not a reliable criterion of purity. There were indications of liquid crystal formation, and melting is apparently accompanied by gas evolution.

Anal. Calcd. for $C_{20}H_{32}N_2O_2$: C, 72.24; H, 9.70; N, 8.43. Found: C, 72.05; H, 9.46; N, 8.76.

Another experiment, in which a dimethylformamide solution of apocamphane-1-carbonyl chloride was added dropwise with stirring to a large excess of hydrazine hydrate, yielded the same product.

N'-p-Toluenesulfonylpivalhydrazide. Pivalhydrazide was prepared from methyl pivalate by the procedure of Wieland *et al.*[8] To a cold solution of 1.4 g. of pivalhydrazide in dry pyridine was added 2.55 g. of *p*-toluenesulfonylchloride. After 0.5 hr. at 0°, the reaction mixture was allowed to stand for 3 hr. at room temperature and then poured into a mixture of ice and dilute hydrochloric acid. The precipitate was filtered off and dissolved in ether. The ether solution was extracted three times with dilute hydrochloric acid, washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness. The residual *N'-p*-toluenesulfonylpivalhydrazide (1.7 g., m.p. 158–160°) was crystallized from 75% aqueous ethanol, m.p. 159.5–161°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2S$: C, 53.32; H, 6.71; N, 10.37; S, 11.87. Found: C, 53.36; H, 6.63; N, 10.69; S, 12.04.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT RIVERSIDE]

The Chemistry of β-Bromopropionyl Isocyanate. IV. Elimination Reactions of Some β-Bromopropionic Acid Derivatives[1]

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The rates of dehydrobromination of two β-bromopropionylcarbamates and two β-bromopropionylureas with chloroform were measured in chloroform and compared with the rates of ethyl β-bromopropionate and β-bromopropionanilide. Differences are attributed to the inductive effect.

The reaction of β-bromopropionyl isocyanate with amines and alcohols leads to β-bromopropionylureas and carbamates,[2] and a study of the rates of elimination reactions of such compounds was of interest. The rates of reactions of ethyl β-bromopropionate with amines were studied by McElvain.[3] Tertiary amines were found to be the principal products from piperidine, though they were apparently formed by an elimination-addition mechanism. The hydrolysis reactions of β-bromopropionic acid derivatives have received considerable study.[4–7] The product to be expected from the reaction of bases with ethyl β-bromopropionate or other derivatives of β-bromopropionic acid depends upon the reaction conditions. In some cases[3,8–10] displacement products have been reported; in others[11] the unsaturated products were obtained. The addition of amines and ammonium salts to acrylyl esters and amides[12,13] has been reported.

Chloroform was chosen as the solvent for the present work in spite of its low boiling point and slow reaction with amines. Its solubility properties for the compounds in question were reasonably good, it could be rendered anhydrous easily, and the rates of elimination were found to be measurable for both simple derivatives of propionic acid and derivatives of β-bromopropionyl isocyanate.

EXPERIMENTAL

Ethyl β-bromopropionate was prepared from β-bromopropionic acid and ethanol with sulfuric acid. The product was worked up in a normal manner to yield the ester, b.p. 45° (3 mm.). The material used in the kinetic determinations was redistilled, a center cut being retained.

The samples of β-bromopropionanilide (m.p. 119–120°)[14] and its *p*-nitro derivative (m.p. 144–145°) were prepared by reaction of the amine with β-bromopropionyl chloride in chloroform. The product was precipitated from the chloroform with ether and crystallized from methanol.

The preparation of methyl and phenyl β-bromopropionylcarbamates from β-bromopropionyl isocyanate and the alcohol has been reported.[15] The preparation of *N*-phenyl-*N'*-β-bromopropionylurea and *N*-(β-phenylethyl)-*N'*-β-bromopropionylurea has been reported. The melting points of the four compounds agreed with those reported, and they were crystallized several times from methanol and chloroform prior to the kinetic runs.

The chloroform was extracted with concentrated sulfuric acid, washed with water, dried with calcium chloride, and stored over calcium hydride. Immediately prior to use the chloroform was distilled from calcium hydride.

(1) Supported by a grant from the National Science Foundation.

(2) H. W. Johnson, Jr., and D. E. Bublitz, *J. Am. Chem. Soc.*, **80**, 3150 (1958).

