gave a colorless product, IX, wt. 1.01 g. (79% yield), m.p. 90–91°, λ_{max} (benzoyl band) 242 mμ (ε 15,600); γbenzoyl C=O, 1690 cm.$^{-1}$/86; γamide C=O, 1635 cm.$^{-1}$/96; γphenyl, 1603 cm.$^{-1}$/48.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.38; H, 7.14; N, 4.23.

(b) **With Morpholine.**—An experiment employing morpholine in place of piperidine, as described in (a), produced 0.4 g. of X, m.p. 132–133°, λ_{max} (benzoyl band) 240 mμ (ε 15,500); γbenzoyl C=O, 1690 cm.$^{-1}$/86; γamide C=O, 1643 cm.$^{-1}$/98; γAr, 1604 cm.$^{-1}$/52.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.37; H, 6.57; N, 4.10.

Both IX and X were soluble in ether, insoluble in water or dil. hydrochloric acid, and neither gave a color change with alcoholic ferric chloride solution.

LINCOLN, NEBR.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Elimination Reactions of α-Halogenated Ketones. III.[1] Dehydrobromination of 4-Biphenylyl 1-Bromocyclohexyl Ketone

BY NORMAN H. CROMWELL AND PATRICK H. HESS

RECEIVED MAY 14, 1959

The α-bromoketone, 4-biphenylyl 1-bromocyclohexyl ketone (II), was synthesized and its reactivity with secondary and tertiary amines investigated. These reactions gave only dehydrobromination with no substitution or rearrangement products being found. On the other hand, silver nitrate was found to react with II in the expected manner to give some of the Faworskii rearrangement product, 1-(4-biphenylyl)-cyclohexanecarboxylic acid, along with larger amounts of the α,β-unsaturated ketone, 4-biphenylyl 1-cyclohexenyl ketone (III). A preliminary discussion of possible factors including Cβ-H participation, responsible for the facile elimination of hydrogen bromide from this tertiary alicyclic α-haloketone is given.

Previous investigations[1,2] have shown that the alicyclic α-bromoketones 2-bromo-2-benzyl-1-tetralones[2] and 2-bromo-2-benzyl-1-indanones[1] are readily dehydrobrominated by amines and various other reagents such as alcoholic sodium hydroxide, sodium methoxide, silver nitrate, etc., to give good yields of α,β-unsaturated ketones.

Several other groups of investigators[3] have reported on studies of the reactions of various types of tertiary α-haloketones with strong bases and with alcoholic silver nitrate. These reactions have been found to lead to a variety of products including epoxy ethers,[3d] substitution products,[3e] α,β-unsaturated ketones[3a,3e] and Faworskii rearrangement products (*e.g.*, carboxylic acids),[3a–d] depending on the structure of the α-haloketone and the conditions of the reaction.

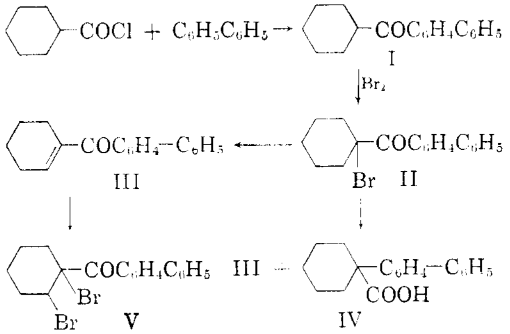
Stevens and Farkas[3e] reported that α-chlorocyclohexyl phenyl ketone reacts with alcoholic silver nitrate to produce an 18% yield of 1-phenylcyclohexanecarboxylic acid and also obtained evidence for the presence of a 68% yield of 1-cyclohexenyl phenyl ketone.

Our current major interest in the reactions of such α-haloketones is concerned with the structural factors and conditions which favor the elimination reaction to produce α,β-unsaturated ketones. We hope to be able to establish the mechanisms of these elimination reactions.

To learn whether amines would give the elimination, substitution or rearrangement reactions with tertiary α-haloketones of the α-halocyclohexyl aryl ketone type, as studied by Stevens and Farkas,[3d–e] we synthesized 4-biphenylyl cyclohexyl ketone (I) by a Friedel–Crafts synthesis with cyclohexanecarbonyl chloride and biphenyl and then brominated it to produce 4-biphenylyl 1-bromocyclohexyl ketone (II).

