Relative Yields of Cyclohexyl Acetate.—Two parallel reactions were run under the conditions described for run IV except that the hydroquinone was omitted from one of the reaction mixtures. The concentration of acetyl peroxide was followed by infrared spectroscopy on aliquots withdrawn at frequent intervals, observing the carbonyl absorptions at 1800 and 1825 cm.$^{-1}$. A plot of these concentrations *vs.* time gave a curve for each compound. The areas under these curves were, after 19 hours, found to be in the ratio of 5:1, the smaller area being for the reaction with added hydroquinone. After 19 hours, 0.005-ml. aliquots of each reaction mixture were introduced into a Carbowax g.l.p.c. column at 130°. Careful reproduction of the conditions of introduction of sample, etc., gave plots from which the relative concentrations of cyclohexyl acetate could be determined for the two reaction mixtures. The ratio of the areas of the peaks corresponding to the ester (retention time 13 min. at a flow rate of 2.58 l. of helium per hour) was 8:1, the smaller concentration being evidenced for the run with added hydroquinone.

Acknowledgment.—This work was sponsored by the Office of Ordnance Research, U. S. Army.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA, LINCOLN 8, NEBR.]

Elimination Reactions of α-Halogenated Ketones. IV.[1] Elimination–Substitution Reactions with α-Bromo-*p*-phenylisobutyrophenone

BY NORMAN H. CROMWELL AND PATRICK H. HESS

RECEIVED SEPTEMBER 23, 1960

The acyclic tertiary α-haloketone, α-bromo-*p*-phenylisobutyrophenone, has been found to react with morpholine to give the substitution product, α-morpholino-*p*-phenylisobutyrophenone, and with a stronger base with similar steric demands, piperidine, to produce the elimination–addition product, β-piperidino-*p*-phenylisobutyrophenone. The α-amino- and β-amino-*p*-phenylisobutyrophenones were synthesized for comparison purposes by independent means. Silver nitrate was shown to react with the α-bromoketone II to give mainly the Favorski rearrangement acid, 2-(4-biphenylyl)-2-methylpropanoic acid. A discussion of the reactivity of II compared with that of the previously studied[1] alicyclic α-haloketone, 4-biphenylyl 1-bromocyclohexyl ketone, is given.

Introduction.—In general α-halogenated ketones of the primary and secondary type (RCHXCOR', R = H, alkyl or aliphatic-aromatic or aromatic) are expected to give substitution rather than elimination reactions with various nucleophilic reagents under ordinary conditions. Although these substitution reactions have been found almost certainly to be bimolecular reactions, showing second-order kinetics,[2] there has been no general agreement as to the nature and geometry of their transition states.[3]

Several groups of investigators have studied the reactions of tertiary α-haloketones ($R_2CBrCOR$) with bases and reported a variety of products[4] including α,β-unsaturated ketones.

Previous investigations in this Laboratory have shown that tertiary α-haloketones of an alicyclic type (*e.g.*, 2-bromo-2-benzyl-1-tetralones[5] and 2-bromo-2-benzyl-1-indanones[6]) are readily dehydrobrominated with amines or various other reagents, such as alcoholic sodium methoxide, sodium hydroxide, silver nitrate, etc., to give excellent yields of α,β-unsaturated ketones. Also tertiary α-haloketones of the α-halocyclohexylarylketone type are known to react with silver nitrate[1,7] or amines[1] to produce good yields of 1-cyclohexenylarylketones. The silver nitrate reaction also gives some Favorski rearrangement acid[1,7] with these compounds.

The acyclic tertiary α-bromoketone, α-bromoisobutyrophenone, has been reported to react with ammonia, methylamine and dimethylamine to product the α-amino-,[8] α-methylamino-[9] and α-dimethylaminoisobutyrophenones,[10,11] respectively. Tertiary amines such as triethylamine have been found to dehydrobrominate α-bromoisobutyrophenone to give α-methylacrylophenone.[12] Cope and Graham[13] treated α-bromoisobutyrophenone with alcoholic silver nitrate to produce a 58% yield of the Favorski rearrangement product, α-phenylisobutyric acid.

