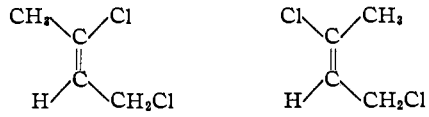
uents are chlorine and hydrogen with a consequent wide difference in the relative reactivity of the geometrical isomers. When the two substituents are chlorine and a methyl group as with 1,3-dichloro-2-butene the difference in reactivity is only slight with the *cis* form being the most reactive.



cis, more reactive *trans*, less reactive

The larger methyl group would be expected to cause the *trans* isomer to be less reactive.

A methyl group increases the reactivity of the allylic chlorine for this reaction when it is not in the *cis* position, where its activating effect is counteracted by its steric hindrance. This activation of the allylic chlorine by a methyl group on the number 3 carbon has been noted by Tamele, *et al.*,[8] and in these laboratories with 1-chloro-3-methyl-2-butene.[9]

Sodium Ethoxide.—The two isomers of 1,3-dichloro-2-butene show a relatively small difference in reactivity with the higher boiling isomer being the more reactive. This is similar to the results obtained with 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene[2] and provides further evidence that this reaction is of a type different from that with potassium iodide and is only slightly affected by geometrical isomerism. As with the reaction with potassium iodide, substituting a methyl group for a hydrogen on the number 3 carbon increases the reactivity of the allylic chlorine. This observation has also been made by Tamele, *et al.*[8]

(8) Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

(9) Unpublished work of Louis S. Gerhardt.

Summary

The relative reactivity of the geometrical isomers of 1,3-dichloro-2-butene has been determined for their reaction with potassium iodide, sodium ethoxide, and the cuprous chloride catalyzed hydrolysis reaction.

The high boiling (beta) isomer was the most reactive with each reagent.

The high boiling (beta) isomer is converted at its boiling point into the low boiling (alpha) isomer.

For these reasons the low boiling (stable) isomer of 1,3-dichloro-2-butene has tentatively been assigned the *trans* structure.

A methyl group on the number 3 carbon increases the reactivity of the allylic chlorine of 1,3-dichloro-2-butene.

AUSTIN, TEXAS RECEIVED APRIL 20, 1948

[CONTRIBUTION FROM PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

Preparation and Properties of Certain Alkyl Azamalonates[1]

BY CHESTER E. SLIMOWICZ AND ED. F. DEGERING

Although urethan, or ethyl carbamate, and many of its derivatives have been investigated as physiologically active agents,[2,3] no record has been found of a similar study of the unsubstituted alkyl azamalonates. The preparation of a few of these compounds has been reported, namely, ethyl methyl,[6] dimethyl,[7] diethyl,[4] and the ethyl phenyl[5] azamalonates.

Recently, Tompkins and Degering[10] have described a series of N-substituted diethyl azamalonates. In connection with this work, it was deemed desirable to prepare a series of N-unsubstituted azamalonates of the general formula ROOCNHCOOEt. These compounds were prepared by a modification of the procedure employed by Kraft.[8] The reaction may be represented by the equations

$$H_2NCOOEt + Na \longrightarrow H(Na)NCOOEt + \tfrac{1}{2}H_2, \text{ then}$$
$$H(Na)NCOOEt + ClCOOR \longrightarrow ROOCNHCOOEt + NaCl$$

It was found, however, that besides the expected mixed alkyl ethyl ester there were obtained the symmetrical diethyl and dialkyl di-esters. It is significant to note that the yield of the dialkyl di-ester, in general, was higher than that for the expected mixed ester. This result may be interpreted by assuming that a redistribution reaction occurred.

The compounds were either white crystalline solids having fairly low melting points, or colorless liquids having high boiling points. In all cases the di-esters were solids and the mixed esters were liquids. All of the compounds were generally soluble in the common organic solvents and insoluble in water. Their identification was based

(1) Abstracted from a thesis presented by Chester E. Slimowicz to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Master of Science, Feb., 1947.

(2) Dixon, "Manual of Pharmacology," Arnold, London, 1908, p. 68.

(3) Hirshfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).

(4) Diels, *Ber.*, **36**, 736 (1903); see also refs. 6, 8, 9a, 9b, 9c.

(5) Diels and Jacoby, *ibid.*, **41**, 2397 (1908).

(6) Diels and Nawiasky, *ibid.*, **37**, 3672 (1904).

