[CONTRIBUTION FROM THE CHEMISTRY DIVISION, LAKESIDE LABORATORIES INC.]

Hypotensive Agents. II. Aminoalkyl Esters of Piperidinecarboxylic Acids and Their "Reversed" Ester Derivatives

BY JOHN H. BIEL, EDWIN P. SPRENGELER AND HARRIS L. FRIEDMAN

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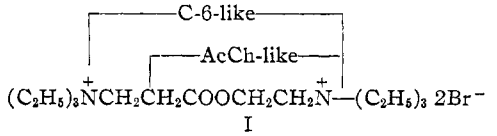
The interesting pharmacologic characteristics of β-diethylaminoethyl β-diethylaminopropionate diethobromide, a compound with both ganglionic blocking and muscarinic properties, prompted the synthesis of a number of "cyclic" analogs of this substance. Aminoalkyl and aminoalkynyl esters of the three isomeric N-alkylpiperidine-carboxylic acids were prepared as well as their "reversed" ester derivatives, amino acid esters of N-alkylpiperidyl alcohols. The synthesis of the esters was accomplished by an ester interchange reaction of the aminoalcohol with the methyl ester of the appropriate acid in *n*-heptane and in the presence of catalytic amounts of sodium methoxide; yields ranged from 50–90% of theory. Several of the compounds displayed potent and sustained hypotensive properties when tested in the form of their bis-quaternary ammonium salts in the normotensive dog. The structural features necessary for optimum hypotensive activity are discussed.

One of the more serious drawbacks of the present "methonium" hypotensive drugs is the fact that they block both parasympathetic and sympathetic ganglia to an equal extent. Parasympathetic ganglionic blockage results in such undesirable side effects as dry mouth, mydriasis, intestinal atony and urinary retention which in many cases preclude the further use of these agents.

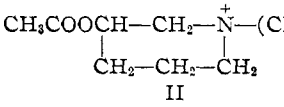
In 1954, an interesting paper appeared by Schueler and Keasling[1] which described the pharmacologic properties of β-diethylaminoethyl β-diethylaminopropionate diethobromide (I). This com-



I

pound embodies certain structural features of both acetylcholine (AcCh) and hexamethonium (C-6) and may be looked upon as a ganglionic blocking agent with a "built-in" muscarinic moiety. This postulate was confirmed by the authors who found I to be more potent as a sympathetic blocking agent, the effects of parasympathetic blockage being partially off-set by the post-ganglionic parasympathetic stimulant properties of the compound.

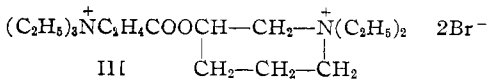
A "cyclic" derivative of acetylcholine, N-methyl-3-piperidyl acetate methiodide (II), had been syn-



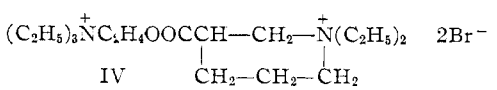
II

thesized earlier by us[2] and found to be a weak muscarinic agent.[3]

It was of interest, therefore, to prepare "cyclic" analogs of I as represented by formulas III and IV



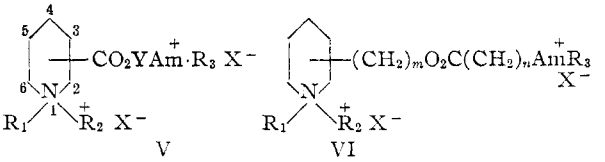
III



IV

in the hope of obtaining compounds with more potent and sustained hypotensive properties and a more favorable therapeutic spectrum. Compound IV is a diethylaminoethyl ester of N-ethylnipecotic acid, while the isomeric compound III is the β-diethylaminopropionate ester of N-ethyl-3-hydroxypiperidine or the "reversed" ester of IV.

It was further the object of this work to prepare homologs, position isomers and other congeners of III and IV and study their hypotensive and ganglionic blocking properties. These compounds may be represented by the general structures V and VI where the side chain was linked to the piperidine ring in the 2-, 3- or 4-position.



