lent of 240 was obtained while by procedure B no detectable consumption of alkali was indicated. In another experiment co-anisatin (10 mg.) was dissolved in excess of 1 *N* sodium hydroxide, heated on the steam-bath for five minutes and allowed to stand at room temperature for 15 minutes. The solution was then acidified with hydrochloric acid and extracted with ethyl acetate. The material so obtained after recrystallization from methanol melted at 275–277° and gave no depression of the m.p. on admixture with an authentic specimen of co-anisatin.

ψ-Anisatin.—This substance was obtained from the ethyl acetate mother liquors after anisatin had crystallized from the early, more potent chromatographic fractions (see above) and was the chief constituent of the later fractions. It was dextrorotatory, $[\alpha]^{22}D$ + 59° (*c* 2, dioxane); m.p. (dec.) 200–210°. No physiological activity could be observed. Its solubility in ethyl acetate at 25° was determined to be 19.8 mg./g. of solvent. It was very soluble in isopropyl alcohol.

Anal. Calcd. for $C_{21}H_{32}O_8$: C, 61.6; H, 7.82; mol. wt., 412. Found[18]: C, 60.96; H, 7.61; mol. wt., 383 (cryoscopic, acetophenone).

When an alkaline solution of ψ-anisatin was heated for 15 minutes and the excess base titrated with alkali to the phenolphthalein end-point, a saponification equivalent of 258 was obtained. The end-point was not permanent, however, and after 2 days the quantity of base consumed corresponded to a saponification equivalent of 390. On the other hand, when excess hydrochloric acid was added to an alkaline solution which had been heated for 15 minutes and the excess acid titrated with base, a saponification equivalent of 431 was obtained. This behavior indicates that the product of hydrolysis may very well be a lactonic acid, stable in acid solution.

Acknowledgments.—The authors wish to express their appreciation to the Research Corporation, New York, N. Y., and to the Rutgers University Research Council for generous grants-in-aid which have supported this work, to Dr. A. P. Richardson, formerly director of pharmacological research in the Squibb Institute, New Brunswick, N. J., for assisting us in setting up the method of bioassay, to Drs. W. C. Bywater and R. W. Price of S. B. Penick and Co., New York, N. Y., for assistance in the processing of large amounts of material in the laboratories of that company, to Dr. T. J. Webb and Mr. F. A. Bacher of Merck and Company, Rahway, N. J., for personal demonstration of the technique of solubility analysis and advice in the interpretation of the initial solubility data obtained, and to Mr. J. M. Devine, Baird Associates, Inc., Cambridge, Mass., and to Dr. David Kendall and Miss Elizabeth A. Frolich of the Calco Chemical Division, American Cyanamid Co., Bound Brook, N. J., for determination of the infrared absorption spectra here reported as well as for their helpful suggestions as to interpretation.

NEW BRUNSWICK, N. J.

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

N-Carboalkoxy Derivatives of Procaine

BY NORMAN RABJOHN, T. R. HOPKINS[1] AND R. C. NAGLER[2]

RECEIVED JANUARY 21, 1952

The methods of synthesis of a series of dicarboalkoxy-bis-procaines, as well as a number of procaine derivatives of monourethans, are described. Preliminary pharmacological data indicate that the bis-compounds resemble procaine in anesthetic potency, but lack the central nervous stimulation characteristic of the latter. The mono-derivatives appear to be quite similar to procaine in their physiological behavior.

In spite of the relatively large number of dialkylaminoalkyl *p*-aminobenzoates which have been investigated for anesthetic activity, comparatively few are known in which the 4-amino group has been substituted. Certain 4-alkyl-,[3] 4-substituted alkyl[3] and 4-dialkylamino[3a,4] derivatives have been prepared. Various acyl and aroyl groups[5] have been introduced at the 4-amino nitrogen atom, and the latter has been diazotized and coupled to give azo compounds.[6] Recently Rao, Iyer and Guha[7] have condensed procaine with a number of diacid chlorides to obtain bis-derivatives. Krishnamacharlu, Iyer and Guha[8] have reported that they have substituted the amino group in procaine with urea, thiourea, cyanamide, guanidine and aminoguanidine.

Several investigators[9] have recognized the possi-

(1) McNeil Laboratories Fellow, 1950–1951.