(7) Franchimont and Klobbie, *Rec. trav. chim.*, **8**, 294 (1889).

(8) Kraft, *Ber.*, **23**, 2786 (1890).

(9) (a) Wurtz and Henninger, *Chem. Zentr.*, **56**, 564 (1885); (b) *Bull. soc. chim.*, **44**, 30 (1885); (c) *Compt. rend.*, **100**, 1419 (1885).

(10) Tompkins with Degering, THIS JOURNAL, **69**, 2616 (1947).

TABLE I

ALKYL AZAMALONATES, $RO_2C{\cdot}NH{\cdot}CO_2R'$

Compound	M. p., °C.[a]	B. p. °C.	Mm.[b]	$n^{27}D$	Molecular formula	Nitrogen, % Calcd.	Found	Fungicidal properties[c] % Inhibition[d] *A. Niger*,[e] *M* 0.01	0.001	*Trichoderma T-1*,[f] *M* 0.01	0.001
Diethyl	49–50				$C_6H_{11}O_4N$	8.70	8.71 8.50	66	18	50	35
Butyl ethyl		104–106	4	1.4407	$C_8H_{15}O_4N$	7.41	7.24 7.44	87	53	100	65
Dibutyl	42–43				$C_{10}H_{11}O_4N$	6.45	6.34 8.28	100	Y	100	Y
Allyl ethyl		112–115	3	1.4544	$C_7H_{11}O_4N$	8.10	8.43 8.11	60	29	49	13
Diallyl	43–45				$C_8H_{11}O_4N$	7.57	7 66 7.78	65	22	45	+1
Amyl ethyl		102–106	1	1.4395	$C_9H_{17}O_4N$	6.90	6.99 6.87	100	60	100	71
Diamyl	61–62				$C_{12}H_{23}O_4N$	5.71	5.80 5.71	76	66	67	83
Ethyl hexyl		111–116	2	1.4468	$C_{10}H_{14}O_4N$	6.45	6.25 6.72	87	80	83	65
Dihexyl	39–40				$C_{14}H_{27}O_4N$	5.13	4.92 5.01	88	82	79	79
Ditetradecyl	77–78				$C_{30}H_{59}O_4N$	2.82	2.96 3.02	X	3	X	+88

[a][b] Melting and boiling points are uncorrected. [c] Results are averages of triplicates. One hundred per cent. inhibition on all standard G-4. 2,2'-Methylene bis-(4-chlorophenol) control plates at 0.01 or 0.001 *M*. No tests performed with *Chaetomium globosum* since medium is not yet satisfactory. No tests performed with *Penicillium citrinum* since this organism is to be used only with mercury containing compounds. [d] % Inhibition = 100 − (Radial growth in mm. per hr. of test compound plate/radial growth in mm. per hr. of untreated control plate × 100). An interesting fungicide is considered to be one which would show 100% inhibition at concentrations of 0.001 *M* or lower. [e] *A. Niger* is TC 215-4247, Steinberg. [f] *Trichoderma T-1* is A. T. C. C. 9645. Y = not tested at this concentration. X = sample insufficient to test at this concentration. + Figures indicate that test compound plate growth exceeded that of normal untreated control.

on the characterization of the saponification products of each and on nitrogen determinations.

The compounds prepared, together with the evaluation of their fungicidal activity and their physical properties are summarized in Table I.

Experimental[11]

The alkyl chloroformates used in this investigation were prepared by a method developed in this Laboratory by Engelman and Degering[12] in which yields of 85 to 95% were obtained.[13] Other investigators have reported yields approximately half these values.[14] The reactions were carried out in an efficiently ventilated hood.

The following examples may be considered as typical.

Butyl Chloroformate.—One mole (74 g.) of butyl alcohol was added dropwise (or in small amounts, if the alcohol is a solid), with stirring, to a half-molar excess (85 g.) of liquid phosgene contained in a large $1\frac{1}{2}'' \times 12''$ test-tube immersed in a salt-ice, or Dry Ice–trichloroethylene bath. (The latter was found a little more convenient to handle.) The reaction temperature during the addition of the alcohol was maintained at 0°, or slightly lower, otherwise the formation of the carbonate is favored. When all of the alcohol had been added, the bath temperature was allowed to rise very slowly to room temperature. (During this period the stopcock of the dropping funnel, which was protected by a drying tube filled with calcium chloride, was left open to permit the escape of excess phosgene. In case the phosgene boiled off too rapidly, it was necessary to cool the bath.) Then the reaction mixture was stirred ten to fifteen hours. The stirrer and dropping funnel arrangement was replaced by a stopper containing an inlet tube extending to the bottom of the reaction vessel and an outlet tube. The inlet tube was connected to a source of air and the reaction mixture aerated to expel the excess phosgene. As a precautionary measure the outlet tube was extended well into the hood vent by means of a rubber tubing connection.