V VI

R_1, R_2 and R_3 = alkyl or *o*-chlorobenzyl
Y = alkylene, alkynylene
Y–Am = N-methyl-3-piperidyl, N-methyl-3-piperidylmethyl
m = 0 or 1; *n* = 1, 2 or 3
Am = dialkylamino, morpholino, pyrrolidino, N-*o*-chlorobenzyl methylamino
X = Br or I

The compounds were conveniently prepared by the ester interchange reaction of a methyl ester with the desired aminoalcohol in normal heptane and in the presence of catalytic amounts of sodium methoxide, the methanol being removed through a Dean–Stark separator.[2] The yields ranged from 50–90% of theory.

Structure–Activity Relationships.—The base esters were submitted for pharmacologic testing in the form of their quaternary ammonium salts.

The pharmacologic work was carried out under the supervision of Mr. P. A. Nuhfer to whom we are indebted for the hypotensive data.

The compounds were administered intravenously and intraduodenally to the nembutalized, normotensive dog. The structure–activity data of the two more promising series are summarized in Tables IV and V.

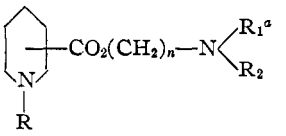
The following structural features appeared critical to potent and sustained hypotensive activity: (1) The position of the ester side chain, (2) the character and length of the alkylene chain and (3) the N-substituents on the terminal amino group. Thus, the dimethylaminoethyl and morpholino-

(1) F. W. Schueler and H. H. Keasling, *J. Am. Pharm. Assoc.*, **43**, 98 (1954).

(2) J. H. Biel, E. P. Sprengeler, H. A. Leiser, J. Horner, A. Drukker and H. L. Friedman, THIS JOURNAL, **77**, 2250 (1955).

(3) F. W. Schueler, *J. Am. Pharm. Assoc.*, **45**, 197 (1956).

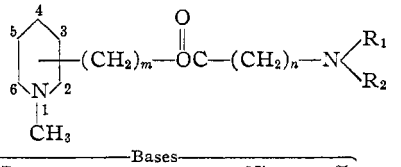
TABLE I



R	$N(R_1)(R_2)$	Bases: B.p. °C.	Mm.	n	Formula	Nitrogen, % Calcd.	Found	Salt	Salts: Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	M.p., °C.
CH_3	$N(CH_3)_2$	113–105	4.0	2	$C_{11}H_{22}N_2O_2$	13.08	13.01	CH_3Br	6.93	6.83	39.60	38.95	230–232
C_2H_5	$N(C_2H_5)_2$	104–106	2.0	2	$C_{14}H_{28}N_2O_2$	10.93	10.87	CH_3Br	6.28	6.24	35.87	35.79	221–222
CH_3	$N(CH_3)_2$	106–109	1.0	3	$C_{12}H_{24}N_2O_2$	12.28	12.35	CH_3Br	6.70	6.72	38.27	38.49	238–239
CH_3	Morpholino	116–120	1.0	2	$C_{13}H_{24}N_2O_3$	10.94	11.02	CH_3Br	6.28	6.54	35.87	35.75	235–236
CH_3	Pyrrolidino	103–105	1.0	2	$C_{13}H_{24}N_2O_2$	11.67	11.74	CH_3Br	6.51	6.51	37.21	37.21	209–211
CH_3[b]	$N(CH_3)_2$	95–96	1.0	2	$C_{11}H_{22}N_2O_2$	13.08	12.80	CH_3Br	6.93	6.93	39.60	39.45	276–277
CH_3[c]	$N(CH_3)_2$	145–147	23	2	$C_{11}H_{22}N_2O_2$	13.08	12.95	CH_3Br	6.93	6.87	39.60	40.09	245
CH_3[c,j]	$N(CH_3)_2$	156–158	23	3	$C_{12}H_{24}N_2O_2$	12.28	11.97	CH_3I	5.47	5.42	49.61	48.58[f]	224–226
CH_3[c]	Morpholino	136–138	1.2	2	$C_{13}H_{24}N_2O_3$	10.94	10.79	CH_3Br	6.28	6.13	35.87	35.46	233–235
CH_3	*o*-Cl-Benzylmethylamino	100–105	0.5	2	$C_{17}H_{25}ClN_2O_2$	8.63	8.54	CH_3I	4.60	4.62	41.74	41.49	185
CH_3	*o*-Cl-Benzylmethylamino	148–153	0.15	2	$C_{17}H_{25}ClN_2O_2$	8.63	8.73	CH_3I	4.60	4.82	41.74	41.72	178–179
o-Cl-Benzylmethylamino	$N(CH_3)_2$												
CH_3	$N(CH_3)_2$	137–141	17	3[d]	$C_{12}H_{24}N_2O_2$	12.28	12.14	CH_3Br	6.70	6.60	38.28	38.48	255–257
..[e]	$N(CH_3)_2$	154–156	19	2	$C_{10}H_{14}N_2O_2$	14.43	14.43	CH_3Br	7.29	7.21	41.67	41.81	218–219
CH_3[c]	Morpholino	140–142	0.8	3	$C_{14}H_{26}N_2O_3$	10.37	10.26	CH_3I	5.05	5.04	45.85	45.46	169–171

