SUMMARY

A number of new triamino-*s*-triazines were prepared.

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Alpha-Chloro-Delta-Aryloxyvaleric Acids*

By DONALD F. WALKER†

A method for the decarboxylation of certain substituted chloromalonic acids is described. A number of new aryloxypropylmalonic and aryloxypropylchloromalonic acids have been prepared and are reported. In antifungal screening tests the two valeric acids exhibited slight activity which was insufficient to warrant further investigation.

THE interesting preliminary antifungal tests obtained with α-chloro-δ-phenoxyvaleric acid in our laboratories prompted a study of variations in the aryl radical of related products. Subsequent to the inception of this work, Weaver and Whaley (1) reported the fungicidal activity of α-bromoacetamides and postulated that this activity may be attributed to the α-halogen atom.

The preparation of these compounds followed a well-known synthetic route. The aryloxyalkyl halides of Table I were prepared by the method of Marvel and Tanenbaum (2). Some difficulty was experienced in attaining analytical purity but the materials were satisfactory for later reactions. The aryloxyalkyl halides were reacted with ethyl malonate by the method of Merchant, Wickert, and Marvel (3). The crude esters, not being distillable at the highest vacuum available in our laboratory, were hydrolyzed at room temperature by the method of Cheney and Piening (4). Modifications of the procedure at this step made it possible to eliminate impurities carried along from previous reactions. As reported by Cheney and Piening (4), sulfuryl chloride gave yields of the α-chloroaryloxypropylmalonic acids which were a substantial improvement over those obtained by direct halogenation. Decarboxylation of the aryloxypropylchloromalonic acid presented the greatest problem encountered in the series. Uncrystallizable gums and undistillable oils often resulted so that many of the final products desired were not obtained.

Results of the antifungal testing of these compounds will be reported at a later time.

EXPERIMENTAL

Aryloxypropyl Bromides.—Following the procedure of Marvel and Tanenbaum (2) for the preparation of phenoxypropyl bromide, a mixture of the appropriate phenol (0.3 mole) and trimethylene bromide (0.5 mole) in water was heated to boiling under reflux with mechanical stirring. A dilute solution of NaOH (0.4 mole) in 75 ml. of water was added dropwise over a period of thirty minutes. Refluxing with vigorous stirring was continued for twenty-four hours. The excess alkylhalide was removed by steam distillation. The alkaline residue was extracted several times with ether. The ether extracts were combined and in turn extracted with dilute alkali. The ether layer was dried and the solvent removed by distillation. The residual oil was distilled *in vacuo* to obtain the desired aryloxypropyl bromide.

4-Chloro-2-isopropyl-5-methylphenoxyethoxyethyl Chloride.—Reaction of the requisite sodium phenate with β,β′-dichloroethyl ether as in the above procedure gave a 43% yield, b. p. 132–138° at 0.2 mm.

Anal. Calcd. for $C_{14}H_{20}Cl_2O_2$: C, 57.74; H, 6.92. Found: C, 58.04; H, 6.93.

α-Methyl-β-[β-(4-chloro-2-isopropyl-5-methylphenoxy)-β-methylethoxy]-ethyl Chloride.—Reaction of the requisite sodium phenate with β,β′-

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TABLE I.—ARYLOXYALKYL GROUP

Compound	Bromide[a] Yield, %	Bromide[a] B. P., °C.[b]	Ethyl Malonates[c] Yield, %
β-Naphthoxypropyl-	40	56–57[d]	85
2,4-Dichlorophenoxypropyl-	66	170–174/12 mm.[e]	82
2,4,5-Trichlorophenoxypropyl-	62	192–193/9 mm.	82
4-Chloro-2-isopropyl-5-methylphenoxypropyl-	25	154–157/5 mm.	82
4-Chloro-2-isopropyl-5-methylphenoxybutyl-	79		69

[a] Identity established in subsequent reactions. [b] Uncorrected. [c] Unable to distlll. [d] Melting point, recrystallized from ethanol. [e] Prepared as an intermediate, Newman, M. S., Fones, W. S., and Renoll, M. W., *J. Am. Chem. Soc.*, **69**, 718(1947). Chloride prepared as an intermediate, Synerholm, M. E., and Zimmerman, P. W., *Contribs. Boyce Thompson Inst.*, **14**, 369(1947). [f] Crude used in next reaction.

dichloroisopropyl ether as in the preceding procedure gave an 8% yield, b. p. 132–133° at 0.3 mm.

