Acknowledgment.—The author wishes to thank Miss Marcia K. Rukwid for her valuable technical assistance.

Summary

The preparation of a series of 2-aryl-3-dialkylaminoalkyl-4-thiazolidones by the reaction of methyl thioglycolate with several benzylidene dialkylaminoalkylamines is reported.

Several of the compounds reported showed marked local anesthetic activity.

Rensselaer, N. Y. Received December 17, 1948

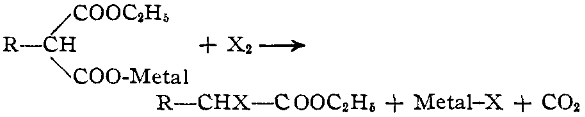
[Contribution from the Chemistry Laboratory of the University of Texas]

A New Method for the Preparation of α-Bromoesters[1]

By J. R. Dice and J. N. Bowden[2]

The reaction of the metal salts of carboxylic acids with chlorine or bromine to yield an alkyl or aryl halide and carbon dioxide[3] is well known. Recently, Hunsdiecker[4] employed this reaction in the preparation of α-bromo aliphatic acids from the half-esters of ω,ω'-dicarboxylic acids. There are no reports in the literature of the use of the metal salts of the half acid esters of alkylmalonic acids in this synthesis.

It was reasoned that if one mole of halogen would react with the metal salts of the monoesters of alkylmalonic acids in the same manner as with simple carboxylic acid salts, the product would be an α-haloester.



$$R{-}CH(COOC_2H_5)(COO\text{-Metal}) + X_2 \longrightarrow R{-}CHX{-}COOC_2H_5 + \text{Metal}{-}X + CO_2$$

To test this hypothesis the dry potassium salts of the monoesters of several alkylmalonic acids were treated with bromine. Although the expected α-bromoesters were obtained, the yields in most experiments were relatively low. In general, bromination of acid chlorides[5] would be a preferred route to these compounds. Compounds prepared by the new method were ethyl α-bromobutyrate, ethyl α-bromoisovalerate, ethyl α-bromocyclohexylacetate, ethyl α-bromocaproate and ethyl α-bromo-β-phenylpropionate.

Although silver salts have been used most frequently in the reaction, other metal salts such as mercury, copper or potassium also have been used successfully.[6] In this study the potassium salts were utilized throughout and carbon tetrachloride was used as solvent.

With the potassium salt of monoethyl malonate we obtained the same result in carbon tetrachloride as that reported by Freund[7] for aqueous solution; *i. e.*, a mixture of ethyl bromoacetate and ethyl dibromoacetate was formed. In this reaction hydrogen bromide was evolved during the addition of bromine. The liberation of hydrogen bromide is apparently caused by a substitution reaction which occurs prior to or simultaneously with decarboxylation. Substitution does not follow decarboxylation, since ethyl bromoacetate does not react visibly with bromine under the conditions of our experiment.

Experimental

Potassium Salts of Monoesters of Alkyl Malonic Acids.—The ethyl alkylmalonates used were prepared from ethyl malonate (b. p. 198° at 746 mm.) and the respective alkyl halides essentially as described by Adams and Johnson,[8] and they were redistilled before use. Potassium salts of the mono acid esters of these compounds were synthesized following the procedure of Freund.[7] To a solution of 0.15 mole of diethyl alkylmalonate in 100 ml. of absolute alcohol was added, with stirring, a solution of 8.7 g. (0.15 mole) of potassium hydroxide in 100 ml. of absolute alcohol. The solution was allowed to stand at room temperature for four to twelve hours; the *p*H of the final mixture had a value between 7 and 8 as measured with *p*-Hydrion paper. Any solids which formed were assumed to be the dipotassium salt of the alkylmalonic acid and were removed by filtration.

Table I

Ethyl α-Bromoesters

α-Bromoesters	Yield,[a] %	B. p., °C.	Mm.	n^{25}_D	d^{25}_4
Acetate[b]	23	165–168	749		
Butyrate	36	177–180	745		
Caproate	67	208–209	748[c]	1.4468	1.2210
iso-Valerate	30	185–187	754[d]	1.4392	1.2325[e]
Cyclohexyl-acetate[f]	45	133–136	13	1.4708	1.1466
β-Phenyl-propionate	80	155–159	15	1.5180[g]	

[a] All yields are based on the weight of diethyl alkylmalonate employed. [b] Hydrogen bromide was evolved during the bromine addition and a 20% yield of ethyl dibromoacetate (b. p. 185–192° (749 mm.)) also was obtained. [c] 111–113° at 25 mm. [d] 105–115° at 25 mm. [e] Schleicher, *Ann.*, 267, 116 (1892), reported d^{12}_{12} to be 1.2276. [f] J. v. Braun, *Ber.*, 2184 (1923). [g] This compound decomposed on standing for twenty-four hours, so a density determination was not obtained.

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[1] This work was supported by a grant from the Research Institute, the University of Texas, Project 186.

[2] From the M. A. Thesis of J. N. Bowden.

[3] Kleinberg, *Chem. Rev.*, **40**, 381 (1947).

[4] Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

[5] *Cf.* Bagard, *Bull. Soc. Chim. France*, [4] **1**, 310 (1907); Ingold, *J. Chem. Soc.*, **119**, 316 (1921); Schwenk and Papa, This Journal, **70**, 3626 (1948).

[6] Hunsdiecker, Hunsdiecker and Vogt, U. S. Patent, 2,176,181 (1939); see also ref. 4.

[7] Freund, *Ber.*, **17**, 780 (1884).

[8] Adams and Johnson, "Elementary Laboratory Experiments in Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, p. 329.