[a] Unless otherwise specified, the compounds are esters of nipecotic acid. [b] Ester of isonipecotic acid. [c] Ester of pipecolinic acid. [d] 3-Dimethylamino-2-propyl. [e] Ester of nicotinic acid. [f] Very hygroscopic.

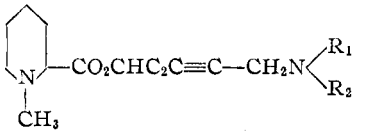
TABLE II



Ring position	m	n	$N(R_1)(R_2)$	Bases: B.p. °C.	Mm.	Formula	Nitrogen, % Calcd.	Found	Salt	Salts: Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	M.p., °C.
2	1	2	Morpholino	140–141	0.8	$C_{14}H_{26}N_2O_3$	10.37	10.16	CH_3Br	6.09	6.14	34.78	35.19	188–189
3	0	2	Pyrrolidino	105–108	0.3	$C_{13}H_{24}N_2O_2$	11.67	11.59	CH_3I	5.34	5.34	48.47	48.23	165–166
3	0	2	Morpholino	126–129	0.7	$C_{13}H_{24}N_2O_3$	10.94	10.83	CH_3I	5.19	5.12	47.04	46.44[b]	182–183
3	0	1	$N(CH_3)_2$	136–138	16	$C_{10}H_{20}N_2O_2$	14.00	13.55	CH_3Br	7.18	7.15	41.03	40.91	183–184
3	0	2	$N(CH_3)_2$	158–160	37	$C_{11}H_{22}N_2O_2$	13.08	12.86	CH_3I	5.62	5.66	51.00	50.77	194–195
3	1	1	$N(CH_3)_2$	147–148	22	$C_{11}H_{22}N_2O_2$	13.08	12.86	CH_3Br	6.93	6.94	39.60	39.36	232–233
4	0	1	$N(CH_3)_2$	110–113	8	$C_{10}H_{20}N_2O_2$	14.00	13.90	CH_3Br	7.18	7.07	41.03	40.99	263–264
3	0	2	*o*-Cl-benzylmethylamino	.....	...	$C_{17}H_{25}ClN_2O_2$	...	...	CH_3I	4.60	4.59	41.74	40.45[b,c]	125
3	0	2	Morpholino[a]	178–188	0.05	$C_{19}H_{27}ClN_2O_3$	7.64	7.50	CH_3Br	5.03	5.23	28.75	28.09[b]	88
3	0	2	Pyrrolidino[a]	169–172	0.05	$C_{19}H_{27}ClN_2O_2$	7.99	7.62	CH_3Br	5.18	5.03	29.60	28.80[b]	82–84

[a] N-*o*-Chlorobenzylpiperidyl instead of N-methylpiperidyl. [b] Very hygroscopic. [c] Could not be recrystallized.