(3) W. V. Drake and S. M. McElvain, *J. Am. Chem. Soc.*, **56**, 697 (1934); **56**, 1810 (1934).

(4) E. Saito, *Bull. soc. chim. France*, **1948**, 404.

(5) J. F. Lane and H. W. Heine, *J. Am. Chem. Soc.*, **73**, 1348 (1951).

(6) E. Saito, and R. Schmitz, *Bull. Soc. chim. France*, **1952**, 513.

(7) J. Eloranta, *Ann. Acad. Sci. Fennicae*, Ser. A., II, No. 70 (1956). *C.A.*, **51**, 9480 (1957).

(8) R. Fusco, G. Palazzo, and S. Chiavarelli, and D. Bovet, *Gazz, Chim. ital.* **79**, 836 (1949).

(9) N. L. Wendler, *J. Am. Chem. Soc.*, **71**, 375 (1949).

(10) Brit. Patent **653,452**. *C.A.* **46**, 1038 (1952).

(11) Swiss Patent **280,474** (1952); *C.A.*, **47**, 6977 (1953). U. S. Patent **2,640,073**; *C.A.* **48**, 3995 (1954).

(12) Ger. Patent **869,489**. *C.A.*, **48**, 11483 (1954).

(13) R. Dobenko, *J. Org. Chem.*, **25**, 1123 (1960).

(14) E. H. Charlesworth and H. J. Anderson, *Can. J. Research*, **28B**, 1 (1950).

(15) H. W. Johnson, Jr., H. A. Kreyssler, and H. L. Needles, *J. Org. Chem.*, **25**, 279 (1960).

The triethylamine was distilled from acetic anhydride and from calcium hydride. In some later work the triethylamine was allowed to stand over calcium hydride until reaction ceased, and then distilled from fresh calcium hydride. No difference in reactivity was noted between samples treated in the two ways.

Kinetic runs were carried out by dissolving 10^{-3} moles of the halide in 99 ml. of chloroform, equilibrating at the desired temperature, and adding 1.00 ml. of 1.00*M* triethylamine in chloroform from a syringe. Samples (5.00 ml.) were withdrawn periodically and added to a solution of 3 ml. of 6*N* nitric acid in 20 ml. of water. The mixture was titrated potentiometrically for bromide ion with 0.1*M* silver nitrate solution using a microburet. The integrated form of the rate expression for a second order reaction (equal concentrations), $k = x/at(a-x)$, was used. Constant k's were usually obtained until approximately 80% of the reaction was completed. A sample run is shown below. Reported constants are the average of at least two runs.

REACTION OF *N*-PHENYL-*N'*-β-BROMOPROPIONYLUREA WITH TRIETHYLAMINE (50.2°)

Time (Sec.)	$AgNO_3$ (Ml.)	$K_2 \times 10$ (1/Mole-sec.)
80	0.49	1.35
173	.97	1.39
313	1.52	1.40
630	2.37	1.43
1259	3.12	1.33
2506	3.88	1.33
8585	4.56	1.60
24 hr.	5.01	—
		av. 1.38± 0.04

A second run yielded $k = 1.39 \pm 0.04 \times 10^{-1}$. Energies of activation were determined from a graph of log k *vs.* 1/T. Entropies of activation were determined from the equation $S^{\ddagger}/R = \ln k_2 - \ln kT/h + (E_a - RT)/RT$.

No reaction between chloroform and triethylamine was noted if the solutions were stored in the dark over a period of 4 to 5 days. When exposed to light the solutions gradually became brown, and the chloride ion could be determined by titration with silver nitrate. No difficulties were noted with evaporation of chloroform. Containers with a minimum free gas space were used; samples were withdrawn with a syringe.

To investigate products, solutions at the same concentrations and temperatures as those of the kinetic runs were allowed to stand for 24 hr. (derivatives of the isocyanate) or several weeks (simple derivatives of propionic acid). Extraction of the chloroform solution with water and evaporation of the water usually gave 95% of triethylammonium bromide, m.p. 252–254°, also identified by infrared spectra and production of silver bromide. From *N*-phenyl-*N'*-β-bromopropionylurea there was obtained 90% of the acrylylurea, m.p. 148–151° (crude), on evaporation of the chloroform. Identification was confirmed with an infrared spectrum. Identification of the olefinic product was also made by isolation in the case of ethyl acrylate and acrylanilide. In the other cases of infrared band at approximately 910 cm.$^{-1}$ of the chloroform solution indicated terminal methylene absorption and thus an olefinic product.

