TABLE I

2,2-DIALKOXYALKANENITRILES $(R'O)_2CRCN$

R′	R	B.p., °C.	Mm.	d^{25}_4	$n^{25}D$	Mol. refract. Calcd.	Found	Carbon, % Calcd.	Found[f]	Hydrogen, % Calcd.	Found[f]	Nitrogen, % Calcd.	Found[f]
CH_3	H	139.5	772	0.9897	1.3818	23.70	23.74	47.52	47.46 ± 0.16	6.93	6.79 ± 0.18	13.85	13.37 ± 0.02
C_2H_5[a]	H	167.7	773[b]	.9288	1.3937	32.74	33.20	55.81	55.58	8.53	8.50	10.82	11.06 ± .02
C_4H_9	H	231	757[c]	.8941	1.4158	51.41	51.90	64.86	64.39 ± .08	10.27	9.98 ± .15	7.57	6.78 ± .14
C_8H_{17}	H	125	0.5	.8804	1.4373	88.35	88.44	72.73	72.53 ± .01	11.79	11.54 ± .10	4.71	5.04 ± .04
CH_3	CH_3	136.5	774[d]	.9604	1.3877	28.32	28.23	52.17	52.43	7.82	7.77	12.17	11.65
C_2H_5	C_6H_5	102.5	3.5[e]	1.0112	1.4794	57.04	57.53	70.24	70.16 ± .26	7.32	7.21 ± .17	6.83	6.98 ± .08

[a] Scheibler, *et al.*, give the b.p. as 55–56° (12 mm.). McElvain and Clarke give the b.p. as 68–70° (20 mm.), $n^{25}D$ 1.3937. [b] B.p. 69° (20 mm.); m.p. −18.5 to −19°. [c] B.p. 71° (1 mm.). [d] B.p. 85° (130 mm.); m.p. −24 to −25°. [e] M.p. −11 to −12°. [f] Usually the average of two analyses with deviation from average.

was not removed. The preparation of the lower orthoformic esters is to be described elsewhere. Methyl orthoacetate was prepared by the method of Pinner[4] and ethyl orthobenzoate by the method of Scalera.[5]

2-Ethylhexyl Orthoformate.—A mixture of ethyl orthoformate (87.5 g., 0.60 mole), 2-ethylhexanol (260 g., 2.00 moles) and zinc chloride (0.20 g.) was refluxed under an 18″ Vigreux column while ethanol (100 ml.) was withdrawn from the top of the column at such a rate that the temperature of the vapor at this point did not exceed 80°. The mixture was washed with dilute sodium hydroxide solution and water, then distilled to give 130.0 g. (54%) of product, b.p. 158° (0.5 mm.), $n^{25}D$ 1.4390.

Anal. Calcd. for $C_{25}H_{52}O_3$: C, 75.00; H, 13.00. Found: C, 75.24; H, 13.00.

Reactions of Ortho Esters with Hydrocyanic Acid.—Except where otherwise noted, a 50% excess of hydrocyanic acid was employed. The conversions given are based upon the amounts of ortho esters added to the reaction mixtures; yields are based upon the amounts of ortho esters not recovered from the reactions. The runs were of the order of 0.2–0.5 mole of ortho ester.

Several uncatalyzed runs were made. With methyl orthoformate (and HCN distilled to remove SO_2 stabilizer), dimethoxyacetonitrile was obtained in 48% yield and 6.5% conversion in 17 days at 25° or in 50% conversion in 3 hours at 150°. With ethyl orthoformate and a 100% excess of HCN, diethoxyacetonitrile was obtained in 58.6% yield and 40.6% conversion after 12 hours at 100°. Methyl orthoacetate, heated with a 100% excess of HCN for 3 hours at 200°, gave only a 4% conversion to α,α-dimethoxypropionitrile and much polymer of HCN was formed.

Zinc chloride is the best catalyst studied and was found to be effective with all ortho esters used. Other catalysts may not be equally effective with all ortho esters. For instance, *p*-toluenesulfonic acid has little catalytic effect with methyl orthoformate but works well with ethyl orthoformate and methyl orthoacetate. Ammonium chloride and boron trifluoride etherate were found to have little activity with methyl orthoformate.