TABLE III



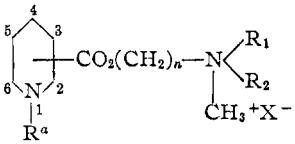
$N(R_1)(R_2)$	B.p. °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found	Salt	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	M.p., °C.
$N(CH_3)_2$	107–109	0.35	1.4824	$C_{13}H_{22}N_2$	11.76	11.57	CH_3Br	6.54	6.42	37.38	36.90	193
$N(C_2H_5)_2$	133–135	.50	1.4824	$C_{15}H_{26}N_2$	10.53	10.41	CH_3Br	6.14	6.02	35.09	34.98	204–205
Pyrrolidino	138–139	.55	1.4972	$C_{15}H_{24}N_2$	10.61	10.51	CH_3Br	6.17	6.04	35.24	36.19[a]	205
Morpholino	149–151	.25	1.5012	$C_{15}H_{24}N_2O_3$	10.00	9.85	CH_3Br	5.96	5.86	34.04	34.92[a]	208–210

[a] Accuracy of halogen assay, ±1%.

ethyl esters of nipecotic acid (nos. 1 and 8) were potent hypotensors while their position isomers (nos. 2 and 9) were inactive. Branching or cyclization of the aminoalkylene side chain (nos. 7, 14 and 15) as well as the introduction of a triple bond (compounds in Table III) abolished hypotensive activity. While an N-*o*-chlorobenzyl substituent on the side chain (nos. 11, 12 and 24) proved detrimental to hypotensive activity, its introduction into the piperidine ring yielded some of the most potent hypotensive agents in this series (nos. 25 and 26).

In conclusion we might state that the replacement of an aminoalkyl moiety by a piperidine ring in compounds of the type shown in formula I has yielded several derivatives which are superior to hexamethonium with respect to potency and duration of action. The ganglionic stimulating properties exhibited by the dimethobromide of β-dimeth-

TABLE IV

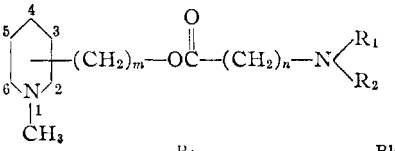


(X = Br, I)

No.	Ring position	n	$N(R_1)(R_2)$	Blood p. lowering, % I.v. dose 1.0 mg./kg.	Oral dose 10 mg./kg.	Duration,[f] min. I.v.	Oral
1	3	2	$N(CH_3)_2$	−34	−40	30	30
2	4	2	$N(CH_3)_2$	Inactive			
3	2	2	$N(CH_3)_2$	−41	−50	60	210
4	2	3	$N(CH_3)_2$	−51	−33	120	120
5	3	3	$N(CH_3)_2$	−25*	−11	40	85
6	3	2	$N(C_2H_5)_2$[c]	−12	..	15	
7	3	3[b]	$N(CH_3)_2$	Inactive			
8	3	2	Morpholino	−77	−70	270	300
9	2	2	Morpholino	Inactive			
10	2	3	Morpholino	−23	−15	35	90
11	3	2	*o*-Cl-benzyl methylamino	Inactive			
12	2	2	*o*-Cl-benzyl methylamino	Inactive			
13	3[d]	2	$N(CH_3)_2$	−13	..	5	
14	3		[e]	Inactive			
15	3		[g]	Inactive			
16	3	2	Pyrrolidino	−13	−24	30	115
Hexamethonium				−18	−30	65	75

i.v. dose = 2.0 mg./kg. [a] R = methyl, unless otherwise indicated. [b] 3-Dimethylamino-2-propyl ester. [c] R = ethyl [d] Ester of nicotinic acid. [e] $(CH_2)_nNR_1R_2$ = N-methyl-3-piperidyl. [f] The "duration" of action figures cannot be taken as absolute values. In some instances the b.p. had come back to normal, in other cases the experiment had to be discontinued, with the b.p. still at its lowest point, because additional anesthesia would have had to be administered. Usually, with the longer-acting (>60 minutes) hypotensives b.p. was still reduced substantially at the end of the experiment. [g] $(CH_2)_nNR_1R_2$ = N-methyl-3-piperidylmethyl.