Anal. Calcd. for $C_{16}H_{24}Cl_2O_2$: C, 60.19; H, 7.58. Found: C, 60.31; H, 7.40.

Ethyl γ-aryloxypropylmalonates (3).—Sodium ethoxide was prepared in absolute ethanol in the usual manner. Freshly distilled malonic ester (0.25 mole) was added slowly with mechanical stirring to the solution of sodium ethoxide (0.5 mole). The mixture was stirred and heated to reflux while a solution of aryloxypropyl bromide (0.2 mole) in 150 ml. absolute ethanol was added dropwise over a period of one hour. Stirring and refluxing were continued for four hours. Ethanol was then removed by distillation. The reaction mixture was cooled, suspended in water, and extracted with several portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed and all constituents volatile at a bath temperature of 200° in a vacuum of 12 mm. were distilled off. A sufficiently high vacuum to effect distillation of the crude esters could not be achieved. The crude esters were used in the hydrolysis.

Aryloxypropylmalonic Acids (4).—A solution of the aryloxypropyl malonic ester (0.25 mole) in 20 ml. of ethanol was hydrolyzed by adding dropwise a solution of KOH (1.2 moles) in 300 ml. of water with stirring and cooling in an ice bath. The mixture was mechanically stirred at room temperature for twenty-four hours to obtain a pale yellow to amber colored solution. The alkaline solution was extracted with several portions of ether to remove alkali-insoluble unreacted materials, charcoaled, and filtered. The filtrate was cooled in an ice bath to 0–5° and slowly acidified with a dilute solution of HCl until acid to congo red. The semisolid precipitate was extracted with ether and the ether extracts combined and dried. The ether was removed in a stream of air and the residual gummy solid was treated with 200 ml. of low boiling petroleum ether to obtain a light tan solid material which could be filtered off. The solid malonic acids were dried *in vacuo* at room temperature (see Table II).

Aryloxypropylchloromalonic Acids (4).—Sulfuryl chloride (0.1 mole) was added slowly to a mechanically stirred solution of the aryloxypropylmalonic acid (0.1 mole) in 200 ml. of anhydrous ethyl ether. The reaction mixture was stirred for one hour at room temperature and heated to reflux for one hour. The reaction mixture was cooled and the ether removed in a stream of air at room temperature. The residual oil was suspended in 100 ml. of low-boiling petroleum ether, whereupon it solidified slowly. The desired aryloxypropylchloromalonic acids were filtered off and dried *in vacuo* over KOH at room temperature. The yields were nearly quantitative (see Table III).

α-Chloro-δ-(β-naphthoxy)valeric Acid.—Ten grams of γ-(β-naphthoxy)-propylchloromalonic acid was decarboxylated by heating in a suitable bath at 170° until all evolution of gas had ceased and for five minutes longer. A dark oil which solidified on cooling was obtained in 87% yield.

Recrystallization from carbon tetrachloride gave a light tan solid, m. p. 125–217° (uncorr.).

Anal. Calcd. for $C_{15}H_{15}ClO_3$: C, 64.63; H, 5.42; Neutral Eq., 278.7. Found: C, 64.73; H, 5.28; Neutral Eq., 278.0.

TABLE II.—ARYLOXYPROPYLMALONIC ACID[a]

	Formula	Yield, %	M. P., °C.[b]	Neutral Equivalent Found	Neutral Equivalent Calcd.
γ-(β-Naphthoxy)propylmalonic acid	$C_{16}H_{16}O_5$	62	168–170, dec.	145.8	144.2
γ-(2,4-Dichlorophenoxy)propylmalonic acid[c]	$C_{12}H_{12}Cl_2O_5$	60	120, dec.	152.6	153.6
γ-(2,4,5-Trichlorophenoxy)propylmalonic acid	$C_{12}H_{11}Cl_3O_5$	70	145–147	171.4	170.8
γ-(4-Chloro-2-isopropyl-5-methylphenoxy)propylmalonic acid	$C_{16}H_{21}ClO_5$	67	139–140	164.4	164.4

[a] Unstable to heat. [b] Uncorrected. [c] Prepared as an intermediate, Synerholm, M. E., and Zimmerman, P. W., *Contribs. Boyce Thompson Inst.*, **14**, 369(1947).