The practical dehydrobromination of II to produce the α,β-unsaturated ketone, 4-biphenylyl 1-cyclohexenyl ketone (III), was readily accomplished by heating with 4-picoline at 80–90° for two hours. At room temperature 4-picoline gave no measurable amount of reaction with II in four hours. The stronger secondary amines, morpholine and piperidine, also produced the unsaturated ketone III in good yields even at a room temperature, with no trace of a substitution, rearrangement or addition product being found.

A comparative product study with 4-picoline, 3-picoline and γ-collidine at about 80° showed no appreciable difference for the first two bases in their ability to eliminate hydrogen bromide from this alicyclic tertiary α-haloketone II; both gave a 93% reaction in 2.25 hours. Under these conditions the sterically hindered γ-collidine gave only an 8.5% reaction.



It appears that the elimination of hydrogen bromide from the cyclic α-bromoketone II is sensitive to both the basic strength and the steric

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[1] For the previous paper in this series see, N. H. Cromwell and R. P. Ayer, THIS JOURNAL, **81**, 133 (1959).

[2] (a) A. Hassner and N. H. Cromwell, *ibid.*, **80**, 901 (1958); (b) N. H. Cromwell, R. P. Ayer and P. W. Foster, *ibid.*, **81**, 130 (1959).

[3] (a) B. Tchoubar and O. Sackur, *Compt. rend.*, **205**, 1020 (1939); (b) A. C. Cope and E. S. Graham, THIS JOURNAL, **73**, 4702 (1951); (c) R. B. Loftfield, *ibid.*, **73**, 4707 (1951); (d) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952); (e) **74**, 5352 (1952).

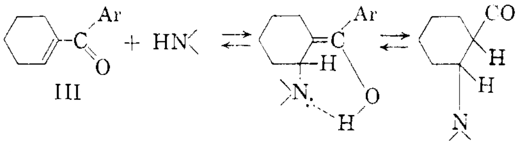
requirements of the amine.[4] Preliminary kinetic studies of the elimination reaction of the α-bromoketone II with piperidine in benzene solution indicate the reaction to be essentially second order.[5] Various possible mechanisms for the dehydrobromination of 2-bromo-1-tetralones, which are also second-order reactions, have been discussed in previous publications.[2] Whether or not these second-order base-catalyzed eliminations are E2 reactions or involve some other type of transition state, as previously considered,[2] may best be decided by kinetic studies with β-deuterated analogs.

In 1,1-disubstituted cyclohexanes, the more bulky group would be expected to occupy an equatorial position to reduce the non-bonded interactions to a minimum.[6] It is probable that the *p*-phenylbenzoyl grouping is larger than bromine in this system and in any case it seems reasonable to assume that the conformation with an axial bromine would become readily available under the conditions of dehydrobromination. Consequently a *trans* diaxial loss of hydrogen bromide is available to the α-haloketone II, irrespective of the other details of the reaction mechanism.[2b]

The α-bromoketone II reacted readily at 80° with alcoholic silver nitrate to give the unsaturated ketone III (68.4% yield) and the Faworskii acid, 1-(4-biphenylyl)-cyclohexanecarboxylic acid (IV) (18.7% yield). This result compares very favorably with the results of Stevens and Farkas[3e] for the reaction of 1-bromocyclohexyl phenyl ketone. These investigators established[3d] that an epoxyether is not an intermediate in the rearrangement. They suggested a mechanism similar to that proposed by Cope and Graham,[3b] which involves initial hydration of the carbonyl group followed by a pinacol type of rearrangement. In our view the elimination reaction is essentially a metal-assisted E1[2b] type with or without concomitant hydration of the carbonyl group. The ionization of the α-bromine as Br$^-$ may be somewhat assisted by the electron pairs of the axial C$_\beta$–H and C$_{\beta_1}$–H bonds (H-participation without migration)[7] in this tertiary α-haloketone. The shift of the phenyl group to the α-carbon to form the acid IV competes, but not too successfully, with *trans* axial hydrogen participation and loss of a proton to give the olefin III.