The alcohol was distilled until only a thick sirup remained in the flask. The last traces of solvent were removed *in vacuo* and the resulting crystals were placed in a vacuum desiccator for twelve hours. The salts were used without further purification.

Preparation of α-Bromoesters.—The dried, finely pulverized, potassium salt was mixed with 100 ml. of carbon tetrachloride. The ice-cold mixture was stirred vigorously while a solution of 25 g. (0.15 mole) of bromine in 50 ml. of carbon tetrachloride was added dropwise over a period of two to four hours. The bromine was decolorized rapidly at the start of the reaction, but persisted after all of the bromine solution had been added. The mixture was filtered and the solvent was removed in a current of air. The residue was distilled at reduced pressure to give in every case a colorless, strongly lachrymatory liquid. The yields and physical constants of the compounds prepared are given in Table I.

Summary

The reaction of the potassium salts of monoethyl alkylmalonates with bromine provides a new method of preparing α-bromoesters.

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[CONTRIBUTION FROM THE VIRUS LABORATORY, UNIVERSITY OF CALIFORNIA[1]]

The Apparent Sulfur in Cucumber Virus 4

BY C. A. KNIGHT

Rather extensive chemical analyses have been made of tobacco mosaic virus (TMV) and several of its strains; and cucumber viruses 3 and 4 (CV3 and CV4) have been included in these studies.[2] The consideration of CV3 and CV4 as strains of TMV has been based on their mutual possession of an uncommon size and shape, on weak but definite serological cross reactions, on a common unusual resistance to heat and desiccation, and on possession of apparently identical quantities of protein and pentosenucleic acid.[3–5] On the other hand, it has not been possible to perform one of the tests of strain relationship, the cross-protection test, for as yet no common host has been reported for TMV and the cucumber viruses. Furthermore, it appears that the particles of CV3 and CV4 differ slightly but significantly in size from those of TMV and some of its other strains.[6,7] However, whether they are actually distantly related strains of TMV as supposed, or whether they are distinct viruses, it seems evident that the facts revealed from their study could ultimately be brought to bear on problems of the relationship of biological, serological, and physical properties to the chemical composition and structure of the virus, or of biologically active proteins in general. As a consequence of this viewpoint, it seemed imperative to determine the nature of the sulfur in CV3 or in CV4, for, while the sulfur of TMV and of most extensively studied proteins has been shown to occur mainly in well-known sulfur-containing amino acids, the sulfur apparently present in CV3 and CV4 has eluded identification.[3,8]

It will be shown in the present report that CV4 differs decidedly from TMV and some of its strains in that CV4 probably contains no sulfur at all.

Materials and Methods

Preparation of Virus.—Highly purified preparations of CV4 were obtained from the expressed juice of appropriately diseased cucumber plants by differential centrifugation as previously described.[3] The salt content of the preparations was reduced to a very low level by handling the virus in distilled water during two or more cycles of centrifugation, by dialysis against flowing distilled water, or by electrodialysis. These preparations were then frozen and dried *in vacuo*, and then further dried to constant weight at 110° in a drying oven.

Sulfur Analyses.—The first sulfur values for highly purified, dried preparations of CV3 and CV4 were those of Bawden and Pirie in which a range of 0.0 to 0.6% sulfur was reported.[9] No explanation of the possible significance of this range of results was advanced, and the value recorded later by Bawden appears to be a mean of the earlier determinations, namely, 0.3%.[4] A figure of 0.85% sulfur was given by Knight and Stanley as the mean of 8 analyses made on 3 different preparations of CV4.[3] Since that time and including the individual analyses leading to the figure just given, a total of forty-one analyses have been made by three different analysts on thirteen of our preparations. The analyses were made by the customary Carius pressure-tube method and yielded an average of 0.6% sulfur, but the individual values obtained ranged from 0.07 to 1.26%. Furthermore, a given analyst obtained with the same preparations of virus, but on different occasions, sulfur values which differed by as much as 50%. Also, different analytical laboratories, analyzing portions of the same sample of virus, reported results equivalent to three- to ten-fold differences in sulfur content. No analyst was consistently high or low in his results.

Despite this confusing situation, the results seemed to indicate that there is some sulfur in CV4, but that it is for some unknown reason, inherently difficult to obtain a reliable estimate of its quantity.

Attempts to Identify Sulfur in CV4.—A series of tests made on numerous preparations of CV4 over a period of several years has established the absence from this virus of amounts greater than traces of the amino acids, cys-

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(1) This investigation was begun in the laboratories of the Rockefeller Institute for Medical Research, Princeton, N. J. Presented in part before the Division of Biological Chemistry at the 115th Meeting of the American Chemical Society at San Francisco, March 28–April 1, 1949.

(2) C. A. Knight, *J. Biol Chem.*, **171**, 297 (1947).

(3) C. A. Knight and W. M. Stanley, *ibid.*, **141**, 29 (1941).

(4) F. C. Bawden, "Plant Viruses and Virus Diseases," second ed., Chronica Botanica Company, Waltham, Mass., 1943, p. 162.

(5) C. A. Knight and W. M. Stanley, *J. Biol. Chem.*, **141**, 39 (1941).

(6) J. D. Bernal and I. Fankuchen, *Nature*, **139**, 923 (1947).

(7) C. A. Knight and G. Oster, *Arch. Biochem.*, **15**, 289 (1947).

(8) C. A. Knight, Abstracts, Meeting of the American Chemical Society, September 8–12, 1941.

(9) F. C. Bawden and N. W. Pirie, *Brit. J. Exptl. Path.*, **18**, 275 (1937).