Drake and McElvain,[14] in studying the rates of reaction of bromoesters with piperidine, found that ethyl α-bromoacetate and ethyl α-bromopropionate both react quite rapidly by bimolecular substitution to give an α-amino product, whereas ethyl α-bromoisobutyrate reacts much slower to give a β-amino product, presumably by a slow bimolecular elimination reaction followed by a rapid addition of piperidine.

To obtain a better insight into the chemistry of tertiary α-haloketones in connection with our studies of the mechanism of the elimination reactions,[1] it seemed important to investigate more thoroughly the behavior of an acyclic tertiary α-bromoketone with various amines.

Results.—For the current studies we chose the known α-bromo-*p*-phenylisobutyrophenone (II). This acylic tertiary α-haloketone reacted with mor-

(1) For paper III in this series, see N. H. Cromwell and Patrick H. Hess, *J. Am. Chem. Soc.*, **82**, 136 (1960).

(2) (a) R. S. Pearson, *et al.*, *ibid.*, **74**, 5130 (1952); (b) D. L. Brebner and L. C. King, *ibid.*, **75**, 2330 (1953).

(3) For a brief general discussion see E. L. Eliel in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 103.

(4) See B. Tchoubar, *Bull. soc. chim. France*, **10**, 1363 (1955), for an excellent review of the reactions of α-halogenated ketones with nucleophiles and ref. 1 for a brief mention of the products.

(5) (a) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 901 (1958); (b) N. H. Cromwell, R. P. Ayer and P. W. Foster, *ibid.*, **81**, 130 (1959).

(6) N. H. Cromwell and R. P. Ayer, *ibid.*, **81**, 133 (1959).

(7) (a) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952); (b) **74**, 5352 (1952).

(8) H. Larramona, *Compt. rend.*, **232**, 849 (1951).

(9) C. Mannich and H. Budde, *Arch. Pharm.*, **271**, 51 (1933).

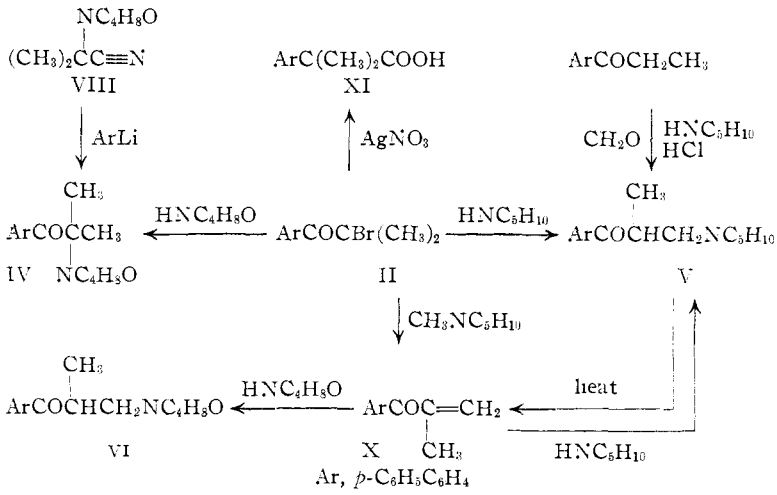
(10) T. Thompson and T. S. Stevens, *J. Chem. Soc.*, 1932 (1932).

(11) E. Eidebenz, *Arch. Pharm.*, **280**, 49 (1942).

(12) C. L. Stevens and B. V. Etting, *J. Am. Chem. Soc.*, **77**, 5412 (1955).

(13) A. C. Cope and E. S. Graham, *ibid.*, **73**, 4702 (1951).

(14) W. V. Drake and S. M. McElvain, *ibid.*, **56**, 697 (1934).



pholine in refluxing benzene solution to give at least an 88% yield of the substitution product α-morpholino-*p*-phenylisobutyrophenone (IV). This product was identical with an authentic sample of IV prepared by the reaction of the known α-morpholinoisobutyronitrile (VIII) on treatment with biphenylyllithium.