In the following runs, zinc chloride was employed as catalyst, to the extent of 0.003 mole per mole of ortho ester. Except in one case, the catalyst was neutralized at the end of the reaction period by the addition of a solution of KOH in alcohol. The reaction mixtures were then distilled under reduced pressure to remove the neutralization products and fractionated to yield the product and unreacted ortho ester. These fractionations were done under atmospheric pressure except for dibutoxyacetonitrile, bis-(ethylhexyloxy)-acetonitrile and diethoxyphenylacetonitrile. Methyl orthoformate gave dimethoxyacetonitrile in 90.4% yield and 87.4% conversion after 6 days at 25°. Ethyl orthoformate gave diethoxyacetonitrile in 88.2% yield and 79.0% conversion after 3 days at 25°. Butyl orthoformate gave dibutoxyacetonitrile in 95.2% yield (no ortho ester was recovered) after 7 days at 25°. 2-Ethylhexyl orthoformate stood for 3 days at 25° with a 100% excess of HCN, then was washed with dilute NaOH and distilled to give an 80.6% yield of bis-(ethylhexyloxy)-acetonitrile; no ortho ester was recovered. Methyl orthoacetate gave a 89.3% yield of dimethoxypropionitrile after 11 days at 25°; no ortho ester was recovered. Ethyl orthobenzoate was 45.2% converted to diethoxyphenylacetonitrile after 24 days at room temperature.

The physical properties and analytical data for the products are given in Table I.

STAMFORD, CONN. RECEIVED JULY 17, 1950

(4) Pinner, *Ber.*, **16**, 1643 (1883).

(5) Scalera, Ph.D. thesis, Yale University, 1935, p. 58.

[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Dialkylaminoethyl Esters and Aminolactones Derived from 2,2-Diphenyl-4-pentenoic and 2,2-Diphenyl-4-methyl-4-pentenoic Acids[1]

BY PAUL N. CRAIG, IVAN H. WITT,[2] EDWARD MACKO, JOAQUIN G. DACANAY, EDWIN J. FELLOWS AND GLENN E. ULLYOT

A series of β-aminoethyl esters of 2,2-diphenylpentanoic, 2,2-diphenyl-4-pentenoic, 2,2-diphenyl-4-methylpentanoic and 2,2-diphenyl-4-methyl-4-pentenoic acids was prepared. A series of aminolactones derived from 2,2-diphenyl-5-bromo-4-pentanolactone and 2,2-diphenyl-5-bromo-4-methyl-4-pentanolactone was prepared. The new amines were tested for local anesthetic and antispasmodic activities; preliminary pharmacological results are given.

The ready availability of 2,2-diphenyl-4-pentenoic and 2,2-diphenyl-4-methyl-4-pentenoic acids[3] prompted an examination of certain derivatives as possible therapeutic agents. The dialkylaminoalkyl esters of these acids may be considered as alkyldiarylacetic esters related to Trasentin.[4] Few alkylated esters of this type are known; however, Larsen, *et al.*,[5] have recently reported on a series of esters closely related to the present series. Two of the esters reported herein were prepared by Larsen, *et al.*, but no pharmacological data are given by them.

In the present work, a series of dialkylaminoalkyl esters was synthesized and tested for activity as antispasmodic and local anesthetic agents (Table I).

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society at Atlantic City, N. J., September 18 to 23, 1949.

(2) Deceased.

(3) General Mills, Inc., Research Department, Minneapolis, Minnesota.

(4) R. R. Burtner, Synthetic Antispasmodics, G. D. Searle & Co., 1946 (paper presented at Medicinal Chemistry Section, A. A. A. S. Meeting, Gibson Island, Md., July 2, 1945).

(5) A. A. Larsen, A. W. Ruddy, B. Elpern and M. MacMullin, THIS JOURNAL, **71**, 532 (1949).

