[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. VIII. Azabicyclo[3.2.1] octane Derivatives[1]

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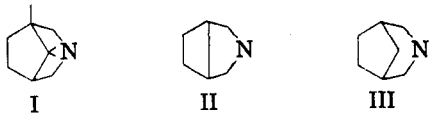
A series of *N*-dialkylaminoalkyl-3-azabicyclo[3.2.1]octane-2,4-diones have been prepared employing *cis*-1,3-cyclopentane dicarboxylic anhydride, obtained by permanganate oxidation of norbornylene, and appropriate dialkylaminoalkylamines. These diones were smoothly reduced to the corresponding *N*-dialkylaminoalkyl-3-azabicyclo[3.2.1]octanes by means of lithium aluminum hydride in ether solution. Monohydrochlorides and monomethiodides were prepared from the imides and dihydrochlorides and dimethiodides from the bases. All simple acid addition and quaternary salts were screened for hypotensive activity in dogs. The bis-quaternary salts possessed a good hypotensive action and a favorable therapeutic index.

In our studies of the preparation of fused ring nitrogen heterocycles, and their use as one or both of the bridgehead groups in symmetrical and unsymmetrical bis-quaternary salts, we have recently reported the synthesis and hypotensive properties of compounds of these types containing the 3-aza-1,8,8,-trimethylbicyclo[3.2.1]octane (camphidine) nucleus.[4] Since these compounds proved to be very potent hypotensive agents at low dosage levels either by oral or parenteral administration,[5] we decided to vary the size of the fused ring system and bridging within the rings and study such variations in relation to physiological activity. To this end we have prepared and evaluated series of compounds of this type in which the 3-azabicyclo-[3.2.0]heptane nucleus, II, was thus employed.[6]

The present communication deals with the synthesis and evaluation of series of compounds derived from the 3-azabicyclo[3.2.1]octane nucleus, III. It will be noted from structures I and III that this series is similar to the camphidine series, I, except that the methyl substituents at positions 1 and 8 have been removed. On comparison with the camphidine series, I, the present series, III, might



I II III

be considered as derived from norapocamphidine. In the azabicycloheptane series, II, both the methyl substituents and the central bridging carbon atom have been removed.

The desired bases in other series previously studied[4-8] were readily accessible by a two-step process from the dicarboxylic acid anhydride and the appropriate primary amine. The key intermediate in the present series was likewise the dicarboxylic acid anhydride. The anhydride of *cis*-1,3-cyclopentane dicarboxylic acid was obtained by the oxidation of norbornylene by means of sodium permanganate according to the procedure of Birch *et al.*[9] and treatment of the resultant dicarboxylic acid with acetyl chloride and acetic anhydride.

This anhydride was reacted with appropriate dialkylaminoalkylamines to yield the corresponding amic acids. Reaction of the amine and anhydride in this case proceeded less readily than in previous series,[4,6] including that derived from camphoric anhydride. It was necessary to apply heat to the reaction mixture to obtain a clear melt of anhydride and amine. The resultant amic acids were cyclized to the imides by heating at 170–180° for several hours and isolated from the reaction flask by vacuum distillation. Several imides thus prepared are listed in Table I and their corresponding monohydrochlorides and monomethiodides in Table II.

Reduction of the diones (imides) with lithium aluminum hydride in ether solution proceeded smoothly to give the expected bicyclic bases in good yield. The bases were also conveniently isolated by vacuum distillation. Representative bases are listed in Table III and their dihydrochlorides and bismethiodides in Table IV. The dihydrochlorides were readily obtained in the usual manner; but in order to obtain the bismethiodides it was necessary to heat the base with methyl iodide in methanol at 100° in a bomb tube for several hours. Thus, the reaction of the bases derived from norapocamphoric anhydride (cyclopentane-1,3-dicarboxylic anhydride) was similar to that of those derived from camphoric anhydride in the relative difficulty of bis-quaternization.

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TABLE I

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.1]OCTANE-2,4-DIONES

Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
Dimethylaminoethyl	$C_{11}H_{18}N_2O_2$	110–113	0.5	62.83	63.07	8.63	8.53	13.32	13.40	1.4985
Dimethylaminopropyl	$C_{12}H_{20}N_2O_2$	130–135	0.5	64.25	64.43	8.99	9.00	12.49	12.71	1.4968
Diethylaminoethyl	$C_{13}H_{22}N_2O_2$	116–119	0.5	65.51	65.66	9.31	9.20	11.76	11.53	1.4940
Diethylaminopropyl	$C_{14}H_{24}N_2O_2$	138–142	0.6	66.63	66.78	9.59	9.70	11.10	10.82	1.4968
Morpholinopropyl	$C_{14}H_{22}N_2O_3$	145–150	0.4	63.13	63.07	8.33	8.43	10.52	10.40	...