(2) Abstracted in part from a thesis submitted by R. C. Nagler to the Graduate College of the University of Missouri, 1949, in partial fulfillment of the requirements for the degree of Master of Arts.

(3) (a) T. P. Carney, in C. M. Suter, "Medicinal Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 338; (b) R. O. Clinton, U. J. Salvadore, S. C. Laskowski and J. S. Buck, THIS JOURNAL, **72**, 1331 (1950); (c) Farbwerke vorm. Meister, Lucius and Bruning, British Patent 241,767 (1925); (d) I. G. Farbenindustrie, British Patent 349,640 (1930); (e) E. Ghigi, *Ann. chim. farm.*, Dec., 39 (1939); *C. A.*, **34**, 2346 (1940); (f) C. Provinciali and M. Borasi, *Arch. ital. sci. farmacol.*, **12**, 89 (1943); *C. A.*, **38**, 5297 (1944); (g) J. M. Fulmer and H. Burkett, THIS JOURNAL, **71**, 1209 (1949); (h) L. S. Birnbaum and G. Powell, *ibid.*, **67**, 1464 (1945); (i) J. Giral, *Anales inst. invest. cient., Univ. nuevo Leon*, **1**, 151 (1945); *C. A.*, **41**, 1676 (1947).

(4) E. M. Hancock, E. M. Hardy, D. Heyl, M. E. Wright and A. C. Cope, THIS JOURNAL, **66**, 1747 (1944).

(5) (a) A. Einhorn and E. Uhlfelder, *Ann.*, **371**, 131 (1909); (b) J. von Braun, O. Braunsdorf and K. Rath, *Ber.*, **55**, 1666 (1922); (c) I. G. Farbenindustrie, German Patent 582,390 (1933); (d) R. Knoll, U. S. Patent 1,894,375 (1933); (e) J. L. Regnier, French Patent 815,220 (1937); British Patent 477,822 (1938); German Patent 735,265 (1943); (f) J. L. Regnier, R. Delange and R. Bernier, *Ann. pharm. franc.*, **3**, 60 (1945); *C. A.*, **40**, 5496 (1946); (g) G. Sanna, *Rend. seminar facolta sci. univ. Cagliari*, **10**, 50 (1940); *C. A.*, **37**, 2726 (1943); (h) R. Hazard, E. Corteggiani and A. Pelou, *Compt. rend. soc. biol.*, **138**, 427 (1944); *C. A.*, **40**, 400 (1946).

(6) (a) Farbwerke vorm. Meister, Lucius and Bruning, German Patent 180,292 (1905); (b) J. F. Fulton, *Am. J. Physiol.*, **57**, 153 (1921); (c) F. Biedebach and H. Weigand, *Scientia Pharm.*, **10**, 140 (1939); *C. A.*, **34**, 587 (1940); (d) J. H. Gardner and L. Joseph, THIS JOURNAL, **57**, 901 (1935); (e) A. Neri, *Gazz. chim. ital.*, **61**, 610 (1931).

(7) U. N. Narayana Rao, B. H. Iyer and P. C. Guha, *Current Sci. (India)*, **19**, 180 (1950); *C. A.*, **44**, 11025 (1950).

(8) P. V. G. Krishnamacharlu, B. H. Iyer and P. C. Guha, *Current Sci. (India)*, **19**, 181 (1950).

(9) (a) J. Donald, *Anesthesia & Analgesia*, **8**, 133 (1929); (b) K. Fromherz, *Arch. exp. Path. Pharmakol.*, **76**, 257 (1914); (c) T. H. Rider, THIS JOURNAL, **52**, 2115 (1930); (d) M. L. Bonar and T. Sollman, *J. Pharmacol. Exp. Therap.*, **18**, 467 (1921); (e) R. E. Damschroeder and R. L. Shriner, THIS JOURNAL, **58**, 1610 (1936).

bility of including the normally hypnotic acting urethan grouping in a local anesthetic type structure. The diphenylurethans of certain dialkylaminopropanediols, prepared by Rider,[9c] have found some use as local anesthetics. Horne, Cox and Shriner[10] studied a series of *p*-aminophenylurethans and found that although the compounds were highly irritating, they produced noticeable hypnosis. The animals which died after administration of the compounds did not have convulsions in contrast to the behavior of other local anesthetics.