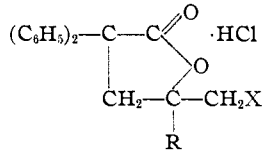
TABLE I

$(C_6H_5)_2C—R—COOCH_2CH_2X.HCl$

R	X	Yield,[a] %	M.p.,[b] °C.	Formula	Analyses, % Theor. C	Theor. H	Theor. Cl	Found[c] C	Found H	Found Cl	Local anesthetic activity[d] 1%	0.1%	0.01%	Antispasmodic[e] activity vs. Histamine	Antispasmodic[e] activity vs. Furmethide[i]
Allyl	$-N(CH_3)_2$	32	147-149.5[h]	$C_{21}H_{26}O_2NCl$	70.08	7.28	9.85	70.17	7.46	9.79	151[g]	10	...	1	1
Allyl	$-N(C_2H_5)_2$	36	108.5-111.0	$C_{23}H_{30}O_2NCl$	71.21	7.80	9.14	71.15	7.82	9.05	....	27[f]	...	1	2
Allyl	$-NC_5H_{10}$[i]	42	153-155	$C_{24}H_{30}O_2NCl$	72.07	7.56	8.87	71.97	7.75	8.82	134[g]	108[f]	None	1	1
n-Propyl	$-N(CH_3)_2$	33	174.5-175.0[h]	$C_{21}H_{26}O_2NCl$	69.69	7.80	9.80	69.56	8.05	9.77	65+[g]	51	None	20	0.1
n-Propyl	$-N(C_2H_5)_2$	40	122-123	$C_{23}H_{32}O_2NCl$	70.84	8.27	9.09	70.82	8.36	8.98	97[g]	88[f]	8	1	1
n-Propyl	$-NC_5H_{10}$[i]	22	144-146	$C_{24}H_{32}O_2NCl$	71.71	8.03	8.82	71.84	8.00	8.76	131[g]	47[f]	...	1	0.1
β-Methallyl	$-N(CH_3)_2$	76	142-144	$C_{22}H_{28}O_2NCl$	70.66	7.55	9.48	70.79	7.85	9.54	60+[g]	70	None	10	1
β-Methallyl	$-N(C_2H_5)_2$	30	151-152.5	$C_{24}H_{32}O_2NCl$	71.71	8.03	8.82	71.71	8.10	8.93	>120[g]	27	...	..	...
Isobutyl	$-N(C_2H_5)_2$	38	151-152	$C_{24}H_{34}O_2NCl$	71.35	8.48	8.78	71.27	8.20	8.76	150[g]	44[f]	0.4	1	0
Pavatrine											....	..	...	0.2	100
Cocaine											18	..	...	..	...

[a] Based on analytically pure compound. [b] Cor. (sealed capillary). [c] Analyses by Mrs. Lillian Shreve, Miss Ruth Savacool and Miss Rita Fox. [d] Duration in minutes of anesthesia of rabbit cornea. [e] 1 represents a dilution of 1 to 1,000,000; 0.1 represents 1 to 100,000, etc. Values represent minimum concentration required to antagonize completely the spasmodic action of 1.5×10^{-4}% Furmethide or 1×10^{-5}% histamine on a cross-section of rabbit intestine or guinea pig intestine, resp. [f] Irritation noticed. [g] Extreme irritation noticed. [h] Ref. 5 reports m.p. for the allyl and *n*-propyl esters as 147–148° and 176–177°, resp. [i] Furmethide, Smith, Kline and French Laboratories trademark for furfuryltrimethylammonium iodide. [j] Piperidine derivatives.

TABLE II

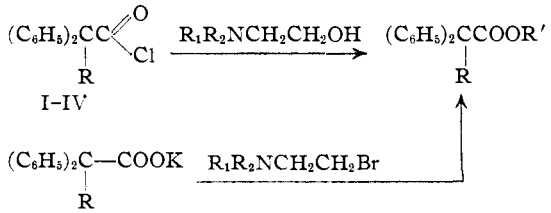


R	X	Yield,[a] %	M.p.,[b] °C.	Formula	Analyses, % Theor. C	Theor. H	Theor. Cl	Found[d] C	Found H	Found Cl	Local[e] anesthetic activity 1%	0.1%	Antispasmodic[f] activity vs. Histamine	Antispasmodic[f] activity vs. Furmethide
H	$-N(CH_3)_2$	29	224-225	$C_{19}H_{22}O_2NCl$	68.77	6.68	10.69	68.72	6.88	10.55	...	..	1	0.1
H	$-N(C_2H_5)_2$	53	202-204.5	$C_{21}H_{26}O_2NCl$	70.08	7.28	9.55	69.94	7.58	9.59	34.6[g]	10.2	0.1	1
H	$-N(C_4H_9)_2$	43	61.5-63.0 (from water)	$C_{26}H_{34}O_2NCl$	72.18	8.24	8.52	72.27	8.46	8.46	...	..	None at 0.1	None at 1
H	$-NC_5H_{10}$[j]	67	195-197	$C_{21}H_{26}O_2NCl$	71.05	7.05	9.54	70.85	7.49	9.58	82.2	50.2	10	1
H	$-NC_4H_8O$[j]	82	238-240	$C_{21}H_{24}O_3NCl$	67.46	6.47	9.48	67.49	6.75	9.53	5.6	..	1	None at 1
H	$-N(C_2H_5)CH_2CH_2OH$	65	137.5-139	$C_{21}H_{26}O_3NCl$	67.10	6.97	9.43	67.22	7.12	9.48	53.5	17.9	0.1	0.1
CH_3	$-NC_5H_{10}$[j]	48	195-196	$C_{23}H_{28}O_2NCl$	71.58	7.31	9.19	71.52	7.33	9.07	6.6[h]	..	10	None at 1
CH_3	$-NC_4H_8O$[j]	34	146-147.5	$C_{22}H_{25}O_3N$[c]	75.18	7.17	...	75.38	7.41	...	...	..	1 sl.	None at 1