After all of the phosgene had been expelled, the butyl chloroformate was purified[15] by distillation at reduced pressure. The fraction, b. p. 35–36° (13 mm.), weighed 117 g. (85% of the theoretical yield).

Butyl Ethyl and Dibutyl Azamalonates.—One mole (89 g.) of urethan was dissolved in 1.2 l. of xylene (purified grade) contained in a 3-l., three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and water-cooled reflux condenser protected by a drying tube filled with anhydrous calcium chloride. One gram atom (23 g.) of metallic sodium was added and the mixture stirred and heated cautiously until all of the sodium had reacted. When the mixture had cooled to approximately 60°, one mole (136 g.) of butyl chloroformate was added dropwise. An exothermic reaction accompanied the addition of the chloroformate. The mixture was stirred at room temperature for approximately thirty hours, after which time it was filtered through a fritted glass filter. Three to five grams of filter-cel was stirred in with the mixture prior to filtration in order to facilitate the separation of the finely precipitated sodium chloride.

A red-brown colored oil was obtained from the filtrate after the solvent had been distilled at reduced pressure. On distillation, 116 g. of colorless liquid, b. p. 138–150° (13 mm.), was collected. This distillate was fractionated to give 20 g. of solid, b. p. 90–104° (3–4 mm.); 52 g. of liquid, b. p. 104–115° (3–4 mm.); and 42 g. of a solid pot residue.

The 20 g. fraction was recrystallized twice from petroleum ether (60–70°) to yield 14 g. of fine white needles, m. p. 48–50°. A mixture of this product with an authentic specimen of diethyl azamalonate, m. p. 49–50°, did not depress the melting point.

The 52 g. fraction was rectified in a 24-in. Podbielniak type column and yielded 25 g. of colorless liquid, b. p. 104–106° (4 mm.). Five grams of this product was refluxed for thirty hours with 40 ml. of 40% aqueous sodium hydroxide. The distillate from the alkaline solution was saturated with anhydrous potassium carbonate. The resulting alcoholic phase was pipetted into a 10-ml. Vigreux type distilling flask and fractionated to give one fraction distilling up to 85°, and the other, 85–115°. The lower boiling fraction gave positive iodoform and ceric nitrate tests; the higher boiling one gave a negative iodoform test and a positive ceric nitrate test. Each of these fractions was treated with 0.5 g. of 3,5-dinitrobenzoyl chloride to yield an ester, m. p.'s 90–91° and 62–63°, respectively, for the lower and higher boiling fractions. The

(11) All melting and boiling points are uncorrected.

(12) Engelman, Doctoral thesis, Purdue University, Feb., 1948.

(13) A thorough search of the literature by the junior author of this paper, however, disclosed that Thiele used a similar procedure in the synthesis of benzyl chloroformate, but failed to report the yield; Thiele and Dent, *Ann.*, **302**, 257 (1898).

(14) Hamilton and Sly, THIS JOURNAL, **47**, 437 (1925).

(15) Tetradecyl chloroformate was not distillable.

reported melting point for the ethyl ester is 93°; for butyl 64°.[16]

Anal. Calcd. for $C_8H_{15}O_4N$: N, 7.41. Found: N, 7.24, 7.44.

The 42-g. pot residue was recrystallized three times from ether–petroleum ether mixture to yield 38 g. of fine white needles, m. p. 42–43°. Four grams of this solid was saponified in the manner previously described. The saponification distillate gave a positive ceric nitrate test and a negative iodoform test. Treatment of the alcoholic phase of the distillate with 3,5-dinitrobenzoyl chloride resulted in an ester, m. p. 63–64°. The reported melting point for butyl 3,5-dinitrobenzoate is 64°.[16]

Anal. Calcd. for $C_{10}H_{19}O_4N$: N, 6.45. Found: N, 6.34, 6.28.

(16) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 185.

Acknowledgment.—The authors wish to express their appreciation to the Hooker Electrochemical Company for the generous supply of allyl chloroformate.