It is known also that if an hypnotic is given simultaneously with, or preceding, the injection of procaine, the effect and duration of the anesthesia will be enhanced.

The purpose of the present work is to describe the preparation of a series of compounds which possess the general formula

$$[(C_2H_5)_2NC_2H_4OCOC_6H_4NHCO_2]_2—R—$$

in which the potentially hypnotic urethan function has been combined chemically with the local anesthetic procaine. In addition, a few monourethans of procaine are reported.

The syntheses were accomplished in general according to the following scheme

$$R(OH)_x \xrightarrow{COCl_2} R(OCOCl)_x \xrightarrow{\text{Procaine}} R[OCONHC_6H_4CO_2C_2H_4N(C_2H_5)_2]_x$$

where x = 1 or 2. The urethan derivatives were isolated usually in the form of the hydrochlorides, but in those cases where the latter were oils, recourse was taken to other salts such as the oxalates and picrates.

It was thought that the presence of a urethan linkage in a procaine-type molecule might alter the physiological behavior of this well known drug. The rate of hydrolysis of the ester linkage could be affected as well as the rate at which the normal hydrolytic products, *i.e.*, β-diethylaminoethanol and *p*-aminobenzoic acid, would be formed. The known lower rate of hydrolysis of a carbamate as compared with that of an ester was verified by treating the di-β-diethylaminoethyl ester of N,N′-di-(*p*-carboxyphenyl)-tetramethylene diurethan (R = $(CH_2)_4$ and x = 2 in the above formula) with boiling dilute hydrochloric acid for two hours. The corresponding acid, N,N′-di-(*p*-carboxyphenyl)-tetramethylene diurethan was isolated in essentially quantitative yield.

Rau and Westfall[11] have carried out pharmacological tests on the simple monourethan derivatives, Table II, as well as the bis-compound (R = $(CH_2)_3$) which has been assigned the arbitrary name, tridiurecaine. Their results, along with further extensive testing,[12] indicate that the monocarboalkoxy-substituted procaines resemble procaine in its physiological behavior. They may be somewhat more active as local anesthetics, but also more toxic. The diurethan derivative, tridiurecaine, on the other hand, has been found to equal or exceed procaine in anesthetic potency and to be slightly less toxic. Its main attribute is that it does not show the undesirable systemic effects associated with procaine. Animals which have received tridiurecaine are anesthetized, but do not appear to exhibit the usual central nervous stimulation produced by procaine.

(10) W. H. Horne, R. F. B. Fox and R. L. Shriner, THIS JOURNAL, **55**, 3435 (1933).

(11) G. C. Rau and B. A. Westfall, *J. Pharmacol. Exp. Therap.*, **99**, 421 (1950).

(12) The authors are greatly indebted to Drs. Rau and Westfall of the Department of Physiology and Pharmacology of the University of Missouri School of Medicine for the original physiological tests. They would like to express also their appreciation to the McNeil Laboratories for screening a number of the compounds reported here, in addition to a more detailed study of tridiurecaine.

Experimental[13]

Materials.—The simple glycols were obtained from the Eastman Kodak Co. and purified prior to use. The tetramethylene glycol and 1,4-butynediol were furnished through the courtesy of the General Aniline and Film Corp. A sample of pentamethylene glycol was supplied by the E. I. du Pont Co. and the hexylene glycol was donated by the Shell Chemical Co. The hexamethylene and decamethylene glycols were prepared by the reduction of diethyl adipate and diethyl sebacate, respectively, using copper chromite catalyst. 2-Methyl-1,3-propanediol was synthesized from diethyl methylmalonate by reduction with lithium aluminum hydride; b.p. 123–125° (20 mm.). 2,2-Dimethyl-1,3-propanediol was obtained by the condensation of isobutyraldehyde with formaldehyde according to the method of Whitmore, Popkin, Bernstein and Wilkins[14]; m.p. 126–128°. 3,3-Dimethyl-1,5-pentanediol (b.p. 150–152° (20 mm.)) was prepared by the reduction of diethyl β,β-dimethylglutarate[15] by means of lithium aluminum hydride. The mixture of 1,4-dihydroxycyclohexanes (m.p. 101–102°), commonly known as *cis*-quinitol, was synthesized from hydroquinone by hydrogenation over Raney nickel catalyst. A sample of procaine hydrochloride was obtained as a gift from Endo Products, Inc.

