dichloro-2-methylpropane was prepared in a 77% yield by treating methallyl chloride with concentrated hydrochloric acid for twenty-four hours at 60–65°. The dichloride had the following constants; b. p. 107° (745 mm.); $n^{25}D$ 1.4362; lit. b. p. 108°; $n^{25}D$ 1.4368.

Four and one-half moles of 1,2-dichloro-2-methylpropane was chlorinated at 60° by passing in chlorine at the rate of 333 cc. per minute. The dichloride was vigorously stirred and illuminated by a 250-watt light placed 3 inches from the flask. The chlorination was discontinued when sufficient time had elapsed for approximately 50% chlorination. The reaction mixture was washed free of hydrogen chloride, dried and distilled, yield of 1,2,3-trichloro-2-methylpropane (106.5–109.0° at 150 mm.) was 56%.

Because the direct chlorination of neither methallyl chloride nor 1,2-dichloro-2-methylpropane gave good yields of 1,2,3-trichloro-2-methylpropane, the method of Mooradian and Cloke[6] for the chlorination of methallyl chloride with sulfuryl chloride was used to prepare most of the trichloride used in this investigation. Yields comparable to theirs were obtained.

3-Chloro-2-methyl-2-propen-1-ol.—The 3-chloro-2-methyl-2-propen-1-ol was prepared by the dehydrochlorination and hydrolysis of 1,2,3-trichloro-2-methylpropane with 10% sodium hydroxide. The reaction vessel was a 5-liter, three-necked, round-bottomed flask fitted with a mercury sealed stirrer, West reflux condenser and thermometer. The flask containing a 10% aqueous solution of sodium hydroxide was immersed in an oil-bath and the contents heated to boiling. The trichloride was then quickly added and the reaction mixture refluxed with vigorous stirring for three hours. The products of the reaction were distilled directly from the reaction mixture as an azeotrope with water. The azeotrope was saturated with sodium chloride, the organic layer separated and the water layer extracted three times with ether. The ether was removed from the ether extract on a steam cone and the residue added to the organic layer. This material was dried with magnesium sulfate and distilled through the 3-foot glass helix-packed column. Yields were 3-chloro-2-methyl-2-propen-1-ol, 65%; bottoms (as the ether of chloro-methallyl alcohol), 30%.

Separation of Low and High Boiling 3-Chloro-2-methyl-2-propen-1-ol.—The two isomers of 3-chloro-2-methyl-2-propen-1-ol were separated at 150 mm. pressure using a 13 mm. × 36″ Podbielniak Hyper-Cal distillation column with a reflux ratio of 75 to 1 and a take off rate of 5 ml. per hour. The course of the distillation was followed by both index of refraction and density. A portion with constant index of refraction and density was taken for each isomer to obtain the data given in Table I. The separation is not as easy as the differences in boiling points would indicate.

1,3-Dichloro-2-methyl-1-propene.—The 1,3-dichloro-2-methyl-1-propenes were prepared from the corresponding chloro-alcohols by treating the alcohols with concentrated hydrochloric acid (mole ratio: 1 to 4) on a steam cone for fifteen minutes and then permitting the mixture to stand for twelve hours at room temperature. The organic layer was separated, washed free of acid and dried over magnesium sulfate. The chlorides were distilled at 150 mm. pressure and a center fraction taken for the determination of the constants given in Table I; yields were 72%.

Subsequent hydrolysis of each isomeric dichloride regenerated the original isomeric chloro-alcohol.

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Summary

The two geometrical isomers of 1,3-dichloro-2-methyl-1-propene have been prepared and index of refraction, density and boiling point of each isomer have been obtained.

More accurate indexes of refraction, densities and boiling points have been obtained for 1,2,3-trichloro-2-methylpropane and the two geometrical isomers of 3-chloro-2-methyl-2-propen-1-ol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Derivatives of Urethan; Azamalonic Esters[1]

BY L. G. R. TOMPKINS[1a] WITH ED. F. DEGERING

Azamalonic esters are compounds analogous to the malonic esters but having a nitrogen atom in place of the methylene carbon atom. A series of these esters has been prepared by us and will be studied for possible pharmacological activity.

The unsubstituted azamalonic esters have been known as carbalkoxy urethans, imidodicarboxylic esters and carbalkoxy alkyl carbamates. The term "azamalonic ester" is used in this paper for its simplicity and unmistakable identity.

