2. As the reactions by which these addition products are formed are reversible, the result of operating in dilute solution is an equilibrium mixture containing all three as well as their components.
3. By selecting suitable conditions it is possible to get any one of the three at will.
4. Pentadienones containing substituted phenyl groups combine with the ester less rapidly than dibenzal acetone but the difference is not pronounced.
5. The hindrance of the malonic ester residue in I, to the addition of another molecule of the ester is not conspicuously greater than that of hydrogen in the same position.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY, NO. 24]

ALKYLCHLOROMALONAMIDES. THE INFLUENCE OF HOMOLOGY ON TASTE

BY ARTHUR W. DOX AND BRUCE HOUSTON

RECEIVED FEBRUARY 8, 1924

In an attempt to prepare a cyclic derivative by condensation of sulfuryl chloride with ethylmalonamide, a white crystalline substance was obtained which was found to possess a decidedly sweet taste. The substance was later identified as ethylchloromalonamide. Instead of the expected condensation a simple chlorination had occurred. A search through the literature convinced us that only three chloromalonamides had previously been described, namely, chloromalonamide,[1] dichloromalonamide[2] and benzylchloromalonamide.[3] In the description of these derivatives no mention is made of taste. Having found that dichloromalonamide also has a decidedly sweet taste, we undertook to prepare a number of homologs to ascertain whether a constant variation in sweetness would occur with increasing size of alkyl groups. The unchlorinated alkylmalonamides were for the most part available as preparations obtained in previous work. These were all practically tasteless.

In addition to the three known derivatives already mentioned, chloromalonamides containing the methyl, ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*butyl, *iso*amyl and *n*-hexyl groups, were prepared and identified and their tastes noted in accordance with the test of sweetness proposed by Mulliken.[4]

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[1] Conrad and Bischoff, *Ann.*, **209**, 231 (1882).

[2] Conrad and Bischoff, *Ber.*, **24**, 2994 (1891).

[3] Bischoff and Emmert, *Ber.*, **15**, 1113 (1882).

[4] Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, **1916**, vol. II, p. 43.

Experimental Part

Chloromalonamide.—This was prepared according to the method of Conrad and Bischoff[1] from ethyl chloromalonate and alcoholic ammonia. Attempts to chlorinate the amide directly gave mixtures that were difficult to purify on account of the presence of the dichloro derivative.

Dichloromalonamide.—This substance, previously prepared and described by Conrad, was made by a new method.

Two g. of malonamide was dissolved in 35 cc. of glacial acetic acid and a current of chlorine passed in for three hours. A white crystalline solid which separated was filtered off and washed with carbon tetrachloride. By evaporating the acetic acid filtrate under reduced pressure to about one-fourth the original volume a further separation of the product was obtained. The yield was 3.4 g. or practically 100% of white crystals melting at 205°.

The following homologs, with the exception of the *iso*propyl derivative, were prepared by the method just outlined. Glacial acetic acid was found to be the most satisfactory solvent, since it dissolves the amides more easily than other organic solvents and there is little chance of hydrolyzing the amide. *iso*Propylmalonamide could not be chlorinated directly. Whether or not other secondary alkyls present the same difficulty has not yet been determined.

TABLE I

HOMOLOGS OF CHLOROMALONAMIDE

R	M. p. °C.	Cryst. form	Yield %	Analysis Chlorine	
				Calc. %	Found %
Methyl	224–225	needles	96	23.58	[a]
Ethyl[b]	135	prisms	98	21.58	21.97
n-Propyl	150	prisms	96	19.88	20.11
*iso*Propyl[c]	177	needles	55	19.88	19.99
n-Butyl	136	needles	96	18.43	18.16
*iso*Butyl	132	scales	92	18.43	18.86
iso-Amyl	157	scales	96	17.24	17.49
n-Hexyl	130	needles	95	16.16	16.06
Benzyl	183–185[d]	prisms	91	15.67	15.36

[a] Determination of chlorine on three separate preparations gave closely agreeing values, all of which were about 2% below the calculated value, however. We are at a loss to explain this, since no difficulty was experienced in identifying the other homologs by their chlorine contents.

[b] The preparation from ethyl malonamide and sulfuryl chloride also melted at 135°.

[c] From a solution of 20 g. of methyl *iso*propylchloromalonate in 200 cc. of saturated alcoholic ammonia by evaporation under reduced pressure after 6 days.

[d] Bischoff and Emmert give 80°.

Methyl *iso*Propylchloromalonate.—On account of the greater ease of amide formation from methyl as compared with ethyl esters, this hitherto undescribed substance was prepared as an intermediate.

Fifty g. of methyl *iso*propylmalonate was placed in a tared flask and a stream of chlorine passed in at a temperature of about 60° until the gain in weight was slightly in excess of that calculated for the substitution of one chlorine atom. The liquid was then treated with water and with thiosulfate solution to remove hydrochloric acid and excess of chlorine, and dried with calcium chloride. Purification was effected by distillation at reduced pressure. The yield was 50 g. or 85% of a colorless oil boiling at 110–112° at 37 mm., 221–222° at 757 mm. The substance has a pungent but not unpleasant odor.