Monochloro- and Dichlorocarbonates.—The monochlorocarbonates and most of the aliphatic dichlorocarbonates were prepared by adding the hydroxy compounds to liquid phosgene after the method of Rabjohn.[16] In the case of 1,4-butynediol, it was necessary to employ the procedure of Oesper, Broker and Cook[17]; this method also was used for the preparation of *p*-phenylenedichlorocarbonate.

The reaction of 2-methyl-2,4-pentanediol (hexylene glycol) with phosgene gave an almost quantitative yield of the corresponding carbonate; m.p. 96–97° (from ether).

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.31; H, 8.54.

When *cis*-quinitol was treated with liquid phosgene, two products were isolated. A solid (m.p. 114–115°, from a mixture of ether and petroleum ether) was obtained in 60% yield and was assumed to have the *trans* configuration.

Anal. Calcd. for $C_8H_{10}O_4Cl_2$: C, 39.85; H, 4.18. Found: C, 40.02; H, 4.43.

The residual liquid (31%) was treated with aqueous ammonia to give a diurethan; m.p. 268–270°. Since the dichlorocarbonates, in general, cannot be purified by distillation, the new ones were identified by means of their diurethans. The melting points and analyses for these compounds are given in Table I.

N-Carboalkoxy Derivatives of Procaine Hydrochloride.—The condensation of ethyl chlorocarbonate with procaine hydrochloride is representative of the procedure by which these compounds were synthesized. To a solution of 27.2 g. (0.1 mole) of procaine hydrochloride, in 100 ml. of water, which had been heated to 50°, was added 10.8 g. (0.1 mole) of ethyl chlorocarbonate. The mixture was stirred until the oil phase had disappeared. Upon cooling, there was obtained 27.7 g. (80%) of a white crystalline solid which melted at 175–177° dec. after two crystallizations from

(13) All melting points are uncorrected. The authors are indebted to Mr. P. D. Strickler, Mr. H. D. Barnstorff and Mr. J. S. Finney for the semimicro analyses.

(14) F. C. Whitmore, A. H. Popkin, H. I. Bernstein and J. P. Wilkins, THIS JOURNAL, **63**, 124 (1941).

(15) J. N. Walker, *J. Chem. Soc.*, **89**, 599 (1906).

(16) N. Rabjohn, THIS JOURNAL, **70**, 1181 (1948).

(17) Oesper, Broker and Cook, *ibid.*, **47**, 2609 (1925).

TABLE I

ALIPHATIC DIURETHANS ($H_2NCO_2ROCONH_2$)

R =	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$CH_2C{\equiv}CCH_2$[a]	194–195 dec.	$C_6H_8O_4N_2$	41.86	42.10	4.68	4.40
$CH(CH_3)CH_2CH_2$[b]	146–147	$C_6H_{12}O_4N_2$	40.90	40.81	6.87	7.01
$CH_2CH(CH_3)CH_2$[c]	185–186	$C_6H_{12}O_4N_2$	40.90	40.63	6.87	7.07
$(CH_2)_6$[a]	161–162	$C_7H_{14}O_4N_2$	44.20	44.12	7.42	7.26
$CH_2C(CH_3)_2CH_2$[d]	149–150	$C_7H_{14}O_4N_2$	44.20	44.26	7.42	7.48
$(CH_2)_2C(CH_3)_2(CH_2)_2$[e]	118–119	$C_9H_{18}O_4N_2$	49.53	49.25	8.25	8.24
C_8H_{10}(*cis*-1,4)[e]	268–270	$C_8H_{14}O_4N_2$	47.51	47.23	6.97	7.10
C_8H_{10}(*trans*-1,4)[e]	322–324	$C_8H_{14}O_4N_2$	47.51	47.50	6.97	6.76
$CH(CH_3)CH_2$[f]	144–145	$C_{17}H_{18}O_4N_2$	64.95	64.69	5.77	5.85

Crystallization solvents: [a] alcohol, [b] water, [c] alcohol–water, [d] methanol–*n*-hexane. [e] Sublimed at 180° (20 mm.). [f] The dicarbanilate; from ether–petroleum ether (60–70°).