When the α-bromoketone II was refluxed with piperidine in benzene solution at least an 81% yield of the elimination–addition product β-piperidino-*p*-phenylisobutyrophenone (V) resulted which was unstable and had to be isolated as its hydrochloride. This same material was obtained by a Mannich-type reaction with *p*-phenylpropiophenone, formaldehyde and piperidine hydrochloride.

For comparison purposes, α-piperidino-*p*-phenylisobutyrophenone (IX) was synthesized by the reaction of biphenylyllithium with α-piperidinoisobutyronitrile (VII), and β-morpholino-*p*-phenylisobutyrophenone (VI) hydrochloride by the Mannich reaction of *p*-phenylpropiophenone with formaldehyde and morpholine hydrochloride.

Based on the rate of formation of the by-product starting amine hydrobromides, the relative rates of reaction of the α-bromoketone II with piperidine and morpholine in refluxing benzene solution was about 1.6 to 1. A qualitative comparison of the rates of the elimination reaction of II and of 4-biphenylyl-1-bromocyclohexylketone[1] employing piperidine in benzene solution indicates that the latter bromoketone reacts about ten times as fast.

It was established that α-piperidino-*p*-phenylisobutyrophenone (IX) shows no tendency to rearrange to the β-isomer V on heating in solution. It was found that amines with high steric demands (*e.g.*, N-methylmorpholine and 2,6-lupitidine) reacted not more than one-tenth as fast as morpholine with the α-bromoketone II.

When a water solution of β-morpholino-*p*-phenylisobutyrophenone (VI) hydrochloride was slowly steam distilled over a period of two days, a low yield (about 30%) of α-methyl-*p*-phenylacrylophenone (X) was produced. This α,β-unsaturated ketone X was also obtained in a somewhat greater yield on refluxing a benzene solution of II with N-methylpiperidine. This new α,β-unsaturated ketone X was found to add piperidine and morpholine readily in benzene solution to give the β-amino ketones V and VI, respectively, isolated as their hydrochlorides.

The treatment of the tertiary α-bromoketone II with alcoholic silver nitrate gave mainly (69% yield) the Favorski rearrangement product 2-biphenylyl-2-methylpropanoic acid (XI). A qualitative comparison of the rate of the alcoholic silver nitrate reaction of this α-bromoketone II with the previously studied 4-biphenylyl 1-bromocyclohexyl ketone[1] showed the acyclic α-bromoketone II to react faster by a ratio of about 3 to 1 as measured by the rate of formation of silver bromide.

The identity of products prepared by two routes was established in all instances by a comparison of infrared spectra as well as by the mixed m.p. technique.

Discussion of the Reactions.—The results reported above clearly indicate that α-bromo-*p*-phenylisobutyrophenone reacts with morpholine by a substitution reaction to produce the α-aminoketone IV while the stronger base piperidine is in all probability giving an elimination of hydrogen bromide to form α-methyl-*p*-phenylacrylophenone (X) as the primary product. The α,β-unsaturated ketone X then readily adds a molecule of piperidine under the conditions of reaction to give β-piperdino-*p*-phenylisobutyrophenone (V), the product actually isolated.

Since piperidine and morpholine have almost identical steric requirements, steric control factors cannot be used to explain the difference in the course of these two reactions. This variation in reaction course is to be ascribed to *nucleophilic control* by the base.

Although the kinetics of these reactions have not yet been determined, it is quite probable that such studies will show both of these to be bimolecular processes in their rate-determining steps by analogy with the behavior of 4-biphenylyl 1-bromocyclohexyl ketone which reacts with piperidine in benzene solution to give second-order kinetics.[15]

It is apparent that in the case of piperidine the elimination reaction competes successfully with substitution while the reverse is true with morpholine where the rate of reaction is slower. This is a remarkable finding and we believe it is the first example of this type of variation in E/SN ratio to be brought about by such a subtle change in basicity and/or nucleophilicity toward carbon in the reagent employed in such reactions. Although morpholine is a considerably weaker base than piperidine[16] it has been found in many instances to be strongly nucleophilic toward carbon.[17]

It will be important to see if a variation in the E/SN ratio with these two bases is experienced

(15) See ref. 1 and Ph.D. thesis, Patrick H. Hess, University of Nebraska, July, 1960.

