-chloromercuribenzoate has been studied by Hellerman and co-workers.[5] Their conclusions were not presented on a molecular basis, but using the data of Sumner[6] it may be calculated that twenty-two equivalents of the sulfhydryl reagent must be added per mole of enzyme before any effect is noted upon the enzymatic activity and twenty-two more equivalents are required before inhibition is complete.

This disparity between the numbers of ions or molecules of the inhibitor required for full inactivation of urease indicated that a more thorough examination of the inhibition by silver ions is desirable. Both of the previous studies evaluated only the total concentration of the inhibiting substance in the enzyme solutions. This left open the possibility that the reaction with the enzyme was not complete. In the present experiments both the total concentration of silver and the concentration of free silver ions were determined, making possible an application of the mass action law.

Experimental Details

Preparation of Pure Enzyme.—The crystalline enzyme was prepared from jackbean meal obtained from the Arlington Chemical Company, Yonkers, New York, batch numbers 490,428 and 490,208. The preparative procedure finally adopted involved repeated crystallizations from acetone–water mixture according to the general method developed by Sumner,[7] although in details some changes were made. In particular, no preservatives of any kind were introduced into the enzyme solutions.

(1) (a) Bell Telephone Laboratories, Murray Hill, N. J. (b) Monsanto Predoctoral Fellow, Shell Development Co., Emeryville, Calif.

(2) (a) J. B. Sumner, *Proc. Soc. Exptl. Biol. Med.*, **24**, 287 (1927); (b) J. B. Sumner and D. B. Hand, *J. Biol. Chem.*, **76**, 149 (1928).

(3) J. B. Sumner and G. F. Somers, "Chemistry and Methods of Enzymes," Academic Press, Inc., New York, N. Y., 1947, p. 157.

(4) J. B. Sumner and K. Myrback, *Z. physiol. Chem.*, **189**, 218 (1930).

(5) L. Hellerman, F. P. Chinard and V. R. Deitz, *J. Biol. Chem.*, **147**, 443 (1943).

(6) J. B. Sumner, N. Gralen and I. B. Eriksson-Quensel, *ibid.*, **125**, 37 (1943).

(7) See also A. L. Dounce, *ibid.*, **140**, 307 (1941).