A comparison of the relative rates of reaction of several alicyclic α-bromoketones with alcoholic silver nitrate at room temperature as measured by the amount of silver bromide formed in four hours showed the order of decreasing rate of reaction to be 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone[8] > α-bromoketone II > 2-bromo-2-benzylindanone-1[1] > 2-bromo-4,4-dimethyl-1-tetralone.[9] Factors expected to influence the rates of elimination with the α-bromotetralones[2b] and the α-bromoindanones[1] have been discussed previously. Further comparable studies with acyclic analogs must be completed before more can be said concerning the differences in the nature of the driving forces for ionization of the bromine which operate in these various series of α-haloketones.

Bromine was added to the α,β-unsaturated ketone III to give 4-biphenylyl 1,2-dibromocyclohexyl ketone (V). Apparently secondary amines, morpholine and piperidine, which caused the elimination of hydrogen bromide from the α-haloketone II, do not add readily to the α,β-unsaturated ketone III. The following equilibrium appears to be unfavorable to the addition product and the reversible reaction to reform the starting materials should be quite facile with this α,β-unsaturated ketone III in its S-*cis* conformation.[8]



Discussion of Absorption Spectra.—The 4-biphenylyl cyclohexyl ketone I has its infrared carbonyl stretching band at 1680 cm.$^{-1}$ and an ultraviolet maximum at 283 mμ (ϵ 24,200) as compared with the values (γC=O[10] 1686 cm.$^{-1}$; $\lambda_{\max}$ 243 mμ (ϵ 11,700)[11]) for phenyl cyclohexyl ketone. Introduction of a bromine atom into the α-position of I to give II shifted the infrared carbonyl band and the ultraviolet maximum to slightly lower frequencies (γC=O 1673 cm.$^{-1}$; λ 287mμ (ϵ 19,400)). Introduction of the double bond into the cyclohexane ring of I to produce III shifted the carbonyl band in the infrared to a considerably lower frequency (γC=O 1648 cm.$^{-1}$) which compares favorably with the value for phenyl cyclohexenyl ketone[12] (γC=O 1642 cm.$^{-1}$). The ultraviolet maximum for the α,β-unsaturated ketone III at λ 281 mμ (ϵ 20,800) seems somewhat anomalous since this represents a hypsochromic shift of 2 mμ when compared with the absorption maximum of the parent saturated ketone I. This seems to be a phenomenon of some cross conjugated systems.[13]

Acknowledgment.—This work was supported in part by grant No. CY-2931, National Cancer Institute, U. S. Public Health Service.

Experimental[14]

4-Biphenylyl Cyclohexyl Ketone (I).—A 21.1-g. (0.144 mole) sample of cyclohexanecarbonyl chloride[15] and 23.7 g.

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[4] Using the series of bases, pyridine, 2-picoline and 2,6-lutedine, T. D. Nevitt and G. S. Hammond, This Journal, **76**, 4124 (1954), found that *trans*-1,2-dimethylcyclohexyl bromide showed a decreased rate of elimination of hydrogen bromide on standing at room temperature, but the kinetics of these reactions were not reported.

[5] Unpublished work with P. H. Hess to be reported elsewhere.

[6] M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 18.

[7] See ref. 6, pp. 269–270.

[8] A. Hassner and N. H. Cromwell, This Journal, **80**, 893 (1958).

[9] R. T. Arnold, J. S. Buckley and J. Richter, *ibid.*, **69**, 2324 (1947).

[10] N. Fuson, M. L. Josien and E. M. Shelton, *ibid.*, **76**, 2526 (1954).

[11] R. P. Mariella and R. R. Raube, *ibid.*, **74**, 521 (1952).

[12] H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

[13] For example, see R. J. Mohrbacher and N. H. Cromwell, This Journal, **79**, 401 (1957), who report for 4-phenylacrylophenone, $\gamma_{C=O}$ 1666 cm.$^{-1}$ and λ 291 mμ (ϵ 22,200); for 4-phenylcrotonophenone, $\gamma_{C=O}$ 1671 cm.$^{-1}$ and λ 287 mμ (ϵ 23,900).

[14] Melting points were read with a calibrated thermometer. Ultraviolet absorption spectra were determined with a Cary model 11-MS recording spectrophotometer using reagent grade methanol solutions. Infrared spectra were measured with a Perkin-Elmer model 21 double beam recording instrument employing sodium chloride optics and matched sodium chloride cells with carbon tetrachloride solutions.