TABLE II

DERIVATIVES OF COMPOUNDS IN TABLE I

Hydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Methiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
$C_{11}H_{19}ClN_2O_2$	188–189	14.37	14.53	$C_{12}H_{21}IN_2O_2$	236–237	36.03	36.08
$C_{12}H_{21}ClN_2O_2$	184–185	13.60	13.83	$C_{13}H_{23}IN_2O_2$	225–226	34.65	34.40
$C_{13}H_{23}ClN_2O_2$	116–117	12.90	13.04	$C_{14}H_{25}IN_2O_2$	165–166	33.37	33.37
$C_{14}H_{25}ClN_2O_2$	141–142	12.28	12.49	$C_{15}H_{27}IN_2O_2$	179–180	32.19	32.40
$C_{14}H_{23}ClN_2O_3$	200–201	11.71	11.63	$C_{15}H_{25}IN_2O_3$	211–213	31.08	31.02

TABLE III

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.1]OCTANES

Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
Dimethylaminoethyl	$C_{11}H_{22}N_2$	69–72	3.5	72.47	72.61	12.16	11.85	15.37	15.30	1.4792
Dimethylaminopropyl	$C_{12}H_{24}N_2$	60	0.3	73.41	73.56	12.32	12.14	14.27	14.30	1.4772
Diethylaminoethyl	$C_{13}H_{26}N_2$	91–94	6.0	74.22	74.19	12.46	12.37	13.32	12.89	1.4782
Diethylaminopropyl	$C_{14}H_{28}N_2$	68	0.3	74.94	75.12	12.58	12.73	12.48	12.25	1.4784
Morpholinopropyl	$C_{14}H_{26}N_2O$	78–82	0.04	70.54	70.59	10.99	11.14	11.75	11.85	1.4976

TABLE IV

DERIVATIVES OF COMPOUNDS IN TABLE III

Dihydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Dimethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
$C_{11}H_{24}Cl_2N_2$	295–297	27.78	27.58	$C_{13}H_{28}I_2N_2$	235–237	54.45	54.85
$C_{12}H_{26}Cl_2N_2$	280–282	26.33	26.53	$C_{14}H_{30}I_2N_2$	270–272	52.85	52.86
$C_{13}H_{28}Cl_2N_2$	242–244	25.03	25.03	$C_{15}H_{32}I_2N_2$	222–223	51.36	51.44
$C_{14}H_{30}Cl_2N_2$	227–228	23.85	24.14	$C_{16}H_{34}I_2N_2$	235–237	49.94	49.89
$C_{14}H_{28}Cl_2N_2O$	299–301	22.78	22.72	$C_{16}H_{32}I_2N_2O$	251–252	48.60	48.45

The compounds prepared in the present series were screened for hypotensive activity in dogs by techniques previously outlined.[4,6] The imides, as their monohydrochlorides or monomethiodides, and the bases as their dihydrochlorides were inactive. The bismethonium salts of the bases produced a good hypotensive response and possessed a favorable therapeutic index. The dimethiodide of the dimethylaminopropyl base had an LD_{50} of 400 mg./-kg. on intraperitoneal administration to rats.

EXPERIMENTAL

The following examples will illustrate the general synthetic procedures employed on this series.

N-Dimethylaminopropyl-3-azabicyclo[3.2.1]octane-2,4-dione. Into a 50 ml. round bottom flask was placed 15 g. (0.107 mole) of powdered cyclopentane-1,3-dicarboxylic anhydride. Dimethylaminopropylamine, 11.5 g. (0.113 mole) was added in one portion. The reaction mixture was heated gently until a clear melt was obtained and then at 170–180° in an oil bath for 2 hr. The reaction mixture was fractionated *in vacuo* to yield 14.8 g., 62%, of an oil with b.p. 130–135°/0.5 mm., n_D^{20} 1.4968.

The *imide hydrochloride* was readily obtained in isopropyl alcohol and precipitated with ether, m.p. 172–175°. Recrystallization from isopropyl alcohol-ether raised the m.p. to 184–185°.

