Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.67, 58.68; H, 6.58, 6.50.

This was confirmed by conversion of the compound to the known 2,4,6-tri-(acetoxymethyl)-phenyl acetate[11] by the action of acetic anhydride in pyridine. The ester boiled at 172–175° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 57.45; H, 5.72; sapn. equiv., 88.08. Found: C, 57.89, 57.75; H, 5.83, 5.98; sapn. equiv., 87.3, 91.6.

A sample of the compound was also converted to the known sodium tri-(hydroxymethyl)-phenate[3] by dissolving in alcohol and treating with a slight excess of alcoholic sodium hydroxide. The sodium tri-(hydroxymethyl)-phenate precipitated from the alcohol solution as a dry white powder upon the addition of a little butanol, and was collected and dried; calcd. for neut. equiv., 206.2; found: neut. equiv., 204.5, 203.9.

PITTSFIELD, MASS.

(11) H. A. Bruson and C. W. Macmullen, THIS JOURNAL, **63**, 270 (1941).

[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

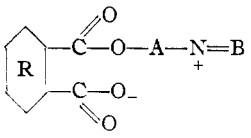
Dialkylaminoalkyl Acid Esters and Salts as Hypotensive Agents[1a,1b]

BY LEONARD M. RICE,[2] ANTOINETTE POPOVICI, MARTIN RUBIN, CHARLES F. GESCHICKTER AND E. EMMET REID[3]

RECEIVED DECEMBER 10, 1951

A series of dialkylaminoalkyl half esters was prepared by the reaction of the appropriate dialkylaminoalkyl alcohol with an anhydride. These compounds have been found to possess hypotensive action.

As part of a research program directed toward the finding of clinically useful hypotensive agents, the investigation of a series of half esters of dialkylaminoalkyl alcohols and some of the corresponding magnesium salts of the structural type illustrated was undertaken.



Representative compounds in which the cyclic nucleus was phenyl, 3-nitrophenyl, *cis*-Δ^4-cyclohexene and 3,6-endomethylene-*cis*-Δ^4-cyclohexene have been prepared. In these compounds the side chains have been varied so that the –A– grouping represents two or three methylene carbon atoms while the –B– grouping represents alkyl groups in the range of methyl to butyl as well as cyclic systems such as the morpholino, pyrrolidino and phthalimido rings. In general these materials have been prepared by the reaction of the appropriate anhydride and amino alcohol in anhydrous acetone. The reactions were exothermic and the product usually separated in crystalline form on standing.

Aqueous 20% solutions of the alkyl amino acid esters have a *p*H of 6.6–7.0 when measured on the Beckman *p*H meter. This neutrality shows that the carboxyl group is not free and that the compound probably exists as a zwitterion. This contention is further supported by the high water-solubility of the compounds. In a similar manner the insolubility in such solvents as benzene, petroleum ether, chloroform and ether is in keeping with the zwitterion formulation.

As the basicity of the nitrogen in the side chain of the molecule decreased, the products became less water-soluble. In the compounds where 2-(β-hydroxyethyl)-pyridine was the alcohol used in the esterification there is a marked decrease in solubility of the product. When the basicity of the nitrogen is further decreased, as in the compound containing the N-(β-ethyl)-phthalimide grouping, the solubility is further decreased.

In the series of compounds derived from 3-nitrophthalic acid it has been shown that the alkylamino group enters the 2-position.[4] These compounds have lower water-solubilities than the other series.

As a variation of the nitrogen-containing portion of the molecule, the *cis*-Δ^4-tetrahydrophthalamic acids shown in Table V were prepared[5] and characterized.

From such a large group of compounds of similar structure it is possible to draw some conclusions as to the relation of structure and activity of these materials. When screened in normotensive dogs it could be established that the most active compounds are those characterized by the alicyclic nucleus such as *cis*-Δ^4-tetrahydrophthalic and the endomethylene *cis*-Δ^4-tetrahydrophthalic. The maximal activity and least toxicity appeared in the compounds where –A– was an ethyl substituent in common with many similar pharmacologically active materials.

In the –B– portion of the molecule lower alkyl groups such as methyl and ethyl showed the most activity. The amic acid class did not show comparable activity. In all cases conversion to the magnesium salts potentiated the hypotensive action of the products.

It is interesting to note that bis-(β-diethylaminoethyl) *cis*-Δ^4-tetrahydrophthalate is a powerful hypotensive compound.

A much more complete report of the pharmacological properties of these compounds will be published elsewhere.

(1) (a) Presented at the XIIth International Congress of Pure and Applied Chemistry, Medicinal Section, New York, N. Y., September, 1951. (b) Supported (in part) by a research grant from the National Heart Institute, U. S. Public Health Service, and the Geschickter Fund for Medical Research, Inc.

