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Elimination Reactions of α-Halogenated Ketones. I. Dehydrobromination of 2-Benzyl-2-bromo-4,4-dimethyl-1-tetralone

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2-Benzyl-2-bromo-4,4-dimethyl-1-tetralone (I) has been found to undergo dehydrobromination to produce mainly the endocyclic α,β-unsaturated ketone, 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (II) employing various bases, water, iodide ions or silver ions. It is suggested that the ionization of the axial α-bromine in I is assisted by steric facilitation and by the electrons of the axial C_β–H bond. The thermodynamic stability of the endocyclic α,β-unsaturated ketone II, relative to the isomeric exocyclic α,β-unsaturated ketone, 2-benzal-4,4-dimethyl-1-tetralone (III), is suggested by the rearrangement of the latter (III) to the former (II) on heating with palladium.

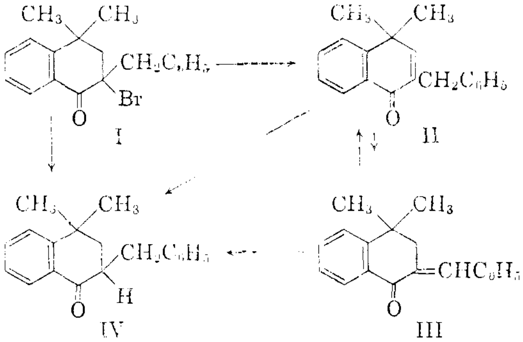
In a previous publication[1] the facile dehydrobromination of 2-benzyl-2-bromo-4,4-dimethyl-1-tetralone (I) with amines at room temperature was reported to produce mainly the endocyclic α,β-unsaturated ketone, 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (II), along with smaller amounts of the exocyclic isomer, 2-benzal-4,4-dimethyl-1-tetralone (III).

The present article reports on some product studies of the reactions of various other types of bases and of silver nitrate with this cyclic α-haloketone I. Indications are that, in general, the bromoketone I produces mainly, if not exclusively, the endocyclic α,β-unsaturated ketone II under ordinary, and some not so ordinary, conditions of dehydrobromination.

Both potassium hydroxide and sodium methoxide were found to react readily at room temperature with the bromoketone I to produce the endocyclic unsaturated ketone II in 67 and 82.5% yields, respectively (amounts isolated, not necessarily the total amounts actually present). Ammonia in ethanol was found to react much more slowly than the amines previously used[1]; *i.e.*, a 42% yield of ammonium bromide was produced only after six days at room temperature.

The bromoketone I undergoes a solvolysis reaction in aqueous dioxane to give a 20% yield of the unsaturated ketone II after nine hours of heating under reflux. Infrared studies with a residual oil indicated some 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone may also have been formed. Heating the bromoketone with dry spectrograde dioxane for the same length of time gave no apparent change.

Even iodide ion in dry acetone at reflux temperature is apparently capable of bringing about some dehydrobromination of I to produce the endocyclic α,β-unsaturated ketone II. This was indicated by an examination of the infrared spectrum of the product isolated after refluxing a sample of ketone I with a dry acetone solution of potassium iodide for four hours.[2] On the other hand, an acidified acetone–ethanol solution of potassium iodide reacted normally with the bromoketone I to give the saturated ketone, 2-benzyl-4,4-dimethyl-1-tetralone (IV) indentical with the ketone previously prepared[3] by the hydrogenation of the unsaturated ketones II and III.



Silver nitrate in ethanol was found to be a very effective reagent for dehydrobrominating ketone I to the unsaturated ketone II. No indication of the presence of the isomeric exocyclic α,β-unsaturated ketone III in the reaction mixture was observed although small amounts may have been present.