Considerable investigation of various types of urethans as physiological agents has been undertaken.[1b,2] Urethan, or ethyl carbamate, is a mild hypnotic and a feeble diuretic. It has proved disappointing from the clinical standpoint since it is rather weak in its action and an immunity is readily acquired. Other esters of carbamic acid, such as Aponal (tertiary amyl carbamate), Hedonal (secondary amyl carbamate), Aleudrin (dichloroisopropyl carbamate), and Voluntal (trichloroethyl carbamate), have been accepted for general clinical usage as hypnotics and sedatives. Generally the toxicity and depressant qualities of these compounds are greater than those of urethan itself.

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(1a) Present address: Department of Chem., University of Idaho, Moscow, Idaho.

(1b) Dixon, "Manual of Pharmacology," Arnold, London, 1908, p. 68.

(2) Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).

No record has been found of the physiological activity of azamalonic esters although the unsubstituted ester, $H—N(CO_2C_2H_5)_2$, has been prepared.[3-6]

Azamalonic ester was first prepared[6] by the reaction of ethyl alcohol on the product obtained from potassium cyanate and ethyl chloroformate. It is a white, crystalline solid (m. p. 49–50°, b. p. 145°, 20 mm.). The compound was obtained also by heating urethan and ethyl chloroformate together.[6] The last reaction is improved[5] by first forming the sodium salt of urethan in ether and then adding the ethyl chloroformate. In later work[3] it was found that the sodium salt of azamalonic ester was readily formed in ether and would react with another molecule of ethyl chloroformate to produce carbethoxyazamalonic ester, $N(CO_2C_2H_5)_3$. The same investigator also found that the sodium salt of phenylurethan can be treated with ethyl chloroformate to produce phenylazamalonic ester.[1] Another of these compounds, bis-(β-chloroethyl)-azamalonate, was prepared by heating the reaction product obtained from ethylene chlorohydrin and potassium isocyanate with more ethylene chlorohydrin for ten hours at 130°.[7]

Salts of azamalonic acid have been obtained by heating the alkali or alkaline-earth salts of carbamic acid.[8,9]

One reference[10] indicates the preparation of *n*-butylazamalonic ester but no direction for the preparation is included and the physical constants given do not agree with those obtained in this Laboratory.

From what is known of the relationship of chemical structure to physiological activity the grouping $—N(CO_2R)_2$ might reasonably be expected to exhibit a more favorable therapeutic index than the urethan structure. Accordingly this investigation was undertaken (1) to develop a synthesis for the N-alkylazamalonic esters, and (2) to study their pharmacological properties.

The desired products were obtained in the following manner

1. $H_2NCO_2R + Na \longrightarrow H(Na)NCO_2R + {}^1/_2H_2$ then
   $H(Na)NCO_2R + Cl\cdot CO_2R \longrightarrow HN(CO_2R)_2 + NaCl$
   and
   $HN(CO_2R)_2 + Na \longrightarrow NaN(CO_2R)_2 + {}^1/_2H_2$ then
   $NaN(CO_2R)_2 + R\cdot X \longrightarrow RN(CO_2R)_2 + NaX$
2. $RNHCO_2R + Na \longrightarrow R(Na)NCO_2R + {}^1/_2H_2$ then
   $R(Na)NCO_2R + Cl\cdot CO_2R \longrightarrow RN(CO_2R)_2 + NaCl$

The first of these was extended to the use of the potassium salt, which gave better yields in the final step but did not improve those of the first step. The second synthesis outlined is applicable to the preparation of arylazamalonic esters but gives only very small yields or fails altogether when applied to the preparation of the alkyl and alicyclic azamalonic esters.

Cyclization of the azamalonic esters with urea to form the monosubstituted cyanuric acids, nitrogen analogs of the barbituric acids, was unsuccessfully attempted.

The alkaline hydrolysis of the azamalonic esters yielded the corresponding urethans whereas the acid hydrolysis produced the corresponding amines. These results are consistent with the assigned structure of the alkylazamalonic esters. Pharmacological tests have not yet been completed on the products of this investigation.