Summary

The synthesis of a number of new alkyl azamalonate has been described and a redistribution reaction has been postulated for the formation of the symmetrical di-esters. These compounds are to be tested for their pharmacological activity.

Fungicidal data are presented.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED, HUNGARY]

A Synthesis of Adrenaline-like Compounds

BY GÁBOR FODOR AND ÖDÖN KOVÁCS

According to a recent review[1] on the subject, the best method of obtaining aryl methylaminoethanols, *e. g.*, synephrine, is the condensation of ω-chloro-*p*-benzoyloxyacetophenone with methylbenzylamine, followed by hydrolysis and subsequent hydrogenation.[2] Another useful method[3] consists of the condensation of hydroxy derivatives of benzaldehyde bisulfite with a salt of nitromethane, followed by the reductive condensation of the nitro ethanol with formaldehyde[3] to the corresponding aryl aminoethanol.

An excellent synthesis of ephedrine is described by Manske and Johnson[4] from phenyl methyl methyl diketone with methylamine. In this process the authors applied, for the first time, ketonic aldehydes and diketones as starting materials[5]; no similar reactions have been reported previously in the literature.

However, the use of methoxy and hydroxy derivatives, even in the case of diketones, offered some difficulties. It was thought, therefore, to be of interest to work out a synthesis of hydroxy aryl ethanolamines, starting from hydroxy arylglyoxals, similar to that of phenyl-methylaminopropanol.[4]

4-Hydroxyphenylglyoxal[6] (II) has been obtained from phenol through 4-hydroxyphenyltrichloromethyl-carbinol.[7] We have synthesized it in another manner: first, 4-hydroxyacetophenone (I) was prepared according to Meerwein.[8] This was then oxidized with selenium dioxide, without protecting the phenolic group, to 4-hydroxyphenylglyoxal; this latter was isolated as a crystalline hydrate and further identified by its well defined quinoxaline derivative (V). Several attempts were made for the condensation of this ketonic aldehyde with methylamine, with subsequent or simultaneous reduction of the azomethine formed (III). However, when this amorphous compound or an equimolecular mixture of the glyoxal and of methylamine was reduced catalytically, a sudden initial reaction occurred, but the hydrogen consumption stopped with an absorption of only 0.5 to 0.8 mole of hydrogen against the calculated 2 moles. The expected 1-(4-hydroxyphenyl)-2-methylamine ethanol (IV) could not be obtained from the reaction mixture. We supposed that our failure to obtain the desired compound was due to the fact that the 4-hydroxyphenylglyoxal reacted with methylamine in much the same manner as phenylglyoxal, which gives heterocyclic condensation products with hydroxylamine,[9] ammonia[10] and methylamine.[11] In order to prevent these undesired reactions, we carried out experiments in which the azomethine was reduced instantaneously after its formation: the alcoholic solution of 4-hydroxy-phenylglyoxal was added under vigorous mechanical stirring drop by drop to a suspension of palladium on charcoal in an alcoholic solution of methylamine in a hydrogen atmosphere. Two moles of hydrogen were consumed for each mole of 4-hydroxy phenylglyoxal hydrate and a colorless solution resulted giving 1-(4′-hydroxyphenyl)-2-methylaminoethanol with good yield and high degree of purity. It seems, there-

(1) Priestley and Moness, *J. Org. Chem.*, **5**, 355 (1940).

(2) Stolz and Hallensleben, *Chem. Zentr.*, **102**, II, 1056 (1931), German Patent 526,087.

(3) Kamlet, *ibid.*, **110**, II, 3451 (1939).

(4) Manske and Johnson, THIS JOURNAL, **51**, 580 (1929).

(5) Manske, *ibid.*, **51**, 1907 (1929).

(6) Boehringer, *Chem. Zentr.*, **101**, II, 2442 (1930), German Patent 496,646.

(7) Pauly and Schanz, *Ber.*, **56**, 981 (1923); *cf.* Austrian Patent 141,159.

(8) Meerwein, *Ber.*, **66**, 411 (1933).

(9) Angelico and Cusmano, *Gazz. chim. ital.*, **66**, 791 (1936).

(10) Müller and Pechmann, *Ber.*, **22**, 2559 (1889); *cf.* Pinner, *ibid.*, **35**, 1134 (1902).

(11) Gastaldi, *Gazz. chim. ital.*, **51**, 233 (1921).