(2) Abstracted in part from the thesis submitted to Georgetown University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Professor Emeritus, Johns Hopkins University, Baltimore, Md.

(4) Blicke and Otsuki, THIS JOURNAL, **63**, 1945 (1941).

(5) L. M. Rice, M. Rubin, Jean Scholler and E. E. Reid, *J. Org. Chem.*, **16**, 501 (1951).

TABLE I

DIALKYLAMINOALKYL TETRAHYDROPHTHALATES

Type	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen % Calcd.	Nitrogen % Found
β-Dimethylaminoethyl[a]	133–134	$C_{13}H_{19}NO_4$	59.73	60.07	7.94	7.66	5.80	5.81
β-Diethylaminoethyl[b]	83–84	$C_{14}H_{23}NO_4$	62.43	62.35	8.31	8.33	5.20	5.04
β-(N-Ethyl)-morpholino[c]	141–143	$C_{14}H_{21}NO_5$	59.37	59.05	7.44	7.44	4.95	4.89
β-(N-Ethyl)-piperidino[c]	148–149	$C_{15}H_{23}NO_4$	64.03	63.71	8.24	8.10	4.98	4.73
β-(N-Ethyl)-pyrrolidino[d]	160–161	$C_{14}H_{21}NO_4$	62.90	62.82	7.54	7.39	5.24	5.06
β-(2-Ethyl)-pyridine[e]	119–120	$C_{15}H_{17}NO_4$	65.44	65.92	6.22	6.22	5.09	5.04
γ-Diethylaminopropyl[f]	Glass	$C_{15}H_{25}NO_4$	63.58	63.32	8.89	8.97	4.94	4.81
β-Dibutylaminoethyl[f]	Glass	$C_{18}H_{31}NO_4$	66.43	66.16	9.60	9.53	4.30	4.58
β-(N-Ethyl)-phthalimide[a]	129–130	$C_{18}H_{17}O_6N$	62.96	62.63	4.99	4.83	4.08	4.09
2-(1-Dimethylaminopropyl)[a,g]	.....	$C_{13}H_{21}NO_4$	61.15	60.93	8.29	8.30	5.49	5.24

[a] Rx from methanol. [b] Rx from acetone. [c] Rx from methanol. [d] Rx from 90% ethanol. [e] Rx from acetone–ethanol Ether precipitation. [g] Melted over a wide range.

TABLE II

DIALKYLAMINOALKYL *cis*-3,6-ENDOMETHYLENE-Δ^4-TETRAHYDROPHTHALATES

Type	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
β-Dimethylaminoethyl[a]	96–98	$C_{13}H_{19}NO_4$	61.64	62.12	7.56	7.41	5.53	5.45
β-Diethylaminoethyl[a]	90–91	$C_{15}H_{23}NO_4$	64.03	64.07	8.24	8.09	4.98	4.67
β-(N-Ethyl)-morpholino[a]	106–107	$C_{15}H_{21}NO_5$	61.02	61.33	7.17	6.84	4.74	4.74
β-(N-Ethyl)-piperidino[a]	107–108	$C_{16}H_{23}NO_4$	65.50	65.35	7.90	7.92	4.77	4.70
β-(N-Ethyl)-pyrrolidino[a]	126–127	$C_{15}H_{21}NO_4$	64.69	64.51	7.58	7.22	5.01	5.18
β-(2-Ethyl)-pyridine[b]	106–107	$C_{16}H_{17}NO_4$	66.88	66.90	5.96	5.96	4.88	4.70
γ-Diethylaminopropyl[c]	Glass	$C_{16}H_{25}NO_4$	65.08	65.26	8.51	8.34	4.74	4.84
β-Dibutylaminoethyl[c]	Glass	$C_{19}H_{31}NO_4$	67.62	67.33	9.23	9.33	4.15	4.27

[a] Rx from acetone. [b] Rx from acetone–ethanol. [c] Precipitated with ether.

TABLE III

DIALKYLAMINOALKYL PHTHALATES

Type	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
β-Dimethylaminoethyl[a]	171–172	$C_{12}H_{15}NO_4$	60.75	60.48	6.39	6.49	5.90	5.92
β-Diethylaminoethyl[a]	119–120	$C_{14}H_{19}NO_4$	63.37	63.53	7.22	7.38	5.28	5.62
β-(N-Ethyl)-morpholino[b]	114–116	$C_{14}H_{17}NO_5$	60.20	60.59	6.14	6.23	5.02	5.38
β-(N-Ethyl)-piperidino[a]	172–173	$C_{15}H_{19}NO_4$	64.96	65.07	6.91	7.02	5.05	5.32
β-(N-Ethyl)-pyrrolidino[a]	182–184	$C_{14}H_{17}NO_4$	63.86	64.13	6.51	6.82	5.32	5.45
β-Dibutylaminoethyl	Glass	$C_{18}H_{27}NO_4$	67.26	67.41	8.47	8.40	4.36	4.53
β-(2-Ethyl)-pyridine[a]	134–136	$C_{15}H_{13}NO_4$	66.42	66.20	4.83	4.87	5.16	5.28

[a] Rx from acetone–methanol. [b] Rx from ethanol.