Attempts were made to measure the kinetics of elimination of the *p*-nitroanilide of propionic acid at 40° and 30°, but the compound was not sufficiently soluble in chloroform. Attempts to use dioxane as solvent for the kinetic study failed when triethylammonium bromide precipitated at approximately 30% reaction. The elimination appeared to be slower in dioxane than in chloroform (for *N*-phenyl-*N'*-bromopropionylurea, k_2 approximated 9×10^{-3} l./mole-sec. for the few points obtained at 30.1°). The use of pyridine as a base was unsuccessful; in a solution containing 75 ml. of chloroform, 2 moles of pyridine, and 0.33 g. of *N*-phenyl-*N'*-β-bromopropionylurea at 30.1°, approximately 2% reaction occurred in 25 hr. In an identical solution with triethylamine replacing pyridine the reaction was complete in 5 min. An attempt was made to study the rate of elimination of hydrogen bromide from $BrCH_2CH_2CONHCO—S—C_6H_5$, but a strong odor of thiophenol was noted as the reaction progressed, and the appearance of brown silver salt precipitate rather than a yellowish white silver bromide during the titration for bromide seemed to indicate that thiophenol was being eliminated either in place of or in addition to hydrogen bromide. The reaction has not been studied further as yet.

Upon refluxing 1.00 g. of *N*-phenyl-*N'*-β-bromopropionylurea with 20 ml. of pyridine, 0.7 g. of product, m.p. 215–216°, was obtained upon dilution with petroleum ether. The product was water-soluble, and contained ionic bromide (silver nitrate).

Anal. Calcd. for $C_{15}H_{16}N_3O_2Br$: C, 51.6; H, 4.8; Br, 24.3. Found: C, 51.7; H, 4.5; ionic bromide, 24.2.

The infrared spectrum contained the double carbonyl peaks found in the parent urea. The product thus appears to be the pyridinium salt $Br^-C_5H_5N^+CH_2CH_2CONHCONHC_6H_5$. It could also be obtained (40%) by the reaction of *N*-phenyl-*N'*-acrylylurea with equimolar quantities of pyridinium bromide in refluxing pyridine.

DISCUSSION

The products obtained in the kinetic work reported herein appear to be triethylammonium bromide and the olefin. The isolation of nearly quantitative amounts (95%) of triethylammonium bromide precludes the formation of substitution products of the original halide as ultimate products of the reaction since the ratio of amine to halide was 1. The olefinic product was directly isolated in the case of compounds I, II, and VII; they were identified by comparison with authentic samples. The presence of olefinic products was inferred in the other compounds from a terminal methylene absorption band at approximately 900 cm.$^{-1}$ in the infrared spectrum.

The rate constants are reported in the Table of Results. Compound I and II were chosen as reasonably representative of simple derivatives of propionic acid. These monocarbonyl compounds are from twenty-five to fifty times less reactive (at 50°) than compounds IV and V (imido compounds having terminal alkyl groups), and these in turn are less reactive than compounds VI and VII (imido compounds with terminal aryl groups) by a factor of two or three. This is the order to be expected if the principal effect were to be an enhancement of the acidity of the α-methylene hydrogen by an inductive effect. Compound III (with a *p*-nitro group) exhibits an enhancement in rate of approximately nine over compound II, thus indicating that an electron withdrawing group attached to the amide nitrogen can have a considerable effect on the rate of dehydrobromination.