The *imide methiodide* was prepared in isopropyl alcohol and precipitated with ether. Recrystallization was from isopropyl alcohol-ether, m.p. 225–226°.

N-Dimethylaminopropyl-3-azabicyclo[3.2.1]octane. Into a 1-liter, 3-necked, reaction flask fitted with stirrer, dropping

funnel, and reflux condenser, protected from moisture with a soda lime tube, were placed 8 g. of lithium aluminum hydride and 500 ml. of anhydrous ether. When solution had been effected a solution of 14.8 g. (0.066 mole) of *N*-dimethylaminopropyl-3-azabicyclo[3.2.1]octane-2,4-dione in 200 ml. of anhydrous ether was added over a period of 10 min. The reaction mixture was stirred for 3 hr. and then decomposed by slow addition of water. A slight excess of water was added, the mixture stirred for 0.5 hr., and inorganic solids filtered off. The solid cake was well washed with ether. The ethereal solutions were combined and dried over sodium sulfate, the ether stripped off, and the resultant oil distilled *in vacuo* to yield 9.6 g., 74%, of base boiling at 60°/0.3 mm., n_D^{20} 1.4772. The *dihydrochloride*, prepared in the usual manner by treating an isopropyl alcohol solution with ethanolic-HCl, melted after recrystallization from methanol-ether at 280–282°. The *dimethiodide* was not formed by refluxing the base with excess methyl iodide in methanol. The following procedure was employed. Into a bomb tube were placed 4 g. of the base, 20 ml. of absolute methanol, and 10 ml. of methyl iodide. The tube was sealed and heated at 100° for 4 hr. On cooling much crystalline material separated. The tube was opened and the crystalline residue dissolved in boiling methanol, filtered, and refrigerated. Most of the bis-quaternary salt precipitated on cooling. The remainder was precipitated with ether. After recrystallization from methanol-ether it melted at 270–272° dec.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF A. H. ROBINS COMPANY, INC.]

Preparation of 4-Amino-1-butanols and Some Derivatives of Pharmacological Interest

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The 4-alkylamino and 4-dialkylamino-1-butanols are prepared in good yields by lithium aluminum hydride reduction of the reaction product of equimolar amounts of butyrolactone and a primary or secondary amine. The use of two moles of amine results in the formation of *N,N'*-symmetrically substituted putrescines. The 3-aminopropanols are prepared in a similar manner by the substitution of propiolactone for butyrolactone. The 3,4,5-trimethoxybenzoates, the diphenylacetates, and the benzhydryl ethers of several of the aminobutanols and of *N*-3-hydroxypropylpiperidine and their quaternary salts have been prepared and their pharmacological activity examined.

In view of the fact that the reserpine structure contains a hydroxyl group esterified with 3,4,5-trimethoxybenzoic acid separated from a tertiary amino group by four carbon atoms it seemed of interest to examine several derivatives of the 4-dialkylamino-1-butanols for pharmacological activity. A similarly inspired investigation[1] has recently led to the synthesis of aminoethyl-, aminopropyl-, and aminomethylcyclohexyl-3,4,5-trimethoxybenzoates. Although little interest has been directed toward the 4-amino-1-butanol system some derivatives have been reported to possess pharmacological activity. For example, the diphenylacetate of 4-morpholinebutanol[2] has been reported to be 60% as effective as papaverine in its antispasmodic action on the isolated guinea pig ileum. In addition, it has been reported that tests in laboratory animals indicated the *p*-aminobenzoate of 4-diethylamino-1-butanol[3] to be a more effective local anesthetic than cocaine.

The present work is concerned with the synthesis of the 3,4,5-trimethoxybenzoate and diphenylacetate esters as well as the benzhydryl, and *p*-chlorobenzhydryl ethers of some of the 4-dialkylamino-1-butanols. The detailed pharmacology of the compounds will be the subject of separate communications.[4]

The *N*-substituted 4-amino-1-butanols have generally been prepared by (1) the alkylation of amines with 4-halo-1-butanol[2,5] or its esters[6] and (2) by the lithium aluminum hydride reduction of *N,N*-dialkylsuccinamates[7] or succinamic acids.[8] Catalytic hydrogenation of β-carbethoxypropionylpiperidine to 4-piperidinobutane-1-ol has also been successful.[9]

The disadvantages of the alkylation method are obvious since mixtures are usually obtained. By an adaptation of the reduction method it has been found that the 4-dialkylamino-1-butanols are easily prepared in yields of the order of 60% from the readily available starting materials: butyrolactone,

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