TABLE IV

2-DIALKYLAMINOALKYL 3-NITROPHTHALATES

Type	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
β-Dimethylaminoethyl[a]	157–158	$C_{12}H_{16}N_2O_7$[f]	48.00	48.38	5.37	5.18	9.33	9.46
β-Diethylaminoethyl[a]	167–168[b]	$C_{14}H_{18}N_2O_6$	...	...	..	..	..	..
β-(N-Ethyl)-morpholino[c]	164–166	$C_{14}H_{16}N_2O_7$	51.85	52.10	4.97	4.73	8.64	8.96
β-(N-Ethyl)-piperidino[c]	162–164	$C_{15}H_{18}N_2O_6$	55.89	55.96	5.63	5.77	8.69	8.85
β-(2-Ethyl)-pyridine[d]	151–153	$C_{15}H_{12}N_2O_6$	56.55	56.65	4.52	4.63	8.79	9.00
β-Dibutylaminoethyl[e]	143–144	$C_{18}H_{26}N_2O_6$	59.00	59.20	7.15	6.99	7.65	7.90

[a] Rx 85% ethanol. [b] Prepared previously by Blicke and Otsuki, THIS JOURNAL, 63, 1945 (1941). [c] Rx from ethanol. [d] Insoluble, boiled with methanol, ethanol, ether, benzene and acetone. [e] Rx acetone alcohol. [f] As monohydrate.

TABLE V

AMIC ACIDS FROM TETRAHYDROPHTHALIC ACIDS

Type	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Acid No. Calcd.	Acid No. Found
Cyclohexyl[a]	147–148	$C_{14}H_{21}NO_3$	66.89	67.02	8.42	8.40	5.57	5.52	251	253
Phenylethyl[b]	113–114	$C_{16}H_{19}NO_3$	70.31	70.60	7.01	7.00	5.05	5.19	273	274
N-Propylmorpholino[b]	104–105	$C_{15}H_{24}N_2O_4$	60.79	61.06	8.16	8.15	9.45	9.35	296	302
2-Aminothiazole[c]	172–173	$C_{11}H_{12}N_2O_3S$	52.37	52.56	4.79	4.63	11.10	11.11		

[a] Rx from acetone–methanol. [b] Rx from acetone. [c] Insoluble, boiled with ether, acetone, ethanol and methanol.

Experimental

General Preparation of Dialkylaminoalkyl Half Esters.—The preparation of mono-β-diethylaminoethyl *cis*-Δ⁴-tetrahydrophthalate will illustrate the procedure followed.

A solution of 0.1 mole (11.7 g.) of diethylaminoethanol dissolved in 30 ml. of dry acetone was slowly added dropwise to 0.1 mole (15.2 g.) of *cis*-Δ⁴-tetrahydrophthalic anhydride dissolved in 30 ml. of dry acetone. After the exothermic reaction was over the mixture was boiled for a few minutes and filtered from a small amount of insoluble material. On standing at room temperature overnight a heavy, colorless precipitate (23 g.) formed. The insoluble product was filtered off and washed with anhydrous ether. Recrystallization from dry acetone several times yielded the desired compound, m.p. 83–84°.

Preparation of Magnesium Salts.—A mixture of the amino acid and a slight molar excess of magnesium carbonate were refluxed for 4 hours in 5% alcohol. The solution was then filtered and concentrated to dryness *in vacuo* to obtain a colorless crystalline solid product, which in all cases was very soluble in water.

Preparation of Bis-(β-diethylaminoethyl)-*cis*-Δ⁴-tetrahydrophthalate.—In a flask, equipped with a dropping funnel and a condenser carrying a calcium chloride drying tube, was placed 0.1 mole of β-diethylaminoethyl-*cis*-Δ⁴-acid tetrahydrophthalate and 100 ml. of dry benzene. While the mixture was cooled in an ice-bath, 0.12 mole of oxalyl chloride dissolved in 100 ml. of benzene was added dropwise. The reaction was rapid as was evidenced by the rapid evolution of gas. When all the oxalyl chloride was added, the mixture was refluxed for one hour on a water-bath. The benzene and the unreacted oxalyl chloride were removed under vacuum, fresh benzene was added, and the stripping procedure repeated. The resulting gum was taken up in 200 ml. of dry benzene and 0.11 mole of diethylaminoethanol was slowly added to the solution. After refluxing for four hours the mixture was cooled and extracted with dilute hydrochloric acid. The water solution was separated, filtered, made alkaline with 10% sodium carbonate solution, and extracted with ether. Anhydrous sodium sulfate was added to dry the ethereal extract which was then filtered and concentrated from a water-bath. The resulting oil was fractionated in vacuum. The product was obtained as a clear, colorless oil with a boiling point of 166–171° at 0.5 mm.