TABLE I

ESTERS OF AZAMALONIC AND ALLOPHANIC ACID DERIVATIVES

Ester	Yield, %	M. p. or b. p., °C.	Formula	Nitrogen, % Calcd.	Found
Azamalonic	90	49–50	$C_6H_{11}O_4N$	...	..
Potassium	90	.....	$C_6H_{10}O_4NK$	...	..
Sodium	85	.....	$C_6H_{10}O_4NNa$	...	..
Methyl-	61	(90–93)[f]	$C_7H_{13}O_4N$	8.0	7.8
Ethyl-[a]	81	(92–95)	$C_8H_{15}O_4N$	7.4	7.3
Isopropyl-[b]	36	(96–98)	$C_9H_{17}O_4N$	6.9	6.9
n-Propyl-	53	(102–105)	$C_9H_{17}O_4N$	6.9	6.8
Isobutyl-	37	(107–111)	$C_{10}H_{19}O_4N$	6.45	6.6
s-Butyl-[c]	0.4	(105–108)	$C_{10}H_{19}O_4N$	6.45	6.4
n-Butyl-	56	(110–113)	$C_{10}H_{19}O_4N$	6.45	6.3
Benzyl-[d]	41	(150–152)[g]	$C_{13}H_{17}O_4N$	5.58	5.3
Phenyl-	90	60–62	$C_{12}H_{15}O_4N$	...	..
α-Naphthyl-	30	86–87	$C_{16}H_{17}O_4N$	4.89	4.9
Allophanic-α-methyl-	..	112	$C_6H_{10}O_3N_2$	19.3	19.1
α-Ethyl-	..	90	$C_6H_{12}O_3N_2$	17.5	17.4
α-*n*-Propyl-[e]	..	92	$C_7H_{14}O_3N_2$	16.1	15.9

[a] Reaction temperature 90° for seven hours. [b] Reaction temperature 160° for fifteen hours. [c] Secondary butyl bromide used in place of the iodide. [d] Reaction temperature 200° for fifteen hours. [e] Heavy oily product which crystallized after standing three weeks. [f] Boiling points at 10 mm. except as noted below. [g] Boiling point at 5 mm. pressure.

Experimental

A. Preparation of (1) Azamalonic Ester and (2) Its Salts.—Azamalonic ester was prepared by the method of Wurtz and Henninger[6] but yields were poorer than those reported in the early literature. In contrast with this, the following procedure was developed:

One-half mole (44.5 g.) of urethan was dissolved in 350 ml. of dry xylene (*ortho* and *meta* isomers) contained in a 2000-ml., three-necked flask equipped with a mercury-sealed stirrer, a dropping funnel, and a water-cooled West condenser surmounted by a drying tube filled with calcium chloride. One-half mole (11.5 g.) of metallic sodium was added and the mixture heated and stirred until the sodium had all reacted. One-half mole (54 g.) of ethyl chloroformate was then added dropwise and the mixture was heated until the odor of ethyl chloroformate had disappeared, requiring about one hour. The cooled product was filtered and the filtrate was distilled. Seventy-two grams of azamalonic ester, b. p. 142–145°, at 10 mm., m. p. 49–50°, was obtained, representing a 90% yield. The sodium and potassium salts of azamalonic ester were prepared by the following procedures.

The solution of azamalonic ester in xylene (from the preceding procedure) was treated with one half mole (11.5

(3) Diels, *Ber.*, **36**, 736 (1903).
(4) Diels and Nawiasky, *ibid.*, **37**, 3672 (1904).
(5) Kraft, *ibid.*, **23**, 2786 (1890).
(6) Wurtz and Henninger, *Chem. Centr.*, **56**, 565 (1885); *Bull. soc. chim.*, **44**, 30 (1885); *Compt. rend.*, **100**, 1419 (1885).
(7) Contardi and Ercoli, *IX Congr. intern. quim. pura aplicada Madrid*, **5**, 163 (1934).
(8) I. G. Farbenind. A.-G., German Patent 536,446 (Jan. 8, 1930).
(9) McMullin (to Mathieson Alkali Works), U. S. Patent 2,067,013, Jan. 5, 1937; French Patent 753,038 (Oct. 5, 1933).
(10) Cocco, *Compt. rend.*, **195**, 1086 (1932).

g.) of metallic sodium and heated and stirred until the metal had disappeared. A brown precipitate formed as the sodium reacted, and this was collected on a fritted glass filter, taken up in acetone and refiltered twice, and dried in a vacuum desiccator over sulfuric acid. The yield of sodium azamalonic ester was 70 g., or 75% of the theoretical yield. The substance is a granular material of a yellow to cream color, stable in air but somewhat hygroscopic under humid conditions, completely soluble in water, partially soluble in alcohol, and insoluble in organic solvents.

The previous experiment was repeated, replacing the sodium with potassium in the formation of the final salt. Potassium azamalonic ester is cream to white in color, and is powdery rather than granular. On recrystallization from aqueous alcohol it may be obtained in golden, glistening platelets. It is less hygroscopic than is the corresponding sodium salt. Yields are 85 to 90%.