(16) See H. K. Hall, *J. Am. Chem. Soc.*, **78**, 2570 (1956). for pK_a, H_2O solution, 25°: piperidine, 11.13; N-methylpiperidine, 10.19; morpholine, 8.36; N-methylmorpholine, 7.41.

(17) See N. H. Cromwell in R. C. Elderfield, "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 514–517.

when (1) the concentrations of the bases are varied, (2) the solvent is changed to a more polar one and (3) when temperatures are varied.[18] Such studies may be expected to aid in deciding between alternative bimolecular mechanisms for these reactions.[5]

It is interesting that with the analogous 4-biphenylyl 1-bromocyclohexylketone[1] morpholine and piperidine both give the elimination products apparently by the same type of bimolecular process.[15]

The rate of the dehydrobromination of the acyclic tertiary α-bromoketone II appears to be sensitive to both the basic strength and steric requirements of the amine, as has been found to be the case with the alicyclic tertiary α-bromoketones.[1,5,6]

The explanation of the increased rate of reaction of the acyclic α-bromoketone II (in contrast with 4-biphenylyl 1-bromocyclohexyl ketone[1]) with silver nitrate to produce mainly the Favorski rearrangement product rather than mainly the elimination product may be ascribed to the increased inductive and hyperconjugative effect of the methyl groups and the absence of axial hydrogen to engage in a diaxial loss of hydrogen bromide in II. With 4-biphenylyl 1-bromocyclohexyl ketone the opportunity for a diaxial loss of hydrogen bromide is expected to favor an elimination reaction, although the inductive and hyperconjugative effect of the methyl groups in the acyclic bromoketone II would be expected to facilitate the ionization of the bromine ion in the silver-catalyzed reaction.[1]

In the piperidine reaction, where there is no tendency for the rearrangement process, the opportunity for diaxial loss of hydrogen bromide with the 1-bromocyclohexyl aryl ketone causes it to react at a considerably faster rate than the acyclic α-bromoketone II. A further discussion of the mechanisms of these substitution–elimination reactions seems unwarranted at this time.

It was interesting to compare the absorption spectra of α-methyl-p-phenylacrylophenone (X) (see Experimental) with that of p-phenylacrylophenone[19] (λ_{max} 291 mμ (ε 22,200), $\gamma_{C=O}$ 1666/74) and p-phenylcrotonophenone[19,20] (λ_{max} 287 mμ (ε 23,900), $\gamma_{C=O}$ 1671/74 and 1655–1660/46). The α-methyl group in X interferes considerably with conjugation in the excited state resulting in a hypsochromic shift of 12 mμ for the maximum. The bifurcated carbonyl band in the infrared spectrum of X indicates rotational isomerism in the carbon tetrachloride solution. The strongest band at 1663 cm.$^{-1}$ is in the expected position for vinyl aryl ketones of this type[19,20] and is thus to be assigned to a conjugated conformer, while the weaker band at 1689 cm.$^{-1}$ would seem to belong to a screw or gauche conformation in which conjugation is less extensive.

Acknowledgment.—This investigation was supported in part by a grant from the National Science Foundation, NSF-G14469.

Experimental[21]

α-Bromo-p-phenylisobutyrophenone (II).—p-Phenylisobutyrophenone (I) was prepared by the method of Long and Henze[22] in 70.1% yield; m.p. 61–62°, recrystallized from ethanol; λ_{max} 282 mμ (ε 25,400), $\gamma_{C=O}$ 1687 cm.$^{-1}$. This compound was brominated by the method of Carpenter and Turner[23] to give α-bromo-p-phenylisobutyrophenone (II) in 96.8% yield, m.p. 100–101.5°, recrystallized from ethanol; λ_{max} 288 mμ (ε 20,300), $\gamma_{C=O}$ 1680 cm.$^{-1}$.