[a] Based on analytically pure compound. [b] Cor. (open capillary). [c] Free base. [d] Analyses by Mrs. Lillian Shreve, Miss Ruth Savacool and Miss Rita Fox. [e] Duration in minutes of anesthesia of rabbit cornea. [f] 1 represents a dilution of 1 to 1,000,000; 0.1 represents a dilution of 1 to 100,000, etc. Values represent minimum concentration required to antagonize completely the spasmodic action of 1.5×10^{-4}% Furmethide or 1×10^{-5}% histamine on a cross-section of rabbit intestine or guinea pig intestine, resp. [g] Irritation noticed. [h] Extreme irritation noticed. [i] Piperidine and morpholine derivatives.

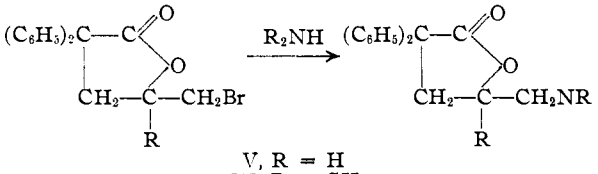
A series of aminolactones was also synthesized and similarly tested (Table II).

The aminoesters were prepared from the acid chlorides[6] (I–IV) and the corresponding aminoalcohols by direct interaction. An alternate method involving the interaction of a salt of the acid with a β-haloethylamine was also satisfactory.



I, R = $-CH_2CH{=}CH_2$ III, R = $-CH_2CH_2CH_3$
II, R = $-CH_2C(CH_3){=}CH_2$ IV, R = $-CH_2CH(CH_3)_2$

The aminolactones were prepared by direct action of the desired secondary amines with the bromolactones[6] (V and VI). The preparation of the aminolactones derived from dimethyl- and diethylamines required sealed tube conditions, whereas the aminolactones derived from the higher boiling secondary amines (piperidine, morpholine, dibutylamine, etc.) were prepared by refluxing the bromolactone with excess amine.



V, R = H
VI, R = CH_3

Acknowledgment.—The helpful interest in this problem shown by Dr. Richard T. Arnold is gratefully acknowledged.

Experimental

β-Diethylaminoethyl Ester of 2,2-Diphenylpentanoic Acid.—The acid chloride[6] was prepared from 22.9 g. (0.09

(6) Craig and Witt, THIS JOURNAL, 72, 4925 (1950).

mole) of 2,2-diphenylpentanoic acid by refluxing for 7 hours with 25 ml. of thionyl chloride. The excess thionyl chloride was removed *in vacuo*, and the residue was refluxed for 2 hours with 21.2 g. (0.18 mole) of β-diethylaminoethanol, 10 g. of phenol and 40 ml. of dry benzene. The precipitate which formed on cooling was dissolved with more benzene, and a slight excess of dry hydrogen chloride was passed into the solution. Anhydrous ether was added, the resultant precipitate was collected, dissolved in 600 ml. of water, and made alkaline with dilute ammonium hydroxide. The oily amine which formed was extracted with benzene; the benzene layer was washed with water until the extracts were practically neutral to alkacid test paper. The benzene solution was concentrated and dried by distillation. Addition of ether precipitated an oil, which solidified on cooling.

Recrystallization of the amino-ester hydrochloride from acetone–ether gave 11.5 g. of needles; m.p. 122–123° (cor. sealed cap.). A second crop (having the same melting point) of 2.7 g. was obtained by diluting the filtrate with ether; total yield 14.2 g. (40%).

β-Dimethylaminoethyl Ester of 2,2-Diphenyl-4-methyl-4-pentenoic Acid.—This was prepared by the following modification of the Horenstein–Pählicke amino-ester synthesis.[7] A suspension of the potassium salt of 20.0 g. of 2,2-diphenyl-4-methyl-4-pentenoic acid (0.075 mole) in toluene was obtained by dissolving the acid in 75 ml. of 1.0 *N* potassium hydroxide, followed by azeotropic distillation of the water with toluene. A solution of 17.5 g. (0.075 mole) of β-dimethylaminoethyl bromide hydrobromide in 50 ml. of water was neutralized with 1% sodium hydroxide and immediately extracted by two portions of benzene. The benzene solution was dried by distillation of one-half of the solvent. The dry benzene solution was added slowly to the stirred dry suspension of the potassium salt. After stirring the mixture at reflux for 90 minutes, water was added. Acidification of the aqueous layer gave 8.5 g. of recovered starting acid (m.p. 117–119°). The benzene layer was dried by boiling, cooled, and hydrogen chloride was introduced. Addition of the ether gave a precipitate which was recrystallized from ethanol–ether; 12.3 g. (44%, 76% on basis of acid used); m.p. 142–144° (cor. sealed cap.).