The difference in rates of the aryl and alkyl carbamates (or the corresponding ureas) is of some interest. In saturated systems the inductive effect

TABLE OF RESULTS

RATES OF DEHYDROBROMINATION OF β-BROMOPROPIONIC ACID DERIVATIVES WITH TRIETHYLAMINE IN CHLOROFORM

Compound	k_2(1/Mole-sec.) at Indicated Temperature 30.1	40.2	50.2	E_a Kcal.	$S^‡$ E.U.
I. $BrCH_2CH_2CO_2C_2H_5$			1.53×10^{-3}		
II. $BrCH_2CH_2CONC_6H_5$	3.01×10^{-4}	5.37×10^{-4}	1.00×10^{-3}	11.6	−39
III. $BrCH_2CH_2CONHC_6H_4NO_2$-*p*			8.63×10^{-3}		
IV. $BrCH_2CH_2CONHCO_2CH_3$	2.96×10^{-3}	4.11×10^{-2}	5.30×10^{-2}	5.6	−51
V. $BrCH_2CH_2CONHCONHCH_2CH_2C_6H_5$			3.96×10^{-2}		
VI. $BrCH_2CH_2CONHCO_2C_6H_5$	7.31×10^{-2}	9.85×10^{-2}	1.42×10^{-1}	6.5	−45
VII. $BrCH_2CH_2CONHCONHC_6H_5$	7.05×10^{-2}	9.15×10^{-2}	1.39×10^{-1}	6.7	−44

decreases rapidly with increasing chain length.[16] The ratio of the rates of VI/IV is 2.7. The difference in ionization constants between pentanoic acid and γ-phenylbutyric acid is 0.05 *p*K units (factor of 1.15). Thus in the saturated acids, the effect on the ionization constant of substituting phenyl for methyl is 1.15 on the fourth carbon atom. In the case of the imides reported here, a rate factor of 2.5 was noted. Presumably the difference implies a greater ease of transmission of inductive effect through the acyl carbamate system where the atoms involved have either unshared pairs of electrons or electrons involved in pi-bonds.

The discussion has treated the eliminations as simple E-2 eliminations. In the case of ethyl β-bromopropionate the E-2 elimination is almost certainly followed (with some reservation concerning a carbanion intermediate). With compounds IV–VII several other mechanisms are possible. In one, a proton is removed from the amide nitrogen by the base; displacement of bromide follows to yield a dihydrouracil which then undergoes elimination to yield the olefin. If the ring opening is fast with respect to either of the first two steps, second order kinetics should be found. However, dihydrouracils are stable to these conditions, and an equally rapid elimination is found with carbamate esters (IV and VI) in which this mechanism is not possible. One alternative mechanism has not been eliminated from consideration by the present work.[17] In this mechanism the imide hydrogen is removed by the base to yield a resonance-stabilized anion which then attacks the α-hydrogen (through oxygen) in a cyclic six-membered transition state to yield the enol of the product, which tautomerizes. On the basis of the result obtained with the nitroanilide (III) it seems unnecessary to postulate the operation of such a mechanism to account for the magnitude of the increase in the rate of the elimination reactions studied. However, experiments to clarify this point are being conducted.

The elimination reactions studied are reasonably rapid and are characterized by low activation energies and high negative entropies. The activation energies of the diacyl compounds are less than those of β-bromopropionanilide as might be expected if the inductive effect were to be operating. The entropies reported seem valueless as a criterion of mechanism (variation among the diacyl compounds (V–VIII) is as large as the difference found between β-bromopropionanilide and *N*-phenyl-*N'*-β-bromopropionylurea.) Such high negative entropies of activation have been reported in many reactions involving the production of ions in nonpolar solvents.[18]

The elimination reaction was affected by the base strength of the amine. Under conditions (excess amine) where triethylamine caused essentially complete dehydrohalogenation in less than five minutes, the use of pyridine in equal concentrations led to less than 2% reaction in twenty-five hours. Refluxing compound VII in excess pyridine gave the displacement product. The possibility of an elimination addition mechanism was indicated when it was found that pyridine hydrobromide and acrylylphenylurea gave the same product in refluxing pyridine. This reaction is very similar to the addition of amines to simpler α,β-unsaturated amides.[18]

The rates of the reaction were also affected by the solvent. The reaction of urea VII with triethylamine in dimethylformamide was too fast to measure titrametrically or conductometrically. This is the expected direction of any rate difference, since ions are being formed.

One consequence of the present work is the knowledge that milder conditions than originally reported[19] may be used in the synthetic dehydrohalogenation of β-bromopropionylarylureas or bromopropionyl carbamates. With equimolar amounts of triethylamine in chloroform two hours of refluxing in chloroform should suffice. With excess

(16) H. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1956, p. 75.

(17) Suggested by Prof. H. Kuivala, University of New Hampshire.

(18) A. R. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 133 *ff.* and examples cited therein.

