Diethyl α-Cyano-β-methylglutarate (IV).—To a solution of 11.5 g. of sodium in 250 ml. of absolute alcohol were added 56.5 g. of ethyl cyanoacetate and 57 g. of ethyl crotonate. The red reaction mixture was heated on a steam-cone for 21 hours, cooled and poured into 1 l. of water containing 50 ml. of acetic acid. The water solution was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The ether was removed on a steam-cone and the residual deep red oil was fractionated. Diethyl α-cyano-β-methylglutarate distilled at 115° (0.5 mm.) and weighed 52 g. (45.8%).

Diethyl α-Cyano-α-ethyl-β-methylglutarate (V).—To 5.75 g. of finely pulverized sodium was added 25 ml. of absolute alcohol. When the mixture became too viscous for further reaction 52 g. of diethyl α-cyano-β-methylglutarate was added. After the initial violent reaction 5 ml. of absolute alcohol was added to facilitate complete solution of the sodium. Then 39 g. of ethyl iodide was added and the mixture was stirred at room temperature for three hours and heated on a steam-cone for one half hour. The viscous mass was poured into 400 ml. of water containing 20 ml. of acetic acid. The cloudy water solution was extracted with ether. The ether layer was dried over anhydrous sodium sulfate and the ether was removed on a steam-cone. The residual oil was fractionated at reduced pressure and the fraction distilling at 112° (0.3 mm.) was collected (45 g., 76%). The diethyl α-cyano-α-ethyl-β-methylglutarate obtained, as reported by Michael and Ross,[5] had the same boiling point as diethyl α-cyano-β-methylglutarate and since physical constants were not available the former was analyzed to prove its identity.

Anal. Calcd. for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29. Found: C, 60.88; H, 8.31.

α-Ethyl-β-methylglutaric Acid.—A mixture of 44 g. of ethyl α-cyano-α-ethyl-β-methylglutarate and 500 ml. of 20% hydrochloric acid was refluxed for 24 hours. By this time, complete solution of the oil had occurred. The cooled solution was thoroughly extracted with ether and the ether extract was washed with three 80-ml. portions of 10% sodium hydroxide. The basic aqueous layer was made acidic with 20% hydrochloric acid and was extracted with ether. The ether was removed on a steam-cone and the residual viscous oil was kept in a vacuum desiccator overnight. In this way 18.2 g. (62.8%) of a mixture of the diastereoisomeric α-ethyl-β-methylglutaric acids were obtained. The desired isomer was obtained by repeated crystallization from a chloroform–petroleum ether mixture. It melted at 97–99° and further recrystallizations failed to raise its melting point.

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[CONTRIBUTION FROM THE CONVERSE LABORATORIES OF HARVARD COLLEGE AND THE HUNTINGTON LABORATORIES OF THE MASSACHUSETTS GENERAL HOSPITAL]

The Alkaline Rearrangement of α-Haloketones. III.[1] Effect of Changing the Halogen

BY ROBERT BERNER LOFTFIELD AND LAWRENCE SCHAAD[2]

RECEIVED JUNE 4, 1953

When α-haloketones react with base, a mixture of rearrangement and substitution products results. On the basis of the proposed reaction mechanism, it is predicted that the proportion of rearrangement product will be greater as the halogen is changed from Br to Cl to F. This prediction is confirmed for the case of bromo- and chloromethyl cyclohexyl ketone. Contrary to Mousseron's report,[7] no ester of cyclohexylacetic acid was obtained from chloromethyl cyclohexyl ketone on treatment with sodium methoxide.

A large number of α-haloketones react with sodium alkoxides to yield mixtures of varying proportions of a rearrangement product (esters IV and V), and a substitution product (ketal IX). The ketal results from the attack of alkoxide ion on the carbonyl carbon followed by cyclization to an alkoxyepoxide.[3] This is then solvolyzed to yield the ketal. We have proposed that the rearrangement proceeds through an entirely different (and competing) course beginning with attack on the α′-hydrogen and proceeding through a cyclopropanone intermediate which is solvolyzed to yield one or both of two esters.[1]