It was important to establish that the rearrangement of the unsaturated ketone III to II, or *vice versa*, was not to be expected under the conditions employed for the dehydrobromination studies. There was no indication of rearrangement of either II or III even after heating with sodium methoxide and methanol or sodium amide in benzene. Rearrangement of III to II also is not readily accomplished with acids.[3]

The exocyclic α,β-unsaturated ketone III was successfully rearranged to the endocyclic α,β-unsaturated isomer II by boiling with palladium-on-charcoal in ethylene glycol.[4] This result implies that the endocyclic isomer II is thermodynamically more stable with respect to III, and fits the empirical generalization of Brown.[5] It is also interesting to observe that the infrared carbonyl stretching vibration[3] for the endocyclic α,β-unsaturated ketone II at 1662 cm.$^{-1}$ implies that this isomer is more nearly coplanar and conjugation is more effective in polarizing the carbonyl group, and in stabilizing the molecule in the ground state than is the case for the exocyclic isomer III, which has its carbonyl band at 1673 cm.$^{-1}$.

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[1] A. Hassner and N. H. Cromwell, THIS JOURNAL, **80**, 901 (1958).

[2] A previous example of iodide ions bringing about a dehydrohalogenation with a cyclic α-halo ketone has been reported by G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *ibid.*, **72**, 4077 (1950), who studied the reaction of 2,4-dibromo-3-ketoallosteroids and found some elimination of hydrogen bromide took place which involved the axial 4-bromine atom.

[3] A. Hassner and N. H. Cromwell, *ibid.*, **80**, 893 (1958).

[4] N. J. Leonard and D. M. Locke, *ibid.*, **77**, 1852 (1955), found that 1-methyl-3,5-dibenzylidine-4-piperidones are readily isomerized by palladium in ethylene glycol to 1-methyl-3,5-dibenzyl-4-pyridones.

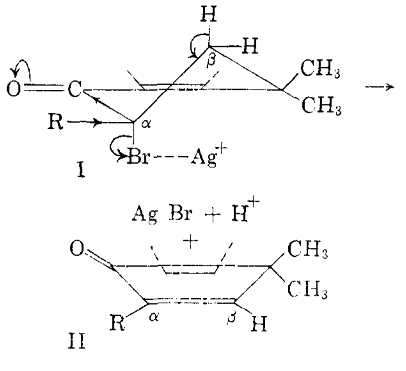
[5] H. C. Brown, J. H. Brewster and H. Schecter, *ibid.*, **76**, 469 (1954); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

Neither the bromoketone I nor the parent saturated ketone IV was found to react with 2,4-dinitrophenylhydrazine under the usual conditions. It seems probable that the normal carbonyl reactions with these ketones are somewhat sterically hindered. It has been reported that 2-bromo-1-tetralone forms the 2,4-dinitrophenylhydrazone[6] in the usual manner, but hydrogen bromide was not eliminated even under vigorous conditions with this reagent.

Discussion of the Dehydrobrominations.—It is quite apparent that endocyclic elimination of hydrogen bromide from the 2-benzyl-2-bromo-1-tetralones is the favored reaction under a rather wide variety of conditions. There are several factors associated with the stereochemical arrangements in these structures which suggest that this should be the case. First of all, as has been pointed out previously,[1] the opportunity for a cyclic *trans*-2,3-diaxial loss of hydrogen bromide to produce the endocyclic α,β-unsaturated ketone is undoubtedly an important facilitating factor, regardless of the mechanism of the reaction. The other factors are associated with the fact that the endocyclic α,β-unsaturated ketone II appears to be the thermodynamically favored isomer, relative to III. Saytzeff influences (conjugative effects) often control the orientation of elimination of HX from alkyl halides in both E1 and E2 reactions.[7] It is possible that the conjugation factors inherent in the incipient endocyclic α,β-unsaturated ketone system favor the formation of its transition state. The opportunity for greater planarity in the endocyclic system may outweigh the factor of the exocyclic phenyl group and its potential ability to conjugate with the incipient exo double bond.