Reaction of Bromoketone II with Morpholine.—A 5.00-g. (0.0165 mole) sample of II and 11.81 g. (0.1357 mole) of redistilled morpholine were dissolved in 30 ml. of dry benzene and refluxed 22 hours. The solvent and excess amine were then removed by vacuum distillation. A 50-ml. portion of dry ether was added to the residue, and the precipitated morpholine hydrobromide filtered off to give 2.77 g. (100% yield).

The ethereal filtrate was washed many times with distilled water, dried over anhydr. magnesium sulfate, and dry hydrogen chloride bubbled into the solution. The α-morpholino-p-phenylisobutyrophenone hydrochloride (III) which precipitated, 5.03 g. (88.4% yield), m.p. 246–248°, was recrystallized from 100% ethanol; λ_{max} 283 mμ (ε 20,600), $\gamma_{C=O}$ 1676 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 7.00. Found: C, 69.04; H, 7.09.

Some of the aminoketone hydrochloride III was dissolved in water, and the solution made basic with potassium carbonate solution. The free amine, α-morpholino-p-phenylisobutyrophenone (IV), which precipitated, was recrystallized from benzene and petroleum ether; m.p. 120–123°, λ_{max} 283 mμ (ε 22,200), $\gamma_{C=O}$ 1679 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.74; H, 7.55; N, 4.73.

Reaction of Bromoketone II with Piperidine.—A 5.00-g. (0.0165 mole) sample of bromoketone II and 7.62 g. (0.0895 mole) of redistilled piperidine were allowed to react in a manner analogous to that outlined above. The product, β-piperidino-p-phenylisobutyrophenone (V) hydrochloride, 4.58 g. (81.1% yield), was recrystallized from 100% ethanol; m.p. 173–174°; λ_{max} 287 mμ (ε 24,900); $\gamma_{C=O}$ 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}ClNO$: C, 73.34; H, 7.63; N, 4.07. Found: C, 73.08; H, 7.69; N, 4.00.

Some of the aminoketone hydrochloride of V was dissolved in water, and the solution made basic with potassium carbonate solution to give the free amine V which was an unstable oil, $\gamma_{C=O}$, 1683 cm.$^{-1}$.

Preparation of β-Piperidino-p-phenylisobutyrophenone (V) Hydrochloride by the Mannich Reaction.—A 38.40-g. (0.1877 mole) sample of p-phenylpropiophenone (prepared by the method of Long and Henze[22]), 22.77 g. (0.1873 mole) of piperidine hydrochloride and 16.92 g. (0.5637 mole of formaldehyde) of trioxymethylene were dissolved in 65 ml. of 100% ethanol. A few drops of concentrated hydrochloric acid was added, and the solution refluxed for 24 hours. An additional 0.1875 mole of formaldehyde (as trioxymethylene) was added, and the reflux continued an additional 24 hours. The solution was cooled and crystals of the hydrochloride of V formed; 47.09 g. (73.2% yield); m.p. 173–174°, recrystallized from 100% ethanol; λ_{max} 287 mμ (ε 25,100), $\gamma_{C=O}$ 1678 cm.$^{-1}$. This product was identical with that prepared from II.

Preparation of β-Morpholino-p-phenylisobutyrophenone (VI) Hydrochloride by the Mannich Reaction.—Morpholine hydrochloride, p-phenylpropiophenone and trioxymethylene were allowed to react in a manner analogous to that outlined above to give a 63.0% yield of VI; m.p. 171–173.5°, recrystallized from 100% ethanol; λ_{max} 286 mμ (ε 23,600), $\gamma_{C=O}$ 1677 cm.$^{-1}$.

Some of ketone VI was dissolved in water, and the solution made basic with potassium carbonate solution to give the free amine VI which was an unstable oil, $\gamma_{C=O}$ 1687 cm.$^{-1}$.

(18) See E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 485–489, for a discussion of competition between elimination and substitution.

(19) R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 401 (1957).

(20) N. H. Cromwell and R. J. Mohrbacher, *ibid.*, **75**, 6252 (1953).

(21) 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 or potassium bromide pellets for the insoluble amine hydrochlorides.

(22) L. M. Long and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 1939 (1941).

(23) B. R. Carpenter and E. E. Turner, *J. Chem. Soc.*, 869 (1934).