TABLE III.—ARYLOXYPROPYLCHLOROMALONIC ACID[a]

	Formula	Yield, %	M. P., °C.[c]	Neutral Equivalent Found	Neutral Equivalent Calcd.
γ-(β-Naphthoxy)propylchloromalonic acid[b]	$C_{16}H_{15}ClO_5$	Quant.	138–140, dec.	160.4	161.4
γ-(2,4-Dichlorophenoxy)propylchloromalonic acid	$C_{12}H_{11}Cl_3O_5$	Quant.	130–133	175.6	170.8
γ-(2,4,5-Trichlorophenoxy)propylchloromalonic acid	$C_{12}H_{10}Cl_4O_5$	Quant.	95–98	180.5	188.0
γ-(4-Chloro-2-isopropyl-5-methylphenoxy)propylchloromalonic acid	$C_{16}H_{20}Cl_2O_5$	98	135–140, dec.	178.6	181.9

[a] Unstable to heat. [b] Calcd., C = 59.54%, H = 4.69%; Found, C = 60.39%, H = 4.76%. [c] Uncorrected.

Dilution of the carbon tetrachloride filtrate with low-boiling petroleum ether precipitated a tan solid, m. p. 85° (uncorr.). This compound has not been identified.

Anal. Found: C, 66.74; H, 5.89.

α-Chloro-δ-(4-chloro-2-isopropyl-5-methylphenoxy)valeric Acid.—By the same procedure as in α-chloro-δ-(β-naphthoxy)valeric acid, a dark, gummy oil was obtained from the corresponding chloromalonic acid. The material was not crystallizable from carbon tetrachloride or other organic solvents. Evaporation of the solvents left a lighter-colored oil which was distilled *in vacuo*. The fraction boiling at 217–218° at 3 mm. was retained for a yield of 34%. Neutral eq. calcd. for $C_{15}H_{20}Cl_2O_3$: 319.2. Found: 320.2.

SUMMARY

1. Decarboxylation of the appropriate substituted chloromalonic acids to obtain α-chloro-δ-(β-naphthoxy)valeric acid and α-chloro-δ-(4-chloro-2-isopropyl-5-methylphenoxy)valeric acid has been accomplished.

2. A number of new aryloxypropylmalonic and aryloxypropylchloromalonic acids are reported.

3. Both valeric acids exhibited slight activity in preliminary antifungal screening but were not of sufficient interest for further investigation.

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The Quantitative Determination of Benzylpenicillin by Ultraviolet Absorption*

By EDWARD A. GARLOCK, JR., and DONALD C. GROVE

An ultraviolet spectrophotometric method for the determination of benzylpenicillin in chloroform solution is presented. Separation of active benzylpenicillin from interfering compounds is obtained using the extraction procedure of Boxer and Everett. The active penicillin is extracted at *p*H 2.0 into chloroform and thus separated from basic and neutral material as well as from any chloroform insoluble acidic substances such as penicilloic acid. A correction for any acidic interfering substances extracted with the chloroform is obtained by a separate chloroform extraction of the acidified alkali-inactivated penicillin. The values obtained by assaying commercial samples by this method are compared with those obtained by the official N-ethyl piperidine method.

VARIOUS ultraviolet spectrophotometric techniques for the determination of benzylpenicillin (penicillin G) in the presence of the other naturally occurring penicillins have been reported in the literature. These procedures are based on the measurement of the intensity of the absorption bands due to the phenyl group present in benzylpenicillin. They differ from one another mainly in the techniques used to distinguish between the absorption due to benzylpenicillin and that due to extraneous interfering substances. This interfering absorption can be of two types: (*a*) enhancement of the phenyl "peak" due to phenyl compounds other than benzylpenicillin; and (*b*) background absorption due to compounds exhibiting general absorption.

Levy, Shaw, Parkinson, and Fergus (1) have reported a method utilizing the base-line optical density technique as a means of eliminating interference from background absorption thus limiting interfering substances to phenyl compounds. Grenfell, Means, and Brown (2) have published an ultraviolet absorption method which they report to be extremely accurate on high purity material. Their criteria of purity is that the optical density at 280 mμ must be less than 0.10 for an aqueous solution of the penicillin sample. This 280 mμ optical density which represents small amounts of penicillin decomposition products is deducted from the optical density of the 263 mμ benzyl peak. Colon, Herpich, Neuss, and Frediani (3) have reported a spectrophotometric method employing corrections for two specific common degradation products of penicillin, namely, penicillenic acid and the penaldates

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