TABLE II

N-CARBOALKOXY DERIVATIVES OF PROCAINE HYDROCHLORIDE, $ROCONHC_6H_4CO_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$

R =	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	193–195	$C_{15}H_{23}O_4N_2Cl$	54.46	54.34	7.01	7.15
C_2H_5	175–177	$C_{16}H_{25}O_4N_2Cl$	55.72	55.74	7.31	7.47
n-C_3H_7	154–156	$C_{17}H_{27}O_4N_2Cl$	56.89	56.63	7.58	7.71
n-C_4H_9	149–151	$C_{18}H_{29}O_4N_2Cl$	57.96	57.82	7.84	8.02

TABLE III

DIETHYLAMINOETHYL ESTERS OF N,N′-DI-(*p*-CARBOXYPHENYL)-URETHANS, $[(C_2H_5)_2NC_2H_4OCOC_6H_4NHCO_2]_2$—R—

R =	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
		Bases				
$(CH_2)_2$[a]	140–141	$C_{30}H_{42}O_8N_4$	61.42	61.18	7.22	7.25
$(CH_2)_3$[b]	116–117	$C_{31}H_{44}O_8N_4$	61.98	61.70	7.38	7.14
$(CH_2)_4$[c]	187–188	$C_{32}H_{46}O_8N_4$	62.52	62.50	7.54	7.51
$(CH_2)_5$[a]	156–157	$C_{33}H_{48}O_8N_4$	63.03	63.10	7.70	7.83
$(CH_2)_6$[d]	190–191	$C_{34}H_{50}O_8N_4$	63.53	63.33	7.84	7.74
$(CH_2)_{10}$[e]	160–161	$C_{38}H_{58}O_8N_4$	65.30	65.35	8.36	8.50
$(C_2H_4)_2$—O[b]	122–123	$C_{32}H_{46}O_9N_4$	60.93	60.65	7.35	7.11
		Dihydrochlorides				
$(CH_2)_2$[b]	199–200 dec.	$C_{30}H_{44}O_8N_4Cl_2$	54.63	54.93	6.72	7.01
$(CH_2)_3$[g]	170–171 dec.	$C_{31}H_{46}O_8N_4Cl_2$	55.27	55.05	6.89	7.17
$(CH_2)_4$[g]	205–206 dec.	$C_{32}H_{48}O_8N_4Cl_2$	55.90	56.00	7.03	7.21
$(CH_2)_5$[f]	176–177 dec.	$C_{33}H_{50}O_8N_4Cl_2$	56.48	56.68	7.18	7.30
$(CH_2)_6$[f]	213–215 dec.	$C_{34}H_{52}O_8N_4Cl_2$	57.05	57.28	7.32	7.24
$(CH_2)_{10}$[h]	201–203 dec.	$C_{38}H_{60}O_8N_4Cl_2$	59.13	59.23	7.84	8.11
$CH_2C{\equiv}CCH_2$[i]	181–183 dec.	$C_{32}H_{44}O_8N_4Cl_2$	56.22	56.35	6.48	6.36
$(CH_2CH_2)_2O$[j]	191–192 dec.	$C_{32}H_{48}O_9N_4Cl_2$	54.63	54.61	6.87	7.18
C_6H_{10} (1,4-Cyclohexylene)[j]	213–214 dec.	$C_{34}H_{50}O_8N_4Cl_2$	57.22	57.01	7.06	6.77
C_6H_4(*p*)[i]	164–166 dec.	$C_{34}H_{44}O_6N_4Cl_2$	57.70	57.60	6.27	6.21
		Dioxalates				
$CH(CH_3)CH_2$[k]	112–114 dec.	$C_{35}H_{48}O_{16}N_4$	53.83	53.54	6.20	6.50
$(CH_2)_4$[l]	186–188 dec.	$C_{36}H_{50}O_{16}N_4$	54.40	54.20	6.34	6.31
$CH(CH_3)CH_2CH_2$[k]	162–164 dec.	$C_{36}H_{50}O_{16}N_4$	54.40	54.33	6.34	6.30
$CH_2CH(CH_3)CH_2$[m]	115–117 dec.	$C_{36}H_{50}O_{16}N_4$	54.40	54.69	6.34	6.46
$(CH_2)_2C(CH_3)_2(CH_2)_2$[n]	150–152 dec.	$C_{39}H_{56}O_{16}N_4$	55.97	55.86	6.75	6.70
		Dipicrates				
$(CH_2)_4$[o]	178–179 dec.	$C_{44}H_{52}O_{22}N_{10}$	49.25	49.00	4.89	4.94
$CH(CH_3)CH_2CH_2$[p]	144–145 dec.	$C_{44}H_{52}O_{22}N_{10}$	49.25	49.51	4.89	5.19
$CH_2CH(CH_3)CH_2$[q]	130–131 dec.	$C_{44}H_{52}O_{22}N_{10}$	49.25	49.00	4.89	4.79
		Other salts				
$(CH_2)_4$[r]	140–141 dec.	$C_{46}H_{58}O_{14}N_4$	61.99	61.69	6.55	6.30
$(CH_2)_4$[s]	235–236 dec.	$C_{40}H_{52}O_{18}N_{10}$	49.99	49.71	5.45	5.63