In considering the relative stabilities of endo- and exo-cycloalkane double bond systems, Turner and Turner[8] have drawn attention to the importance of variations in non-bonded interactions in a given pair of isomers. In the α-haloketone I starting material there is the $CH_3{-}C_4{\sim}C_2{-}Br$ (pseudo axial–axial) interaction, while in the nearly planar[3] endocyclic α,β-unsaturated ketone II product the non-bonded interactions are expected to be less important. In the exocyclic α,β-unsaturated ketone III the methyl groups at C_4 and the hydrogens at C_3 are probably nearly eclipsed and the exo phenyl group may interact with the C_3-methylene group. This non-bonded interaction factor may give an important steric facilitation to both the elimination reaction with I and the isomerization reaction with III to produce the stable endocyclic α,β-unsaturated ketone II. The endocyclic isomer II appears to be both thermodynamically and kinetically favored in these reactions.

The silver-catalyzed elimination of hydrogen bromide from I is probably essentially a metal assisted E1 type reaction[9] but might receive some nucleophilic assistance from nucleophiles in the solution. The ease with which this silver reaction takes place at room temperature gives a clear indication of the considerable ionic character of the bromine in this tertiary alicyclic α-haloketone I.[10] In addition to the steric facilitation suggested above it is also possible that ionization of the bromine as Br^- may be assisted by the electron pair of the axial C_β-H bond.[11] It was found that 2-bromo-4,4-dimethyl-1-tetralone[12a] gives no reaction[12b] with alcoholic silver nitrate under the comparable conditions used with the tertiary alicyclic α-haloketone I. It has also been found that the second-order reaction of this secondary alicyclic α-haloketone with piperidine in benzene to produce a mixture of the elimination product 4,4 - dimethyl - 1 - keto - 1,4 - dihydronaphthalene and the substitution product 4,4-dimethyl-2-piperidino-1-tetralone is about one-eighth as fast as the comparable elimination reaction with ketone I.[1,13] The conformational analysis of this secondary alicyclic α-bromoketone has clearly shown that it possesses an equatorial bromine.[3] Thus C_β-H bond electron assistance for ionization of the α-bromine and a facile diaxial loss of hydrogen bromide in 2-bromo-4,4-dimethyl-1-tetralone is not expected to be as favored as in I. The factor of steric facilitation of ionization is probably also less with this secondary α-haloketone. A general discussion of some possible mechanisms for the base-catalyzed dehydrobrominations of I to II has been given previously.[1] Kinetic studies[13] of the dehydrobromination of ketone I and some related cyclic α-bromoketones by amines in benzene, ethanol or acetonitrile solutions show these reactions to be essentially second-order reactions. Related studies now being undertaken with the β,β-dideuterio analog of I are expected to help in deciding between various possible bimolecular



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[6] F. Ramirez and A. F. Kirby, THIS JOURNAL, **74**, 4331 (1952).

[7] C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 443.

[8] R. B. Turner and R. H. Turner, THIS JOURNAL, **80**, 1424 (1958).

[9] See ref. 7, pp. 357–358, for a discussion of silver assisted SN1 reactions.

[10] In general, primary acyclic α-haloketones react very slowly in ionization (*i.e.*, SN1) reactions and this slowness of reaction has been ascribed to the destabilizing effect of the positive end of the $C^+{=}O^-$ dipole on the stability of the carbonium ion; see E. L. Eliel in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, New York (1956), p. 103.

[11] So-called hydrogen participation or $C\beta$-H bond electron assistance in bond breaking at the α-carbon in cyclohexane derivatives is well discussed by D. J. Cram in the ref. cited in (10); see especially pages 270 and 327, and also see S. Winstein, *et al.*, THIS JOURNAL, **74**, 1127 (1952).

[12] (a) R. T. Arnold, J. S. Buckley and J. Richter, *ibid.*, **69**, 2322 (1947); (b) N. H. Cromwell and P. H. Hess, *ibid.*, **81**, 136 (1959).