Preparation of α-Aminoisobutyronitriles.—Following the procedure of Jacobson,[24] α-morpholinoisobutyronitrile (VIII) was prepared in 42.6% yield, b.p. 94° (3 mm.) and α-piperidinoisobutyronitrile (VII) in 45.8% yield, b.p. 43° (0.15 mm.) m.p. 39–43°.

α-Piperidino-*p*-phenylisobutyrophenone (IX).—A 4.87-g. (0.0322 mole) sample of nitrile VII was dissolved in 100 ml. of dry ether. To this solution was added dropwise, with stirring, an excess of biphenylyllithium[25] in 150 ml. of dry ether. After the addition the solution was stirred and refluxed 3 hours, followed by decomposition of the complex by the addition of saturated ammonium chloride solution. The product was isolated by extracting the ether layer from the decomposition with dilute hydrochloric acid, then precipitating the free aminoketone IX by making the extract basic. The aminoketone was collected; 3.06 g. (30.9% yield), m.p. 105–106°, recrystallized from benzene and petroleum ether; λ_{max} 282 mμ (ε 22,600), $\gamma_{C=O}$ 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.27; H, 8.19; N, 4.66.

The hydrochloride of IX was prepared, m.p. 218–220° dec., and recrystallized from 100% ethanol; λ_{max} 281 mμ (ε 22,900), $\gamma_{C=O}$ 1680 cm.$^{-1}$.

α-Morpholino-*p*-phenylisobutyrophenone (IV).—In a manner analogous to that outlined above for IX, aminoketone IV was prepared from VIII in 27.0% yield; m.p. 121–123°, recrystallized from benzene and petroleum ether; λ_{max} 283 mμ (ε 20,800), $\gamma_{C=O}$ 1680 cm.$^{-1}$. The compound was identical with that obtained from II.

Comparative Rates of Reaction of Bromoketone II with Piperidine and Morpholine.—Five-gram samples of II were dissolved in 30 ml. of dry benzene, and sufficient amine was added to give an amine-to-bromoketone ratio of 2.50 to 1. The solutions were refluxed 18 hours, after which time a 50-ml. portion of dry ether was added, and the precipitated amine hydrobromide collected and weighed. Based on the yield of the amine hydrobromides, the piperidine and morpholine reactions were 83.3% and 50.8% complete, respectively.

Equilibration Tests.—A 0.480-g. (0.00139 mole) sample of α-piperidino-*p*-phenylisobutyrophenone hydrochloride (V) and 0.036 g. (0.00029 mole) of piperidine hydrochloride were dissolved in 5 ml. of 100% ethanol. One drop of concentrated hydrochloric acid was added, and the solution refluxed for 24 hours. The amino ketone hydrochloride was recovered in 91.5% yield. It was identified by a mixed melting point experiment with the pure reactant.

A 0.720-g. (0.00254 mole) sample of α-piperidino-*p*-phenylisobutyrophenone (IX), 0.430 g. (0.00506 mole) of piperidine and 0.020 g. (0.00120 mole) of piperidine hydrobromide were added to 6 ml. of dry benzene, and the mixture refluxed 24 hours. The aminoketone IX was recovered in 88.7% yield. It was identified by mixed melting point experiment with the pure reactant.

Comparative Rates of Reaction of Bromoketone II with Other Amines.—One-gram samples of II were dissolved in approximately 0.067-mole amounts of the amines (piperidine, morpholine, N-methylmorpholine, 2,6-lupitidine) and heated in closed flasks for 1 hour at steam-bath temperature. The excess amine was then removed by vacuum distillation at steam-bath temperature over a period of 15 minutes. A 20-ml. portion of dry ether was added to each flask, the precipitated amine hydrobromide collected and weighed; piperidine hydrobromide, 0.55 g. (100% reaction); morpholine hydrobromide, 0.56 g. (100% reaction); N-methylmorpholine hydrobromide, 0.08 g. (13.3% reaction); 2,6-lupitidine hydrobromide, 0.08 g. (12.5% reaction).