[15] (a) G. Darzens and H. Rost, *Compt. rend.*, **153**, 773 (1911);

(0.154 mole) of biphenyl were dissolved in 250 ml. of carbon disulfide, cooled and treated with 21.4 g. (0.160 mole) of anhyd. aluminum chloride over a 30-minute period employing efficient stirring. Working up the reaction mixture produced 34.9 g. (91% yield) of the ketone I, m.p. 85–86°, recrystallized from ethanol; λ_{max} 283 mμ (ϵ 24,200), γC=O 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.03; H, 7.61.

This ketone I gave a 2,4-dinitrophenylhydrazone, m.p. 176–177°.

4-Biphenylyl 1-Bromocylohexyl Ketone (II).—A 45.9-g. (0.174 mole) sample of ketone I was heated between 80 and 85° with 28.0 g. (0.175 mole) of bromine in 350 ml. of gl. acetic acid for 30 minutes. The reaction mixture was cooled and poured over ice to precipitate the bromoketone II, 51.6 g. (86.5% yield), m.p. 109–110°, recrystallized from ethanol–benzene solution; λ_{max} 287 mμ (ϵ 19,400), γ C=O 1674 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{19}BrO$: C, 66.48; H, 5.58; Br, 23.28. Found: C, 66.33; H, 5.66; Br, 23.42.

4-Biphenylyl 1-Cycohexenyl Ketone (III).—A 20.0-g. (0.0582 mole) sample of the bromoketone II was heated on the steam-bath for two hours with 50 ml. of 4-picoline. The reaction mixture was cooled and 50 ml. of dry ether added to precipitate 9.88 g. (97.8 % yield) of 4-picoline hydrobromide. The excess 4-picoline was removed from the filtrate by water and dil. hydrochloric acid washing. Evaporation of the ether gave the unsaturated ketone III, 14.74 g. (96.5% yield), m.p. 70–71°, recrystallized from ethanol; λ_{max} 281 mμ (ϵ 20,800), γ C=O 1647 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{18}O$:C, 86.98; H, 6.91. Found: C, 86.76; H, 6.88.

Comparative Rates of Reaction of Bromoketone II with Pyridine Derivatives.—One-gram samples of II were dissolved in 10-ml. amounts of the amines (4-picoline, 3-picoline, γ-collidine) and heated in closed flasks at steam-bath temperature for 1.75 hours. The excess amine was then removed by vacuum distillation at steam-bath temperature over a period of 30 minutes. A 20-ml. portion of dry ether was added to each flask, the precipitated amine hydrobromide collected and weighed; 3-picoline hydrobromide, 0.48 g. (93.0% reaction); 4-picoline hydrobromide, 0.47 g. (93.0% reaction); γ-collidine hydrobromide 0.05 g. (8.51% reaction).

Reaction of Bromoketone II with Piperidine and Morpholine.—A 5.0-g. (0.0147 mole) sample of II was allowed to stand at room temperature for 72 hours with 2.75 g. (0.0323 mole) of piperidine in 20 ml. of benzene. From this reaction mixture was isolated 1.38 g. (56.6% yield) of piperidine hydrobromide and 2.18 g. (50.3% yield) of the unsaturated ketone III, m.p. 69–71°. No amino derivatives or acidic products were formed in isolable quantities in this reaction.

When 8.5 g. (0.0248 mole) of II was heated for two hours on the steam-bath with 5.9 g. (0.0693 mole) of piperidine in 20 ml. of benzene, a 97.3% yield of piperidine hydrobromide and a 71% yield of the unsaturated ketone III were isolated. After standing in 40 ml. of morpholine at room temperature for 22 hours, 5.0 g. (0.0147 mole) of II produced a 99% yield of morpholine hydrobromide and a 61% yield of the unsaturated ketone III. No hydrochloric acid or sodium hydroxide soluble materials were formed in this reaction.