Crystallization solvents: [a] ethyl acetate–petroleum ether (60–70°), [b] ether–petroleum ether (60–70°), [c] acetone, [d] alcohol, [e] ethyl acetate, [f] alcohol–*n*-hexane, [g] alcohol–acetone. [h] alcohol–water. [i] alcohol–ether. [j] methanol–acetone [k] methanol–ether, [l] methanol, [m] alcohol–ether, [n] alcohol, [o] acetone–alcohol, [p] ethyl acetate, [q] acetone–ether, [r] disalicylate; ethyl acetate–petroleum ether (60–70°), [s] dididiturate–acetic acid.

water. The analytical data and melting points of the N-carboalkoxy derivatives are reported in Table II.

Condensation of Dichlorocarbonates with Procaine Hydrochloride.—The following example is illustrative of this reaction. A solution of 33.4 g. (0.122 mole) of procaine hydrochloride in 200 ml. of acetone and 25 ml. of water was stirred while 14.0 g. (0.61 mole) of pentamethylene dichlorocarbonate was added dropwise. The solution turned cloudy and crystallization was complete within 10 minutes after all of the dichlorocarbonate had been introduced. The reaction mixture was cooled, filtered and sucked as dry as possible. The white mass was dried in a vacuum oven at 65° (20 mm.) to give 42.5 g. (99%) of product. After crystallization from a mixture of alcohol and *n*-hexane, the compound melted at 175–177° dec.

The melting points, analytical data and crystallization solvents for the free bases, dihydrochlorides and other salts of the N,N′-disubstituted dicarbamates, which were all isolated in high yields, are given in Table III.

The free bases were obtained by carrying out the preceding type condensation in the presence of a slight excess of triethylamine. The latter was added dropwise, along with the dichlorocarbonate, to the aqueous acetone solution of procaine hydrochloride. The additions were controlled so that the dichlorocarbonate was in excess until near the end of the reaction. The acetone was evaporated by warming, and, after cooling the residue, the product was removed by filtration. Those bases which were liquids were isolated by extraction with *n*-butyl alcohol or chloroform.

The dioxalates, dipicrates, disalicylate and didilituarate were prepared by mixing hot, saturated alcohol solutions of the appropriate bases with hot, saturated alcohol solutions of the corresponding acids.

Hydrolysis of the Di-β-diethylaminoethyl Ester of N,N′-Di-(*p*-carboxyphenyl)-tetramethylene Diurethan.—Two grams of the ester dihydrochloride was refluxed with a solution of 15 ml. of concentrated hydrochloric acid in 100 ml. of water for two hours. The solid which had separated from solution was removed by filtration of the hot reaction mixture and dried; weight 1.2 g. The material was dissolved in 5% sodium hydroxide solution, the solution was filtered and the filtrate was acidified. The precipitate was collected, washed with water and dried; m.p. 300–301° dec. A mixed melting point determination with a sample of N,N′-di-(*p*-carboxyphenyl)-tetramethylene diurethan showed no depression.

Preparation of N,N′-Di-(*p*-carboxyphenyl)-tetramethylene Diurethan.—Twenty-seven and four-tenths grams (0.20 mole) of *p*-aminobenzoic acid was dissolved in 200 ml. of acetone and 21.5 g. (0.1 mole) of tetramethylene dichlorocarbonate was added dropwise with stirring. The reaction mixture was stirred for a further 10 minutes, allowed to cool and filtered. The product was washed several times with acetone and dried. There was obtained 39.0 g. (94%) of a light tan-colored solid which was purified further by dissolving it in dilute alkali, reprecipitating with acid and washing with hot methanol; m.p. 301–302° dec.