Analysis. Subs., 0.2310: AgCl, 0.1556. Calc. for $C_8H_{13}O_4Cl$: Cl, 17.02. Found: 16.64.

The mono- and dichloromalonamides and the methyl-, ethyl-, *n*-propyl-, *iso*propyl-, *n*-butyl- and *n*-hexylchloromalonamides are all decidedly sweeter than sucrose when compared in dilute aqueous solution. Monochloro- and methylchloromalonamide have approximately three times the sweetening power of sucrose. Dichloromalonamide, and ethyl-, *n*-propyl-, *iso*propyl- and *n*-butylchloromalonamides have about nine times the sweetening power of sucrose. The *n*-hexyl derivative is quite remarkable in this respect, having about three hundred times the sweetening power of sucrose. This observation was further substantiated by comparison with a solution of "dulcin" (*p*-phenetyl-urea) which is stated to be 250 times as sweet as sucrose. The *n*-hexyl derivative showed greater sweetening power than dulcin. On the other hand, the *iso*butyl, *iso*-amyl and benzyl derivatives stand in sharp contrast with the other members of the series. They are decidedly bitter, and devoid of any sweet taste. The *n*-butyl derivative is both bitter and sweet.

Cohn[5] in his exhaustive treatise on the taste of organic substances, mentions dibromomalonamide as having an extremely unpleasant sweetish taste and causing irritation in the throat. We tested this substance also and found that it has at first a sweet taste, followed immediately by a disagreeable "oxidizing" taste almost indistinguishable from that of hydrogen peroxide. The dichloro derivative is evidently much more stable than the dibromo derivative and functions less readily as an oxidizing agent. The sweet taste of the hexyl derivative was free from any disagreeable aftertaste, and in this respect differed markedly from the four derivatives in which sweetness was either accompanied or entirely obscured by bitterness.

Incidentally, it may be stated that *n*-hexylchloromalonamide is probably the sweetest known aliphatic substance. It is less sweet than saccharin, which is said to be 550 times as sweet as sucrose. Dulcin is 250 times as sweet as sugar, and "glucin," a phentriazine derivative, is 100 times as sweet as sugar. Sweetening power of artificial products in terms of sugar varies, of course, with the concentration. Our comparison is on the basis of a 6% sucrose solution. The sweetest substance thus far prepared is the α-anti-aldoxime of perillaldehyde[6] with a sweetness 2000 times that of sucrose, but the constitution of this substance is not known.

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[5] Cohn, "Die organischen Geschmacksstoffe," F. Siemenroth, Berlin, **1914,** p. 139.

[6] Jap. pat., 35,332, **1919**; *C. A.* **14,** 2528 (1920).

At any rate, a simple aliphatic derivative, such as *n*-hexylchloromalonamide, with a sweetening power of 300, is something of a novelty. This substance has the disadvantage, however, of difficult solubility in water.

Summary

In a series of alkylchloromalonamides, with alkyl varying in size from methyl to hexyl, all the normal derivatives were found to have a decidedly sweet taste. The *n*-butyl derivative was both bitter and sweet. With branched-chain alkyls, such as *iso*butyl and *iso*-amyl, bitterness predominated and entirely masked any evidence of sweetness. The maximum sweetness was reached with the *n*-hexyl derivative of which 1 part in 5000 of water had the sweetness of a 6% sucrose solution. Most remarkable is the fact that the next lower homolog, *iso*-amylchloromalonamide, which differs by one carbon and a branching of the chain, is intensely bitter. No constant variation in sweetness could be established in this series.

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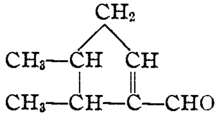
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

STUDIES ON THE REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES. IX. SYNTHESIS OF 2,3-DIMETHYL-CYCLOPENTENE ALDEHYDE[1]

BY ROLAND R. READ AND HAROLD HIBBERT

RECEIVED FEBRUARY 9, 1924

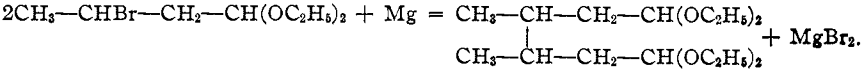
In the previous communication (Part VIII) it was shown that crotonaldehyde on electrolytic reduction yields an unsaturated aldehyde to which the following structure was assigned,



namely, 2,3 dimethyl-cyclopentene aldehyde.

In view of the unusual course of this reaction, it was considered advisable to establish, definitely, the structure of the product by direct synthesis, and this has been effected in the following manner:

β-Bromobutyraldehyde diethyl acetal, on treatment with magnesium in ether solution, is converted into the diethyl acetal of adipic aldehyde.



$$2\mathrm{CH_3—CHBr—CH_2—CH(OC_2H_5)_2} + \mathrm{Mg} = \begin{array}{l}\mathrm{CH_3—CH—CH_2—CH(OC_2H_5)_2}\\ \qquad\;|\\ \mathrm{CH_3—CH—CH_2—CH(OC_2H_5)_2}\end{array} + \mathrm{MgBr_2}.$$

This, on hydrolysis with dil. sulfuric acid, yields 2,3-dimethyl-cyclo-

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[1] This work was carried out at the University of Vermont.