[13] Unpublished work with Dr. Peter Foster, research associate, University of Nebraska, 1957–1958, to be reported in detail elsewhere.

mechanisms for these base-catalyzed elimination reactions.

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Experimental

The dehydrobromination studies were carried out with various reagents and pure 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone (I), m.p. 101–102°, prepared by the previously described method.[3]

Potassium Hydroxide in Ethanol.—A 5.0-g. (0.0146 mole) sample of the bromoketone I was dissolved in 800 ml. of abs. ethanol and 4.1 g. (0.73 mole) of potassium hydroxide in 150 ml. of abs. alcohol added at room temperature. After standing in the dark at 25–28° for three days, neutralization with acetic acid and concentration of the reaction mixture produced 2.55 g. (67% yield) of pure 2-benzyl-4,4-dimethyl-1-keto-1,4-dihydronaphthalene (II), m.p. 113–114°.[3]

Sodium Methoxide and Methanol.—A 5.0-g. (0.0146 mole) amount of the bromoketone I was added to a solution of 8.6 g. (0.073 mole) of sodium methoxide in 1.5 l. of abs. methanol. After standing at room temperature in the dark for three days the solution was neutralized with acetic acid and concentrated to produce 3.15 g. (82.5% yield) of the pure endocyclic unsaturated ketone II,[3] m.p. 113–114°. No evidence for the presence of 2-benzal-4,4-dimethyl-1-tetralone (III) was found.

Ammonia in Ethanol.—A 0.5-g. (0.00146 mole) sample of the bromoketone I was dissolved in 75 ml. of abs. ethanol which was then saturated with anhydrous ammonia at room temperature. This reaction mixture was allowed to stand at room temperature for six days and concentrated to produce 0.06 g. (42% yield) of ammonium bromide and 0.05 g. (13% yield) of the unsaturated ketone II. Unchanged bromoketone I (0.17 g.) was also recovered.

Aqueous Dioxane.—A 2.0-g. sample of bromoketone I was refluxed for 9 hours in 300 ml. of 50% aqueous dioxane. Evaporation of the solvent and crystallization of the residual oil from methanol gave 0.29 g. (19% yield, not maximum obtainable) of the pure endocyclic α,β-unsaturated ketone II, m.p. 112–113°. The residual oil had an infrared spectrum in CCl$_4$ indicating the possible presence of the starting ketone I, the unsaturated ketone II and a hydroxyketone, possibly 2-hydroxy-2-benzyl-4,4-dimethyl-1-tetralone; γOH, 3600 cm.$^{-1}$/20; γassoc. OH, 3200 cm.$^{-1}$/45; γC=O, 1730 cm.$^{-1}$/78, 1700 cm.$^{-1}$/78, 1690 cm.$^{-1}$/78, 1660 cm.$^{-1}$/64; γAr, 1600 cm.$^{-1}$/49.

Heating a 1.0-g. sample of the bromoketone I with 50 ml. of dry spectrograde dioxane for 9 hours at reflux temperature gave no appreciable change.

Silver Nitrate in Ethanol.—A 0.69-g. (0.002 mole) sample of the bromo-ketone I and 0.35 g. (0.002 mole) of silver nitrate were dissolved in 30 ml. of abs. ethanol and 2 ml. of water. Silver bromide formation was observed within two minutes of mixing at room temperature. After standing at room temperature in the dark for 3.5 days, 0.336 g. (89% yield) of silver bromide was removed by filtration. Concentration of the filtrate and purification of the residue by recrystallization from methanol produced 0.46 g. (90% yield) of the pure unsaturated ketone II, m.p. 113–114°.