B. Preparation of N-Substituted Azamalonic Esters

Methylazamalonic Ester.—Two moles (284 g.) of methyl iodide and 0.25 mole (50 g.) of potassium azamalonic ester were placed in a reaction vessel, with a ball-joint stirring seal, and heated for seven hours by means of an oil-bath maintained at 65–70°. Four-tenths mole of the iodide escaped by volatilization during the reaction, as indicated by the loss in weight of the mixture (no loss of weight was experienced with the higher boiling iodides). The cooled product was filtered and the residue washed with two 50-ml. portions of methyl iodide. The filtrate and washings were combined and distilled in a small (30-inch, 8 mm. bore) Podbielniak column. One mole of the iodide was recovered in addition to that used for washing the residue during filtration, leaving 0.6 mole of methyl iodide unaccounted for. The other discrete material obtained was a 27-g. fraction boiling at 90–93° (10 mm.), which was identified as methylazamalonic ester, $CH_3 \cdot N(CO_2C_2H_5)_2$. Nearly as good results were obtained by the use of sodium in the place of potassium.

Phenylazamalonic Ester.[4]—Phenylazamalonic ester was prepared by the method of Diels and Nawiasky.[4]

α-Naphthylazamalonic Ester.—One mole (215 g.) of α-naphthyl urethan was dissolved in 500 ml. of xylene contained in a 2000 ml., three-necked flask equipped with a mercury-sealed stirrer, a dropping funnel and a water-cooled West condenser surmounted by a drying tube filled with calcium chloride. One mole (23 g.) of metallic sodium was added and the mixture heated to boiling. The reaction proceeded rapidly and exothermically, requiring cessation of heating during the early stages. After one hour the mixture was allowed to cool, and 1 mole (108.5 g.) of ethyl chloroformate was added over a period of about fifteen minutes. The mixture was allowed to reflux until the odor of the ethyl chloroformate was no longer noticeable, requiring about one hour of boiling. The mixture was cooled and filtered, and the xylene removed by distillation. The residue solidified on cooling. It was dissolved in 400 ml. of petroleum ether, b. p. 60–70°, boiled for five minutes with 10 g. of decolorizing charcoal, and filtered while hot. The filtrate was cooled in an ice-bath and 60 g. of white, crystalline solid was obtained, m. p. 86–87°, representing a 30% yield of *alpha*-naphthylazamalonic ester, $C_{10}H_7 \cdot N(CO_2C_2H_5)_2$.

C. Reactions of N-Substituted Azamalonic Esters

Ammonolysis of Methylazamalonic Ester.—Twenty-five grams of methylazamalonic ester and 200 ml. of aqueous ammonia (specific gravity 0.9) were placed in a 500-ml. flask and warmed on a steam cone, with frequent shaking, until solution was obtained. The cooling of the solution in an ice-bath caused about 5 g. of white powdery crystalline material to precipitate. The product was collected on a suction filter and dried in a vacuum desiccator over sulfuric acid. The dried material melted at 111–112°. It was also recrystallized from benzene, the m. p. remaining the same, and is thought to be α-methylallophanic ester (calcd. N, 19.3; found: N, 19.1).

Alkaline Hydrolysis of *n*-Butylazamalonic Ester.—Ten grams of *n*-butylazamalonic ester was added to 50 ml. of 10% aqueous sodium hydroxide and warmed to 60° for ten hours. The organic layer was separated and dried over anhydrous calcium sulfate and distilled. Three grams of *n*-butylurethan was obtained and the balance of the *n*-butylazamalonic ester was recovered.

Acid Hydrolysis of *n*-Butylazamalonic Ester.—A 5-gram sample of *n*-butylazamalonic ester was added to 25 ml. of 50% sulfuric acid and refluxed for thirty minutes. The cooled mixture was then neutralized with 25% sodium hydroxide solution and placed in a separatory funnel. A small amount of *n*-butylurethan was separated. The neutral aqueous solution had a strong ammoniacal odor. This solution was treated with 3 g. of phenyl isothiocyanate and cooled in an ice-bath. The solid which formed was separated by filtration and the residue was washed with ligroin and with 50% alcohol, then recrystallized from aqueous alcohol. The glistening white platelets were collected on a filter and dried in a vacuum desiccator over sulfuric acid. The product melted at 64–64.5° (uncor.) whereas the m. p. of the phenyl isothiocyanate derivative of *n*-butylamine is 65°.

Variations in preparative procedures are noted under Table I.

Summary

1. A series of N-substituted azamalonic esters has been prepared and the members are to be tested for possible pharmacological activity as sedatives, hypnotics, and/or local anesthetics.

2. Ammonolysis was effective on three members of the series. The products are believed to be α-alkylallophanic esters.

3. Cyclization of alkylazamalonic esters with urea was not effected by the usual methods.

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