(19) H. W. Johnson, Jr., R. Lovins, and M. Reintjes, *J. Org. Chem.*, 24, 1391 (1959).

amine in chloroform an hour at room temperature should be sufficient. The original conditions were triethylamine in refluxing dimethylformamide which will cause dehydrohalogenation, but which are unnecessarily vigorous.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Cyclopropanes Derived from Diaryldiazomethanes. I. Amino Alcohols of the *cis* Series[1]

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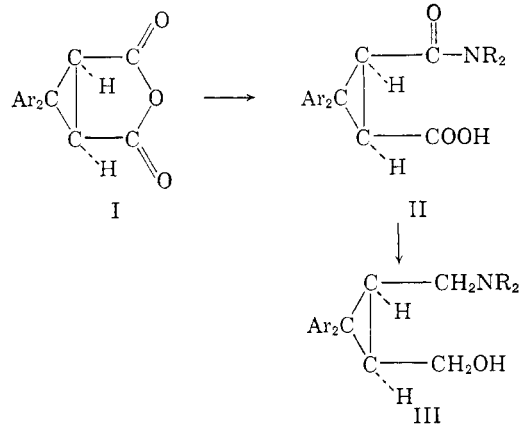
Through the addition of diaryldiazomethanes to unsaturated carbonyl compounds good yields of 1,1-diphenylcyclopropanes were obtained. These were then converted to amides and thence to amines. The route studied most intensively utilized maleic and citraconic anhydrides which were converted to amido acids and to amino alcohols.

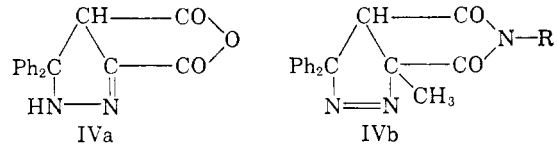
Staudinger[5] and later van Alphen[6] studied the addition of diphenyldiazomethane to unsaturated carbonyl derivatives. It has been established that the pyrazolines and cyclopropanes so obtained from maleic and fumaric esters have their ester functions in the *trans* position, *cis* derivatives being obtained only when the starting compound was cyclic in structure—as maleic anhydride or maleimide. Compounds of type A have been converted by the sequence I–III



I II III

into substances having resemblance to a variety of types possessing known pharmacological activity. Furthermore, the *trans* analogs[7] could also be prepared and structure-activity relationships could be studied through a wide range.

The reaction of diaryldiazomethanes with maleic anhydride and maleimides[8] gave Δ^2-pyrazolines (IVa), since they reduced permanganate in acetone solution at room temperature. In the citraconimide series,[8] the permanganate test was negative, indicating that Δ^1-pyrazolines (IVb) were obtained.



IVa IVb

The ease with which the pyrazolines were converted to cyclopropanes varied considerably. The pyrazolines derived from maleimides and citraconimides are considerably more labile than those obtained from acyclic compounds and those formed from maleic anhydride are still less stable. In most of our earlier work in which solutions of diaryldiazomethanes were employed without isolation of the pure reagents, the pyrazolines could not be isolated at all from reactions with maleic anhydride. Eventually it was discovered that the collapse of the pyrazoline was catalyzed by traces of mercuric ion. The reactions of diaryldiazomethanes with citraconic anhydride are much slower than those with maleic anhydride and the former have never in our hands given even traces of pyrazoline. It is possible that the attack of the reagent on the conjugated system may give an intermediate that does not cyclize instantaneously[9] and which may

(1) A portion of this material was presented by Dr. Mehta before the Organic Division of the American Chemical Society, Boston Meeting, April 1959.

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(4) Present address: Department of Chemistry, Fordham University, New York, N. Y.

(5) H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.*, 49, 1928 (1916).

(6) J. van Alphen, *Rec. trav. chim.*, 62, 210 (1943).

(7) The preparation of the *trans* compounds requires intermediates (preferably maleamic esters) that were not readily available in the early stages of this work. Since also the *cis* compounds appeared more promising in early tests the *trans* series was studied much later. It will be reported in a separate publication.

(8) R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem., in press.*

(9) A kinetic study and discussion of the probable mechanisms of some of these reactions were presented before the Division of Organic Chemistry of the American Chemical Society, New York, 1960.