Anal. Calcd. for $C_{20}H_{36}N_2O_4$: C, 65.2; H, 9.7; N, 7.6. Found: C, 65.3; H, 9.8; N, 7.7.

WASHINGTON 7, D. C.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Rearrangements in Amination by Alkali Amides in Liquid Ammonia and by Lithium Dialkylamides in Ether

BY HENRY GILMAN AND ROBERT H. KYLE

RECEIVED DECEMBER 3, 1951

Several extensions have been made on the scope of rearrangements in amination by alkali amides in liquid ammonia and by lithium dialkylamides in ether.

An earlier study[1a,b] reported a rearrangement of ortho-halogenated ethers by sodamide in liquid ammonia to give *m*-amino ethers. The rearrangement reaction was also shown to take place with an ortho-halogenated sulfide like 4-iododibenzothiophene.[1c] The rearrangement is apparently of a wider scope for it is shown not only with sodamide in liquid ammonia but also with lithium dialkylamides in ether, and with non-ether or -sulfide types like α-halogenated naphthalenes[1d,e] and *o*-bromodimethylaniline.[1f] It is also noteworthy that *p*-bromoanisole and lithium diethylamide give, in addition to *p*-methoxydiethylaniline, the rearrangement product, *m*-methoxydiethylaniline.[1g]

An extension of some of these reactions is now reported. First, results are reported on some optimal conditions for the reaction of *o*-chloroanisole with sodamide in liquid ammonia. Second, potassium amide gives a yield of rearrangement product comparable to that obtained with sodamide. Third, under corresponding conditions, lithium amide does not react appreciably with *o*-chloroanisole, but does show the rearrangement with *o*-bromoanisole. Fourth, lithium diethylamide in ether shows the rearrangement with *o*-iodo-, *o*-bromo-, *o*-chloro- and *o*-fluoroanisole to give *m*-diethylaminoanisole. The reaction with *o*-fluoroanisole is interesting, for α-fluoronaphthalene, unlike α-chloronaphthalene, does not rearrange with potassium amide in liquid ammonia,[1e] whereas the α-fluoro-, α-chloro- and α-bromonaphthalenes give β-diethylaminonaphthalenes with lithium diethylamide. Fifth, *m*-chloroanisole, as might have been expected, gives *m*-diethylaminoanisole. Sixth, lithium di-*n*-butylamide with *o*-chloroanisole gives a higher yield than lithium diethylamide. Seventh, the halogenated phenols may behave like the halogenated ethers, for *o*-bromophenol and lithium diethylamide give *m*-diethylaminophenol. Eighth, cyclic amides like lithium piperidide and morpholide show the same rearrangement observed with lithium dialkylamides.[1b]

In practically all reactions with the *o*-halogenated anisoles, some anisole is obtained. This does not, apparently, owe its formation to a halogen–metal interconversion reaction[1d] which would give an anisyllithium compound that would be hydrolyzed to anisole.

Experimental

***o*-Haloanisoles and Metal Amides.**—In a typical procedure, 0.5 mole of the *o*-haloanisole was added to one mole of sodamide[2] in liquid ammonia over a one-half-hour period. The color gradually changed, first to light green and finally to a deep reddish brown. The mixture was then stirred for an additional 20 minutes, and then one mole of am-

(1) (a) H. Gilman and S. Avakian, THIS JOURNAL, **67**, 349 (1945); see, also, F. W. Bergstrom and W. C. Fernelius, *Chem. Revs.*, **20**, 437 (1937); and (b) C. H. Horning and F. W. Bergstrom, THIS JOURNAL, **67**, 2110 (1945); (c) H. Gilman and J. F. Nobis, *ibid.*, **67**, 1479 (1945); (d) H. Gilman, N. N. Crounse, S. P. Massie, R. A. Benkeser and S. M. Spatz, *ibid.*, **67**, 2106 (1945); (e) R. S. Urner and F. W. Bergstrom, *ibid.*, **67**, 2108 (1945); (f) H. Gilman, R. H. Kyle and R. A. Benkeser, *ibid.*, **68**, 143 (1946); (g) H. Gilman and R. H. Kyle, *ibid.*, **70**, 3945 (1948); see, particularly, R. A. Benkeser and R. G. Severson, *ibid.*, **71**, 3838 (1949).

(2) Prepared in accordance with directions by T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, *ibid.*, **56**, 2120 (1934).