Reaction of II with Silver Nitrate in Ethanol.—A 5.0-g. (0.0147 mole) sample of II was refluxed with 2.5 g. (0.0147 mole) of silver nitrate in 160 ml. of ethanol and 40 ml. of water for four hours in the absence of light. To the cooled reaction mixture was added 5 ml. of 6 *N* nitric acid and the silver bromide removed by filtration; 2.6 g. (95.7% yield). Dilution of the filtrate with water precipitated a product which was separated into a neutral and an acidic fraction by extraction with sodium hydroxide solution. The neutral fraction gave 2.61 g. (68.4% yield) of the unsaturated ketone III, m.p. 69–71°, while the acid fraction produced 1-(4-biphenylyl)-cyclohexane carboxylic acid (IV), 0.76 g. (18.7% yield), m.p. 177–178°, recrystallized from benzene.

Anal. Calcd. for $C_{19}H_{20}O_2$: mol. wt., 280.35; C, 81.39; H, 7.19. Found for IV: neut. equiv., 283; C, 81.05; H, 7.17.

4-Biphenylyl 1,2-Dibromocyclohexyl Ketone (V).—From 3.0-g. (0.0114 mole) of II and 1.83 g. (0.0114 mole) of bromine in 30 ml. of carbon tetrachloride was obtained 4.38 g. (91% yield) of the dibromoketone V, m.p. 137–138°, recrystallized from 60–70° b.p. petroleum ether; λ_{max} 289 mμ (ϵ 19,600), γ C=O 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{18}Br_2O$: C, 54.05; H, 4.30; Br, 37.86. Found: C, 54.02; H, 4.33; Br, 37.60.

Relative Rates of Reaction of Alicyclic α-Bromoketones with Alcoholic Silver Nitrate at 30°.—Solutions were prepared by dissolving 0.00200 molar amounts of the α-bromoketones in 95% ethanol in 100-ml. volumetric flasks. A 25-ml. aliquot sample of the ethanol solution of the α-bromoketone was mixed with 25 ml. of ethanol and 10 ml. of the alcoholic silver nitrate, which contained 0.00600 mole of $AgNO_3$, in glass stoppered flasks. The solutions were shaken at a constant temperature of 29.7° in the absence of light for four hours. To the reaction mixtures were added 3 ml. of 6 *N* nitric acid and the solutions filtered through weighed Gooch crucibles. The precipitates were washed with benzene and then very dil. nitric acid, dried at 80° for two hours and the crucibles weighed. Duplicate runs were made in each case. Under these conditions the amounts of silver bromide formed indicated a 6.32 ± 0.01% reaction for the bromoketone II, a 1.37 ± 0.07% reaction for 2-bromo-2-benzylindonone-1,[1] a 45.33 ± 0.68% reaction for 2-bromo-2-benzyl-4,4-dimethyl-1-tetralone[8] and no measurable reaction for 2-bromo-4,4-dimethyl-1-tetralone.[9]

LINCOLN, NEBR.

(b) H. E. Baumgarten, F. A. Bower and T. T. Okamoto, THIS JOURNAL, **79**, 3148 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

Mechanisms of Elimination Reactions. IV. Deuterium Isotope Effects in E2 Reactions of Some 2-Phenylethyl Derivatives[1]

BY WILLIAM H. SAUNDERS, JR., AND DAVID H. EDISON[2]

RECEIVED JUNE 8, 1959

Kinetic deuterium isotope effects have been determined for E2 reactions of the compounds $C_6H_5CD_2CH_2X$. The values of k_H/k_D with sodium ethoxide in ethanol are in the order Br > OTs > SMe_2 > NMe_3. A change of base and medium to potassium *t*-butoxide in *t*-butyl alcohol increases the isotope effect with the bromide and the tosylate. Experiments with sodium hydroxide in water on the onium salts show no clear pattern. The relation of the present work to other recent studies on the nature of the transition state in E2 reactions is discussed. Some rate constants given earlier[1] for 2-(*p*-acetylphenyl)-ethyldimethylsulfonium bromide are shown to be in error. An interesting case of anomalous orientation in a Friedel-Crafts acylation is reported.

The E2 reaction usually has been considered a completely synchronous process. Although this appears true in the sense that no intermediates can be detected, evidence has accumulated that the ratio of the extent of C–H and C–X bond stretch-

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[1] Paper III in this series: W. H. Saunders, Jr., C. B. Gibbons and R. A. Williams, THIS JOURNAL, **80**, 4099 (1958).

[2] Du Pont Fellow 1957–1958.