If the postulated reaction mechanisms are correct, we may make some predictions regarding the effect of changing halogen (F, Cl, or Br) on the proportion of rearrangement *vs.* substitution product. There would be some change in k_{II}, k_{III} and K_{VI}, but the major effect would probably be in K_{VII}. McCabe and Warner[4] have shown in the quite comparable case of ring closure from ethylene halohydrin anions to ethylene oxide that the rate for halogen = Br is about 100 times greater than for halogen = Cl and about 60,000 times greater than for halogen = F. By analogy, we would expect to find a series of halo ketones where it would be possible to vary the products from all substitution to all rearrangement by changing the halogen, *i.e.*, the rate of substitution might be changed by a factor of 60,000 while the rate of the rearrangement was substantially constant. In addition to the theoretical interest, such control over product composition would be of enormous preparative value.[5]

We chose the halomethyl cyclohexyl ketones for Wagner and Moore[6] had just reported that the bromo derivative gave only the substitution product IX. After the investigation was begun it gained significance when Mousseron, *et al.*,[7] reported that chloromethyl cyclohexyl ketone gives a mixture of esters IVa and Va on treatment with sodium methoxide. Methyl bromocyclohexyl ketone, which presumably rearranges through the same cyclopropanone III, had been reported to give only the ester IVa.[6] It is not reasonable to suggest that in one case III can solvolyze exclusively to IVa and in another give mostly Va. If these observations were confirmed, the theory would need to be revised.

(1) R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951); **72**, 632 (1950).

(2) From a thesis submitted by Mr. Schaad in partial fulfillment of the requirements for the Bachelor of Science degree in Biochemical Sciences, Harvard College, 1952. Contribution 803 from the Cancer Commission of Harvard University.

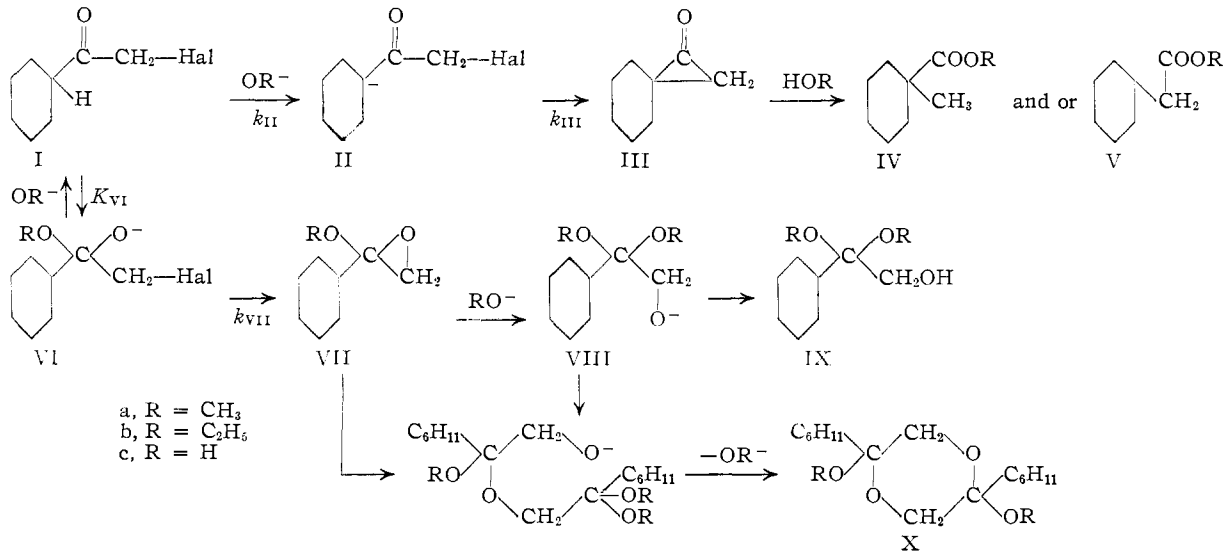
(3) T. I. Termnikova and E. N. Kropacheva, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **19**, 1917 (1949); *C. A.*, **44**, 1929 (1950); C. L. Stevens, W. Malik and R. Pratt, THIS JOURNAL, **72**, 4758 (1950).

(4) C. L. McCabe and J. C. Warner, *ibid.*, **70**, 4031 (1948).

(5) B. Tchoubar, *Compt. rend.*, **235**, 720 (1952), has achieved some of this control by substituting silver salts for alkali in these reactions.