Potassium Iodide in Dry Acetone.—A 0.97-g. (0.0058 mole) sample of finely ground potassium iodide and 0.9 g. (0.00262 mole) of the bromoketone I were refluxed in 100 ml. of dry acetone for 4 hours in the absence of light. The red colored solution was evaporated under vacuum and the residue extracted with ether and the ether solution washed with sodium thiosulfate and water. Concentration of the ether solution produced 0.55 g. of a pale yellow crystalline material, m.p. 65–78°, which when recrystallized once from methanol, m.p. 73–106°, still gave a positive Beilstein test for halogen. The infrared spectrum, 15 mg./ml. CCl$_4$ in matched 1.0-mm. cells, showed two well resolved carbonyl bands, γC=O, sat. ketone, 1685 cm.$^{-1}$/87; γC=O, endocyclic unsat. ketone, 1658 cm.$^{-1}$/94.

Heating the bromoketone I with dry acetone alone for 7 hours produced no change.

Potassium Iodide in Acidified Acetone–Ethanol.—A mixture of a 0.5-g. (0.00146 mole) sample of the bromoketone I, 0.48 g. (0.00292 mole) of potassium iodide, 0.24 ml. (0.00146 mole of HCl) of 6 *N* hydrochloric acid, 16 ml. of dry acetone and 15 ml. of abs. ethanol was allowed to stand at room temperature. The red color of iodine developed immediately upon mixing the reagents. Aqueous sodium thiosulfate was added after 12 hours standing and the solution extracted with ether. From the ether solution was obtained 0.18 g. (46.8% yield) of 2-benzyl-4,4-dimethyl-1-tetralone (IV), m.p. 60–62°.[3]

Equilibration Studies with Unsaturated Ketones II and III. (a) With Sodium Methoxide in Methanol.—When either II or III[3] was allowed to stand at room temperature in the dark for 24 hours or refluxed for 4 hours with one molar equiv. of sodium methoxide in methanol, 90% of the starting ketones was recovered.

(b) **Sodium Amide in Benzene.**—When samples of either unsaturated ketone II or III were heated under reflux with finely ground sodium amide in benzene for 3.5 hours the solutions developed a red color. The cooled solutions were treated with methanol until the evolution of ammonia ceased. Evaporation of the solvent and recrystallization of the residues returned only the starting ketones in each case, 68% of II and 40% of III.

(c) **Acetic Acid and HBr.**—After heating a sample of the exocyclic unsaturated ketone II for 65 hours at 55–70° with a glacial acetic acid solution saturated with HBr gas only impure starting material was recovered as indicated by, m.p. 108–110°, mixed m.p. with ketone III, 107–111°, and the infrared spectrum, γC=O in CCl$_4$, 1673 cm.$^{-1}$.[3]

(d) **Rearrangement of Ketone III to Ketone II with Palladium.**—A 1.0-g. sample of the exocyclic unsaturated ketone III[3] was boiled with 0.1 g. of 10% palladium-on-charcoal in 10 ml. of ethylene glycol for 40 minutes. The catalyst was removed by filtration and the reaction mixture poured into water to precipitate 0.95 g. of colorless solid, m.p. 81–108°. The infrared spectrum of this material in CCl$_4$ showed two unsaturated ketone bands, $\gamma_{\text{exo C=O}}$, 1673 cm.$^{-1}$/50; $\gamma_{\text{endo C=O}}$, 1662 cm.$^{-1}$/98. The ultraviolet spectrum for this mixed product was an exact super-position at all points of a 67.5% endocyclic unsaturated ketone II, 32.5% exocyclic ketone III mixture: λ 253, 290(sh) 320(sh) mμ (ϵ 9,430, 6,810, 5,150) in 95% ethanol.

Attempted Reactions with 2,4-Dinitrophenylhydrazine.—Neither the bromo-ketone I nor the saturated ketone IV (0.5 g., 0.00146 mole) reacted on standing for one week with 0.58 g. (0.00292 mole) of 2,4-dinitrophenylhydrazine in solutions of 60 ml. of ethanol and 6 ml. of water containing 4 ml. of concd. hydrochloric acid. The recovery of starting material was 72% in the case of the bromoketone I and 88% for the saturated ketone IV.

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