TABLE V



No.	Ring position	m	n	$N(R_1)(R_2)$	Blood p. lowering, % I.v. dose 1.0 mg./kg.	Oral dose 10 mg./kg.	Duration, min. I.v.	Oral
17	2	1	2	Morpholino	−21	0	75	
18	3	0	2	Pyrrolidino	−39	−19	75	90
19	3	0	2	Morpholino	−26	− 8	50	70
20	3	0	1	$N(CH_3)_2$	Inactive	..	..	..
21	3	0	2	$N(CH_3)_2$	−40	−31	60	255
22	3	1	1	$N(CH_3)_2$	−10	..	6	
23	4	0	1	$N(CH_3)_2$	−17	0	15	..
24	3	0	2	*o*-Cl-benzylmethylamino	Inactive	Inactive		
25	3	0	2	Morpholino[a]	..	−39	..	240
26	3	0	2	Pyrrolidino[a]	..	−45	..	300
Hexamethonium					−18	−30	65	75

[a] N-*o*-Chlorobenzyl-3-piperidyl instead of N-methyl-3-piperidyl.

ylaminoethyl β-dimethylaminopropionate were not shared by the corresponding cyclic derivative (no. 1 in Table IV). This compound was actually a ganglionic blocking agent. Recently, a paper by Phillips[4] appeared which described the properties of some dialkylaminoalkyl esters of N-methylnipecotic and N-methylisonipecotic acid. Our data agree with those of Phillips concerning the weak ganglionic blocking activities of the nipecotate esters.

Contrary to the Phillips paper, however, is our finding that the isonipecotate ester (no. 2) is inactive as a hypotensive agent.

(4) A. P. Phillips, THIS JOURNAL, **78**, 1930 (1956).

Experimental

4-(N,N-Disubstituted Amino)-2-butyn-1-ols.—The preparation of the acetylenic aminoalcohols is illustrated by the following example:

4-Morpholino-2-butyn-1-ol.—Into a 500-cc. 3-necked round-bottom flask equipped with stirrer, reflux condenser ($CaCl_2$ tube), addition funnel and heating mantle is placed a solution of 87.0 g. of morpholine (1.0 mole) in 135 cc. of benzene. In a rapid dropwise fashion a solution of 41.8 g. of 4-chloro-2-butyn-1-ol[5] (0.40 mole) in 75 cc. of benzene is added; a vigorous exothermic reaction occurs accompanied by separation of morpholine hydrochloride. The mixture is heated at reflux for 3 hr. After cooling to room temperature, the crystalline morpholine hydrochloride is filtered off, washed well with benzene and the combined benzene

(5) W. J. Bailey and E. Fujiwara, *ibid.*, **77**, 165 (1955).

filtrates concentrated by vacuum distillation through a 14" column. The residue is subjected to vacuum distillation through a 5" column. The desired aminoalcohol distils as a viscous oil, b.p. 104–106° (0.1 mm.), yield 56.3 g., (90.8%), $n^{25}D$ 1.5087.

4-Morpholino-2-butynyl N-Methylpipecolinate.—Into a 500-cc. 3-necked round bottom flask equipped with stirrer, reflux condenser, Dean–Stark water separator ($CaCl_2$ tube) and heating mantle is placed a solution of 31.4 g. (0.20 mole) of methyl N-methylpipecolinate and 31.0 g. (0.20 mole) of 4-morpholino-2-butyn-1-ol in 325 cc. of *n*-heptane; 0.5 g. of NaOMe is added and the mixture refluxed. The methanol produced during the transesterification will separate from the heptane in the water separator. Two additional 0.3-g. portions of NaOMe may be required to complete the reaction. The reaction mixture is concentrated by slowly distilling off approximately 50% of the heptane. The residue is chilled, filtered and the balance of the heptane removed by vacuum distillation through a 14" column. The residue is subjected to vacuum distillation through a 3" column. The desired ester boils at 149–151° (0.25 mm.), yield 41.6 g. (74.3%), $n^{25}D$ 1.5012.

4-Morpholino-2-butynyl N-Methylpipecolinate Dimethobromide.—To a solution of 14.0 g. (0.05 mole) of 4-morpholino-2-butynyl-N-methylpipecolinate (0.05 mole) in 80 cc. of isopropyl alcohol is added 19.0 g. (0.20 mole) of methyl bromide. The mixture is refluxed under anhydrous conditions for 3 hr. and then chilled. The solid is filtered off and recrystallized from the minimum amount of hot ethanol, m.p. 208–210° dec., yield 20.8 g. (88.5%).