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.69; H, 4.84. Found: C, 57.51; H, 4.64.

COLUMBIA, MISSOURI

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

Antispasmodics. II. Studies on the Synthesis of 2-Diethylaminoethyl α-(2-Cycloalken-1-yl)-2-thienylacetates

BY FREDERICK LEONARD AND LEON SIMET

RECEIVED JANUARY 4, 1952

The 2-diethylaminoethyl esters (IV) of two α-(cycloalken-1-yl)-2-thienylacetic acids [I, R = 1-(2-C_5H_7) and 1-(2-C_6H_9)] have been synthesized both by condensation of the appropriately substituted 2-thienyl acetic acid with 2-diethylaminoethyl chloride and by transesterification of alkyl α-(2-cycloalken-1-yl)-2-thienylacetates (II) with 2-diethylaminoethanol. Alkylation of 2-thienylacetonitrile (V) with 2-cycloalken-1-yl halides in the presence of basic catalysts gave α-(2-cycloalken-1-yl)-2-thienylacetonitriles (VI) which could be saponified to either a mixture of the corresponding acid (I) and amide (VII) or to the acid alone. An alternative synthesis used in the preparation of one of the disubstituted acetic acids [I, R = 1-(2-C_6H_9)] involved the carbethoxylation of V to ethyl α-cyano-2-thienylacetate (VIII) and alkylation of VIII to ethyl α-cyano-α-(2-cyclohexen-1-yl)-2-thienylacetate (IX). Saponification of the cyanoacetate (IX) gave a mixture of the acid I and amide VII [both R = 1-(2-C_6H_9)]. Acid alcoholysis of the nitriles, VI, direct esterification of the acetic acids, I, and alkylation of ethyl 2-thienylacetate yielded alkyl α-(2-cycloalken-1-yl)-2-thienylacetates (II). The cyanoacetate, IX, was recovered unchanged from an attempted alcoholysis under conditions which converted the nitrile, VI, to the corresponding acetate (II).

The discovery of the clinically useful spasmolytic properties of 2-diethylaminoethyl α-(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride[1,2] [IV, R = 1-(2-C_5H_7)] and its 2-cyclohexen-1-yl homolog [IV, R = 1-(2-C_6H_9)] led to a study, the results of which are presented in this communication, of shorter and potentially more convenient methods of synthesis of the esters, IV, than that originally described.[1]

Esters of commercially available aminoalcohols may be synthesized by a number of general reactions,[3] each having its own peculiar advantages. The method of choice in any one instance is likely, however, to depend primarily on the availability of the starting materials. This investigation on the synthesis of new intermediates for the synthesis of the esters, IV, was predicated on the ultimate condensation of 2-diethylaminoethyl chloride with a disubstituted acetic acid (I) or the transesterification of a lower alkyl disubstituted acetate (II) with 2-diethylaminoethanol.

Since acetic acids and acetic acid esters have been obtained by solvolyzing acetonitriles and cyanoacetates, the synthesis was undertaken of properly substituted acetonitriles (VI) and cyanoacetates (IX) which would be expected to yield, when hydrolyzed or alcoholyzed, the acids (I) and esters (II) required for the preparation of the basic-alkyl esters (IV).

The first attempt to prepare an α-(2-cycloalken-1-yl)-2-thienylacetonitrile (VI) by the alkylation of 2-thienylacetonitrile (V) in the presence of lithium amide failed, probably because V decom-

(1) F. Leonard, THIS JOURNAL, **74**, 2915 (1952).

(2) Neotropine Hydrochloride Warner, U. S. Patent 2,561,385, July 24, 1951.

(3) See Antispasmodics by R. R. Burtner in "Medicinal Chemistry," Vol. I, C. M. Suter, Editor, John Wiley and Sons, Inc., New York, N. Y., 1951, and Histamine Antagonists, Review No. 3, pp. 22, by F. Leonard and C. P. Huttrer, National Research Council, Washington, D. C., 1950.