(6) R. B. Wagner and J. A. Moore, THIS JOURNAL, **72**, 2884 (1950).

(7) M. Mousseron, R. Jacquier and A. Fontaine, *Compt. rend.*, **232**, 1562 (1951).



Sodium ethoxide in ethanol was chosen as the medium for the reaction in order to facilitate separation of the anticipated products by distillation. With bromomethyl cyclohexyl ketone (I, halogen = Br), we obtained results entirely comparable to the results of Wagner and Moore. In addition to the diethyl ketal IXb, we isolated a high-boiling product whose analysis suggests the formula Xb. Such a compound might result from attack of ion VIII on the oxide VII, followed by cyclization and the elimination of ethoxide ion.

When chloromethyl cyclohexyl ketone (I, halogen = Cl) was caused to react with a solution of sodium ethoxide in ethanol, we obtained 20% of the ester IVb, 12% of the ketal IXb and 13% of the dimer Xb. The ester was identified by hydrolysis to the acid which was identical with authentic 1-methylcyclohexanecarboxylic acid in infrared spectrum, melting point and melting point of the amide. The rate of hydrolysis (KOH in diethylene glycol at 100°) was constant and about 10% less than the rate of hydrolysis of methyl 1-methylcyclohexanecarboxylate.

The reaction was then repeated following the method of Mousseron as closely as possible. The chloro ketone was added to a solution of 2.5 equivalents of sodium methoxide in methanol at 0°. The products isolated were IVa (15%), IXa (23%), Xa (16%) and *cyclohexanecarboxylic acid* XI (21%). This IVa hydrolyzed at a rate experimentally identical to that of authentic IVa and 1/20th as fast as authentic Va. The presence of only 5% of Va should have been detectable. The infrared spectrum of this IVa was identical with that of authentic IVa and completely unlike the spectrum of authentic Va. Similarly, the spectrum of the XI isolated here was identical with the infrared spectrum of authentic XI and unrelated to the spectrum of authentic Vc.

Suspecting that water might be involved in the appearance of XI, the experiment was repeated with extreme attention to the exclusion of water. The reaction proceeded quite slowly at 0°. After 45 hours it was possible to isolate the ester IVa (38%), ketal IXa (4%), dimer Xa (20%) and chloride ion (as AgCl, 81%). The total free acid amounted to no more than 1% of the theoretical. The infrared spectrum of this ester IVa was sensibly identical with that of a pure sample of IVa.

It is possible that XI results from hydrolysis of the epoxide to the hydroxy ketone followed by hydrolytic cleavage to the acid and formaldehyde. When hydroxymethyl cyclohexyl ketone was reacting with sodium ethoxide in commercial absolute ethanol with routine precautions against moisture, a 30% yield of the acid XI was isolated. When moisture was more rigorously excluded less than 7% of total acid was formed.

We were unsuccessful in preparing the fluoro ketone I (halogen = F). Reaction of the corresponding diazo ketone with hydrofluoric acid yielded only hydroxyketone. Only starting material was recovered from attempts to combine the bromo ketone with thallium fluoride.[8]

Experimental

Chloromethyl Cyclohexyl Ketone.—A solution of 6.0 g. of the diazo ketone in 50 cc. of petroleum ether was shaken 2 hours with 3.8 cc. of 37% hydrochloric acid. The petroleum ether solution was separated, washed three times with water and dried with sodium sulfate. The chloro ketone crystallized at −40°. After two more recrystallizations it had m.p. 1.0–2.5° and weighed 4.7 g. (74%). The 2,4-dinitrophenylhydrazone had m.p. 132–133.5° (reported 131–132°[7]).

Anal. Calcd. for $C_{14}H_{17}N_4O_4Cl$: C, 49.4; H, 5.03. Found: C, 48.9; H, 5.39.

Bromomethyl cyclohexyl ketone was prepared in an analogous manner, yield 64%, m.p. −1.5–+0.5°, 2,4-dinitrophenylhydrazone m.p. 122.5–123° (reported 130–131°[6]).