2,2-Diphenyl-5-(4′-morpholino)-4-pentanolactone.—A mixture of 14.0 g. (0.423 mole) of 2,2-diphenyl-5-bromo-4-pentanolactone[6] in 42 g. of morpholine (Eastman Kodak Co. practical) was refluxed 2 hours. After 25 g. of morpholine was removed by distillation, ether was added. Filtration gave 7.0 g. of morpholine hydrobromide (theor. 7.9 g.). The filtrate was washed twice with water, and benzene was added to solubilize the product. After three more aqueous extractions, the organic solution was dried over calcium chloride. Addition of dry hydrogen chloride gave a precipitate, which was recrystallized from ethanol and acetone (400 ml. total volume) 12.5 g. (82%) of needles; m.p. 238–240° (open cap. cor.).

2,2-Diphenyl-5-diethylamino-4-pentanolactone.—A mixture of 14.0 g. (0.423 mole) of 2,2-diphenyl-5-bromo-4-pentanolactone[6] and 40 ml. of diethylamine (Eastman Kodak Co., practical) was heated 4 hours at 160° in a sealed bomb. Water was added to the mixture, and the aqueous layer was extracted four times with ether and once with benzene. The combined organic layers were washed with eight portions of water (until a *p*H of eight was obtained for the wash water). The organic solution was dried over calcium chloride, and dry hydrogen chloride was added. The resultant oil solidified readily, and was recrystallized twice from ethanol and ether, using Darco; 8.0 g. (52%) of needles; m.p. 202–204.5° (open cap. cor.).

(7) H. Horenstein and H. Pählicke, *Ber.*, **71B**, 1644 (1938).

PHILADELPHIA, PENNA. RECEIVED SEPTEMBER 20, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Rate Law and Mechanism of the Reaction of Iodine with Thiosulfate Ion: The Formation of the Intermediate $S_2O_3I^-$

BY ALICE D. AWTREY AND ROBERT E. CONNICK

A study has been made of the kinetics of the reactions occurring when thiosulfate and triiodide solutions are mixed. The initial, very rapid reaction results in the formation of $S_2O_3I^-$ and iodide ion. At relatively high iodide concentrations the $S_2O_3I^-$ reacts at a measurable rate to form tetrathionate and triiodide. The following mechanism is consistent with the experimental results

$$S_2O_3I^- + 2I^- \underset{\longleftarrow}{\overset{\text{rapid equil.}}{\longrightarrow}} S_2O_3^{--} + I_2^-$$

$$S_2O_3I^- + S_2O_3^{--} \xrightarrow{\text{slow}} S_4O_6^{--} + I^-$$

where the equilibrium of the first reaction is shifted far to the left.

At low iodide ion concentrations $S_2O_3I^-$ reacts with iodine to give sulfate and iodide. The rate law was determined and possible mechanisms are discussed.

During the mixing a part of the thiosulfate is converted very rapidly to tetrathionate ion by reaction with $S_2O_3I^-$. This reaction is slower than that of thiosulfate with triiodide, yet too fast to measure with the technique available.

Introduction

Visible evidence that the reaction of thiosulfate with iodine is not immeasurably fast, and proceeds in steps, was obtained by the use of a fast mixing device, similar in design to that of Hartridge and Roughton.[1] Solutions of iodine in potassium iodide and of sodium thiosulfate were mixed very rapidly by being forced under pressure from jets into a small circular mixing chamber and thence down a long glass observation tube. The reaction expected is

$$I_3^- + 2S_2O_3^= = S_4O_6^= + 3I^- \qquad (1)$$

which requires two thiosulfate ions for each triiodide. Under certain conditions it was found that the triiodide solution was completely decolorized by the thiosulfate solution at the mixing chamber but that the mixture, while flowing down the observation tube, became colored again. The solution collected at the end of the tube had an easily measurable concentration of triiodide ion.

From the above observation it was apparent that triiodide and thiosulfate can react in a ratio of less than 1 to 2 to form a colorless intermediate.

Assuming the combining ratio to be 1 to 1 (as confirmed by other experiments to be discussed later), the postulated reaction is

$$S_2O_3^= + I^- = S_2O_3I^- + 2I^- \qquad (2)$$

(1) H. Hartridge and F. J. W. Roughton, *Proc. Roy. Soc.* (*London*), **A104**, 376 (1923).