MILWAUKEE 1, WISCONSIN

[CONTRIBUTION FROM THE PHYSIOLOGY DEPARTMENT, TUFTS UNIVERSITY SCHOOL OF MEDICINE]

A Kinetic Study of the Ultraviolet Decomposition of Biochemical Derivatives of Nucleic Acid. I. Purines[1]

BY M. J. KLAND AND L. A. JOHNSON

RECEIVED APRIL 16, 1956

Irradiation of purines of biological interest with ultraviolet light under oxygen and nitrogen gives decomposition rates which are zero order between 8×10^{-5} and 5×10^{-4} *M* after an initial "induction" period which is a function of the extent and nature of purine substitution. Decomposition during the induction period follows a square law. For adenine (I) and hypoxanthine (II), decomposition is faster under oxygen, but the breakdown of guanine (III) and xanthine (IV) is inhibited by oxygen as compared with nitrogen.

Sensitivity to ultraviolet (uv.) radiation in purines and pyrimidines may be qualitatively correlated with the number[2] and position[3] of C=O groups in the molecule. In conjunction with a chemical examination of the complex mixtures obtained on irradiation of the biologically interesting purines adenine (I), hypoxanthine (II), guanine (III), xanthine (IV) and uric acid (V), more detailed studies of their ultraviolet decomposition rates in the presence of oxygen and the inert gas, nitrogen, have been carried out.

Experimental

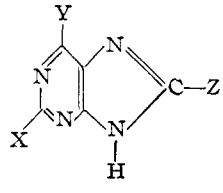
Source and Purity of Purines.—All compounds were recrystallized from distilled water, except guanine which is too insoluble. The recrystallized material was then chromatographed on Whatman No. 1 filter paper in a descending butanol–water–urea system,[4] and in butanol–water–ammonia (1%).[5] The presence of one spot at the end of 72 hours in the former system, and 120 hours in the latter was inter-

TABLE I

PHYSICAL DATA FOR PURINES IRRADIATED

Purine	Source	Purity (chrom.)	*p*H	Spectroscopic purity D^a	D^b	D^c	D^d
Adenine	Schwartz AD-5401	Pure	2.18	0.76	0.76		
			5.94	0.76			
Hypoxanthine	Schwartz HX-5202	Pure	2.02	1.37	1.43		
			5.95	1.35			
Xanthine	Schwartz XA-5201	Pure ($BuOH–NH_3–H_2O$)	2.13	0.59	0.58		
			5.79	0.59			
Guanine	GN-5402	.....	1.97	1.39	1.37	0.82	0.84
			5.98	1.39			
Uric acid[e]	Fisher, Lot. No. 543969	.....	1.92	0.97	1.0	2.71	2.7
			5.35	1.21			

[a] Ratio of optical densities at 250 and 260 mμ: D_{250}/D_{260}. [b] Literature[6,7] data at *p*H 2 for D_{250}/D_{260}. [c] Ratio of optical densities at 280 and 260 mμ: D_{280}/D_{260}. [d] Literature[6,7] data at *p*H 2 for D_{280}/D_{260}. [e] Uric aid data were obtained from ref. 7 only.



I, Adenine (Y = NH_2; X = Z = H)
II, Hypoxanthine (Y = OH; X = Z = H)
III, Guanine (X = NH_2; Y = OH; Z = H)
IV, Xanthine (X = Y = OH; Z = H)
V, Uric acid (X = Y = Z = OH)

(1) This work was done under the terms of Contract No. AT(30-1)-911 of the Physiology Dept., Tufts University School of Medicine, with the Atomic Energy Commission.

(2) J. R. Loofbourow and M. M. Stimson, *J. Chem. Soc.*, 844 (1940).

(3) A. Canzanelli, R. Guild and D. Rapport, *Am. J. Physiol.*, **167**, No. 2, 364 (1951).

(4) Butanol saturated with 10% aq. urea.

(5) Butanol, saturated with water, and equilibrated with concd. aq. ammonia (99 parts *BuOH*:1 part NH_4OH).

(6) E. A. Johnson (unpublished) in Chargaff and Davidson, "The Nucleic Acids," Vol. I, Academic Press, Inc., New York, N. Y., 1955, p. 502.

(7) E. Volkin and W. E. Cohn, "Methods of Biochemical Analysis," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1954, p. 304.