Reaction of Chloromethyl Cyclohexyl Ketone with Sodium Ethoxide in Ethanol. (A).—A cold solution of 4.48 g. (0.028 mole) of the chloro ketone in 20 cc. of ethanol was added dropwise with stirring to a solution of 0.66 g. (0.029 mole) of sodium in 20 cc. of ethanol. After 40 minutes the alcohol was removed by vacuum distillation and the precipitate was extracted with petroleum ether. Distillation at 20 mm. yielded ethyl 1-methylcyclohexanecarboxylate IVb (b.p. 80–85°, 0.92 g., 20%), a fraction probably hydroxymethyl cyclohexyl ketone diethyl acetal IXb, (b.p. 100–120°, 0.71 g., 12%) and a fraction probably Xb (b.p. *ca.* 200°, 0.62 g., 13%. *Anal.* Calcd. for $C_{20}H_{32}O_4$: C, 71.4; H, 9.59. Found: C, 71.0; H, 9.57). The ethyl

(8) P. C. Rây, H. C. Groswami and A. C. Rây, *J. Indian Chem. Soc.*, **12**, 93 (1935).

ester was hydrolyzed in a number of sealed tubes by treatment with 0.08 *N* potassium hydroxide in diethylene glycol at 100°. Examined thus, the rate of hydrolysis was about 10% less than that of authentic methyl 1-methylcyclohexanecarboxylate and about $1/_{20}$ of the rate of hydrolysis of methyl benzoate or authentic methyl cyclohexylacetate. There was no indication of a change in rate of hydrolysis corresponding to the presence of mixed esters.

When bromomethyl cyclohexyl ketone was treated as in A above, 25% of IXb and 17% of Xb were isolated. There was no IVb.

The Reaction by the Method of Mousseron. (B).—A solution of 6.0 g. (0.037 mole) of the chloro ketone in 30 cc. of absolute methanol was added with stirring at 0° to a solution of 2.15 g. (0.091 mole) of sodium in 30 cc. of absolute methanol. The methanol was removed by distillation *in vacuo* at 50–60° and the residue was extracted with 25 cc. of water and 25 cc. of petroleum ether. The aqueous layer yielded cyclohexanecarboxylic acid (identified by its infrared spectra, 0.0079 mole, 21%) and 4.88 g. of silver chloride or 91% of the chloro ketone chloride. The organic extract gave on distillation 0.85 g. of methyl 1-methylcyclohexanecarboxylate (IVa) (identified by infrared spectra and rate of hydrolysis, b.p. 60–62° (20 mm.) 15%), 1.60 g. of the dimethyl ketal IXa (b.p. 120° (20 mm.) 23%) and 0.96 g. of the methyl dimer Xa (b.p. 180° (3.5 mm.), 16%).

Reaction of the Chloroketone under Anhydrous Conditions. (C).—A mixture of 50 cc. of methanol and 5 cc. of benzene was placed in a glass tube and warmed until about one-fourth had distilled out. To this dry methanol was added 2.5 g. of sodium hydride. When solution was complete, a solution of 7.05 g. of the chloro ketone (0.044 mole) in 30 cc. of petroleum ether was added. The tube was sealed and kept at 4° for 45 hours. The tube was opened and the excess base was neutralized by the addition of 10 g. of citric acid in 40 cc. of methanol. The solution was concentrated at the water pump and partitioned between water and ether. The water layer gave a precipitate of 5.11 g. of silver chloride or 81% of the theoretical. Extraction of the ether with sodium carbonate solution gave 0.00042 mole of ether soluble acid which could not be further identified. Distillation of the ether solution gave 2.61 g. of ester IVa (38%, b.p. 58° (15 mm.)), 0.34 g. ketal IXa (b.p. 95–100° (15 mm.), 4%) and 1.53 g. of dimer Xa (b.p. 170° (2 mm.), 20%).

When hydroxymethyl cyclohexyl ketone was treated as in B above, 0.65 g. of a white substance precipitated from solution. From this precipitate, there was isolated 0.28 g. of pure cyclohexanecarboxylic acid, m.p. 29–31°, amide m.p. and mixed m.p. with authentic XI amide 185–187° (reported for cyclohexanecarboxamide, 186°,[9] reported for cyclohexylacetamide 171–172°[10]).

When the hydroxy ketone was treated with sodium methoxide under anhydrous conditions as in C above (but at 100° for 45 hours) there was obtained only a 7% yield of ether soluble acid which was not pure enough to identify with certainty.

