ester with a pancreatic enzyme, and, more recently, Brenner and co-workers obtained both optical isomers of tryptophan[24] and of methionine[25] by the asymmetric action of chymotrypsin on their esters. It was not possible to resolve the methyl ester of α-aminocaprylic acid with crystalline chymotrypsin because of the low rate of enzymatic hydrolysis and because appreciable spontaneous hydrolysis occurred under the conditions employed. The hydrolysis of this ester by chymotrypsin was followed for 21 days during which time fresh enzyme was repeatedly added. The free amino acid formed was filtered off at various intervals and each fraction recrystallized twice. The first fraction of amino acid had a specific rotation of +18.4°.[26] The ester remaining after 21 days was hydrolyzed with NaOH and the isolated amino acid had a specific rotation of −21.7°.[26] Each isomer was therefore contaminated with its enantiomorph. Spontaneous hydrolysis was also observed in control experiments without enzyme.

The problem of inversion in the nitrous acid reaction has been discussed in detail.[27,28] Inversion appears unlikely in the case of the aliphatic α-amino monocarboxylic acids. The α-hydroxy acids were prepared as the barium salts rather than as the free acids because of the marked hygroscopicity of the latter. Except in one case (the barium salt of L-α-hydroxyisocaproic acid), good agreement with values in the literature was found where comparison could be made with identical compounds (zinc L-lactate, L-α-aminoisocaproic acid and its barium salt, and L-β-imidazole lactic acid).

Acknowledgment.—The authors wish to thank Mr. R. J. Koegel for the analyses herein reported.

(24) M. Brenner, E. Sailer and V. Kocher, *Helv. Chim. Acta*, **31**, 1908 (1948).

(25) M. Brenner and V. Kocher, *ibid.*, **32**, 333 (1949).

(26) 0.900% solution in 6 *N* HCl in a 2-dm. tube.

(27) A. Neuberger, "Advances in Protein Chemistry," Vol. IV, Academic Press, Inc., New York, 1948, pp. 297–383.

(28) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature*, **166**, 178 (1950).

BETHESDA, MD. RECEIVED SEPTEMBER 29, 1950

[CONTRIBUTION FROM THE RESEARCH DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID CO.]

2,2-Dialkoxyalkanenitriles

BY JOHN G. ERICKSON

2,2-Dialkoxyalkanenitriles may be prepared in very good yields by reactions of hydrocyanic acid with alkyl esters of aliphatic and aromatic ortho acids, especially in the presence of acidic catalysts.

The only 2,2-dialkoxyalkanenitrile which appears to be described in the literature is diethoxyacetonitrile. It was first prepared by Scheibler, Beiser, Cobler and Schmidt,[1] who obtained it in 30% yield by the dehydration of diethoxyacetamide with quinoline and phosphorus pentoxide. McElvain and Clarke[2] later modified this method.

It has recently been found in these laboratories that compounds of this type may be obtained in excellent yields by reactions of hydrocyanic acid with alkyl esters of ortho acids

$$RC(OR')_3 + HCN \rightleftarrows (R'O)_2CCN + R'OH$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad R$$

The ortho esters used may be orthoformic or higher aliphatic ortho esters, such as orthoacetic esters, or may be esters of aromatic ortho acids, such as orthobenzoic acid. In the absence of catalysts, the reactions proceed rather slowly at room temperature but at higher temperatures, such as 150°, the reactions go well. The use of a catalyst is desirable and makes it possible to carry out the reactions in a short time at room temperature. Only acidic materials seem to be effective as catalysts, basic compounds causing polymerization of the hydrocyanic acid. With a catalyst such as zinc chloride, the reaction is rapid and equilibrium, usually well over to the dialkoxynitrile side, is established probably within a few hours at room temperature. Because of this equilibrium, it is desirable to neutralize the catalyst before working up the reaction mixtures; otherwise the equilibrium will be shifted toward the ortho ester side by removal, during distillation, of the hydrocyanic acid.

The structures given the products of these reactions depend upon the mode of formation, analyses and hydrogenation to aminoacetals.[3] The assigned structures are also supported by the close agreement of physical properties of samples of diethoxyacetonitrile prepared in this manner and by McElvain and Clarke in their dehydration of diethoxyacetamide. Further, the infrared absorption spectra of these compounds are fully in agreement with the assigned structures.

These dialkoxynitriles are quite sensitive to moisture, being hydrolyzed to hydrocyanic acid and, presumably, alcohol and the normal ester of the carboxylic acid involved. They are difficult to purify for analytical purposes for this reason and also because compounds of this type, containing alkoxyl groups other than methoxyl, slowly decompose if heated to temperatures of the order of 150° or higher. Even when very carefully purified, the compounds gave some trouble in analysis, the nitrogen and alkoxyl determinations tending to be low.

Acknowledgments.—The high temperature reactions were carried out by the High Pressure Group of these laboratories. Analyses were performed by the Microanalytical Group.

Experimental

All recorded boiling points are corrected.

Reagents.—The hydrocyanic acid was stabilized with a trace of sulfur dioxide. Except in one run, this stabilizer

(1) Scheibler, Beiser, Cobler and Schmidt, *Ber.*, **67**, 1513 (1934).

(2) McElvain and Clarke, THIS JOURNAL, **69**, 2661 (1947).

(3) To be reported elsewhere.

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).