α-Methyl-*p*-phenylacrylophenone (X). A. By Steam Distillation of the Hydrochloride of VI.—A 3.02-g. (0.00873 mole) sample of β-morpholino-*p*-phenylisobutyrophenone (VI) hydrochloride was dissolved in water, and steam distilled. Over a period of 2 days of distillation, 0.90 g. of X was collected; m.p. 70–71°, recrystallized from ethanol; λ_{max} 284 mμ (ε 19,000) (in isooctane, λ_{max} 279 mμ (ε 21,500)); $\gamma_{C=O}$ 1663/40 cm.$^{-1}$, 1689/53 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.44; H, 6.46.

B. From II and N-Methylpiperidine.—A 2.0-g. (0.0066 mole) sample of II and 4.65 g. (0.0469 mole) of N-methylpiperidine in 30 ml. of dry benzene were refluxed for 22 hours to give 0.98 g. (82% yield) of N-methylpiperidine hydrobromide and 1.1 g. (75.4% yield) of X; m.p. 69–71°, recrystallized from ethanol.

The Addition of Piperidine and Morpholine to X.—A 0.045-g. (0.000202 mole) sample of X and 0.120 g. (0.00141 mole) of redistilled piperidine were dissolved in 5 ml. of dry benzene, and allowed to stand overnight at room temperature. The benzene and excess amine were removed by vacuum distillation, and the residue taken up in 20 ml. of dry ether. Dry hydrogen chloride was bubbled into the ether solution. The product was separated by filtration; 0.055 g. (78.6%), m.p. 173.5–174.5°. It was identified as V by its infrared spectrum and by a mixed melting point experiment with an authentic sample of V.

A 0.04-g. (0.00018 mole) sample of X and 0.46 g. (0.00549 mole) of redistilled morpholine were dissolved in 5 ml. of dry benzene, and the solution treated as above. The amount of VI isolated was 0.055 g. (88.7% yield), m.p. 173–178°; this product was identified as VI by its infrared spectrum and by a mixed melting point experiment with an authentic sample of VI.

Reaction of Bromoketone II with Alcoholic Silver Nitrate.—A 5.00-g. (0.0165 mole) sample of II was refluxed, with stirring, with 2.80 g. (0.0165 mole) of silver nitrate in 160 ml. of ethanol and 40 ml. of water, for 4 hours in the absence of light. To the cooled reaction mixture was added 5 ml. of 6 *N* nitric acid, and the silver bromide was removed by filtration and weighed; 3.09 g. (100% yield). Dilution of the filtrate with water precipitated a product which was separated into neutral and acidic fractions by extraction with sodium hydroxide solution. The neutral fraction gave 1.98 g. of a semi-solid which was not characterized. The acid fraction gave 2-(4-biphenylyl)-2-methylpropanoic acid (XI), 2.73 g. (68.9% yield); m.p. 175–177°, recrystallized from benzene.

Anal. Calcd. for $C_{16}H_{16}O_2$: mol. wt., 240.29; C, 79.97; H, 6.71. Found: neut. equiv., 246; C, 79.74; H, 6.49.

Relative Rate of Reaction of II with Alcoholic Silver Nitrate at 30°.[26]—Reaction mixtures containing 0.00200 mole of II and 0.00599 mole of silver nitrate in 60 ml. of ethanol solution were placed in 100-ml. glass-stoppered flasks. The solutions were shaken at a constant temperature of 30.0°, in the absence of light, for 4 hours. To the reaction flasks were added 3 ml. of 6 *N* nitric acid, and the mixtures filtered through weighed Gooch crucibles. The precipitates were washed with benzene, and then with very dilute nitric acid, dried at 80° for 2 hours, and weighed. For the duplicate run, the amount of silver bromide formed indicated an 18.93 ± 0.64% reaction for bromoketone II.

(24) R. A. Jacobson, *J. Am. Chem. Soc.*, **67**, 1996 (1945).

(25) Prepared as outlined by H. Gilman, E. A. Zoellner and W. M. Selby, *ibid.*, **55**, 1252 (1933).

(26) Relative to the rates reported in ref. 1.