The infrared absorption maxima of authentic cyclohexanecarboxylic acid and of the XI isolated in B above are 1256, 1212, 1295, 1307, 935, 892, 1181, 1134, 1143, 1105 and 1017 cm.$^{-1}$ in order of decreasing prominence. The maxima for authentic cyclohexylacetic acid are 1292, 939, 1191, 1232, 1250, 1262, 903, 1330, 1169, 1117, 1069, 1080, 1142, 1032 and 1052 cm.$^{-1}$. The maxima for methyl 1-methylcyclohexanecarboxylate are 1207, 1155, 1132, 1108, 1237, 1308, 1187, 1273, 993, 1263, 1045, 1022, 977, 824, 762, 962 and 771 cm.$^{-1}$. The maxima for methyl cyclohexylacetate are 1162, 1284, 1233, 1220, 1187, 1114, 1256, 1005, 1015, 1311, 1079, 897, 937, 840, 828 and 960 cm.$^{-1}$.

(9) W. Markownikoff, *Ber.*, **25**, 3355 (1892).

(10) J. Gutt, *ibid.*, **40**, 2067 (1907).

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[CONTRIBUTION FROM THE DEPARTMENT OF ENTOMOLOGY, UNIVERSITY OF CALIFORNIA CITRUS EXPERIMENT STATION]

Insecticidal Action of Heterocyclic Analogs of 2,2,2-Trichloro-1-(*p*-chlorophenyl)-ethanol[1]

BY R. C. BLINN, F. A. GUNTHER AND R. L. METCALF

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Compounds of the type R–CH_2OH·CCl_3, when R is phenyl, *p*-chlorophenyl, *p*-tolyl, thienyl, 5-chlorothienyl, furyl, pyrryl, or N-methyl pyrryl, were prepared and tested as insecticides against four species of insects. From the toxicity data against mosquito larvae and greenhouse thrips it would appear that the pseudo-aromatic heterocyclic rings function as spacers with polarizable characteristics.

The over-all mechanism of insecticidal action of DDT, 2,2,2-trichloro-1,1-bis-(*p*-chlorophenyl)-ethane (I) has not yet been ascertained even for a single species of insect, and the effect on insect toxicity of changing the ring substituents is still under study. Few investigations have been concerned with the effect of interchanging heterocyclic and aromatic rings. Several reports have appeared on the insecticidal properties of thiophene analogs of DDT.[2–5] These revealed that thiophene substitution for the benzene ring was accompanied by a decrease in toxicity upon most of the test insects. However, the mode of action of 2,2,2-trichloro-1,1-bis-(5-chlorothiophene-2)-ethane was shown to resemble qualitatively that for DDT and appeared to affect the same locus in the insect nervous system.[5] Compounds of the 2,2,2-trichloro-1-aryl-ethanol type are synthetic precursors of the DDT-type molecule, yet they exhibit narrow-spectrum insecticidal properties; they are thus ideally suited for activity–structure studies with certain insects.

The compounds in Table I were synthesized. These compounds and their acetates were assayed against mosquito larvae (*Culex quinquefasciatus* Say), greenhouse thrips (*Heliothrips haemorrhoidalis* Bouché), the house fly (*Musca domestica* L.), and citrus red mite (*Paratetranychus citri* McG.).

The preparation of the 2,2,2-trichloro-1-aryl type ethanols using chloral and aromatic Grignard reagents has been reported.[6] Recently the synthesis

(1) Paper No. 771, University of California Citrus Experiment Station, Riverside, California. Presented before the Division of Agricultural and Food Chemistry, 123rd Meeting, Am. Chem. Soc., Los Angeles, 1953.

(2) R. L. Metcalf and F. A. Gunther, THIS JOURNAL, **69**, 2579 (1947).

(3) E. A. Prill, M. E. Synerholm and A. Hartzell, *Contrib. Boyce Thompson Inst.*, **14**, 341 (1946).

(4) P. Truitt, M. Mattison and E. Richardson, THIS JOURNAL, **70**, 79 (1948).

(5) R. L. Metcalf, *Science*, **108**, 80 (1948).

(6) H. L. Haller, P. D. Bartlett, H. L. Drake, M. S. Newman, S. J. Cristol, C. M. Eaker, R. A. Hayes, G. W. Kilmer, B. Magerlein, G. P. Mueller, A. Schneider and W. Wheatley, THIS JOURNAL, **67**, 1591 (1945).