N-(3-Chloro-4-methylphenyl)glycinamide. A mixture of 3.6 g. (0.02 mole) of *N*-(3-chloro-4-methylphenyl)glycinonitrile and 60 ml. of a 1% aqueous solution of sodium hydroxide was heated at 94–95° for several minutes under vigorous stirring until ammonia began to be generated as detected by means of litmus paper. Heating was continued for an additional 20 min. The product separated from the cooled reaction mixture was contaminated with the unchanged nitrile. Repeated extraction with 20 ml. of hot water gave 2.6 g. (66%) of white needles melting at 142–145° (decomposition). Two recrystallizations from aqueous alcohol afforded a pure sample, m.p. 152–153° (decomposition). From the filtrate *N*-(3-chloro-4-methylphenyl)glycine was precipitated in the usual manner, yield 0.8 g. (20%).

The diethylamine salts of glycines were prepared by cautious addition of a little excess of the base to a solution of the purified acid in a small amount of alcohol. Products of high purity were obtained in one step. For analysis, they were recrystallized from a mixture of alcohol and diethylamine (1:1).

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

Hypotensive Agents. VII.[1] Azabicyclo[3.2.0]heptane Derivatives[2]

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Series of *N*-alkyl and *N*-dialkylaminoalkyl-3-azabicyclo[3.2.0]heptane-2,4-dione have been prepared from the reaction of the appropriate primary amines and *cis*-1,2-cyclobutane dicarboxylic anhydride and cyclization of the resulting amic acids. The *N*-alkyl and *N*-dialkylaminoalkyl imides thus obtained were reduced to the corresponding *N*-alkyl and *N*-dialkylaminoalkyl-3-azabicyclo[3.2.0]heptanes with lithium aluminum hydride. These bases were characterized as hydrochlorides, mono- and bis-methiodides and picrates. The bis-quaternary salts derived from the 3-azabicyclo[3.2.0]heptane nucleus with a dialkylaminoalkyl side chain possessed hypotensive activity in cannulated dogs. The most favorable structure was one in which the number of methylene carbon atoms between the onium centers was 2 or 3 and the introduced quaternary group was a short chain alkyl group such as methyl or ethyl.

In a study of optimum ganglionic blockage in a series of *alpha, omega* symmetrically substituted bis-trimethylammonium compounds, Paton and Zaimis[5] have shown that for this type of compound the most desirable structure is one that contains 5 to 6 methylene carbon atoms between the positive centers. That this is not necessarily the case when the *alpha, omega* symmetrically substituted polymethylene chain bears bis-quaternary groups, part of which consists of a heterocyclic ring attached at the secondary amine ring nitrogen, has been shown by a comparison of several ring variations of the basic isoindole nucleus.[6] In the case of unsymmetrical bis-quaternary salts containing a large group at one of the quaternary centers and a trimethylammonium group on the other, it has turned out in most cases that a chain of 2 or 3 methylene carbon atoms between the nitrogen atoms gives the most favorable configuration when judged by the criteria of therapeutic index, minimum toxicity, and blood pressure lowering.

In continuation of our work in the synthesis of bis-quaternary salts containing a heterocyclic amine as one of the ammonium centers we have synthesized a series of compounds in which the azabicyclo[3.2.0] heptane nucleus is thus employed. The key starting material in our present investigations was *cis*-1,2-cyclobutane dicarboxylic anhydride. This anhydride was found to be readily accessible through the procedure of Buckman *et al.*[7] The bases prepared in these studise were obtained through the reaction of primary alkyl or dialkylaminoalkyl amines with the anhydride and proceeded through the amic acid, I, and imide, II, to the bases, III, as shown in Figure 1. The only example of any compound of this type previously re-

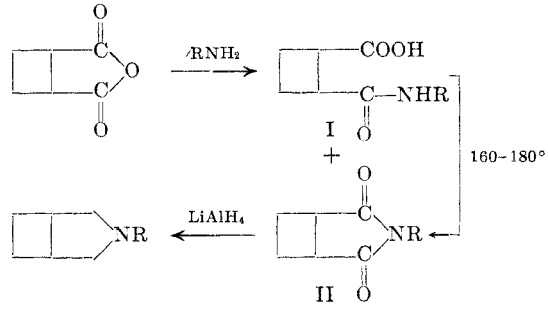

FIG. 1

(1) Hypotensive Agents. VI, L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 185 (1957).

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(5) W. D. M. Paton and E. J. Zaimis *Brit. J. Pharmacol.* **4**, 381 (1949).

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TABLE I

N-ALKYL-3-AZABICYCLO[3.2.0]HEPTANE-2,4-DIONES

N-Substitution	Formula	B.p., °C.	Mm.	n_D^{20}	Analysis					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Methyl	$C_7H_9NO_2$	123–127	14	47.5–48.5[a]	60.42	60.63	6.52	6.75	10.06	9.80
Ethyl	$C_8H_{11}NO_2$	82–84	0.7	46–47[a]	62.73	62.62	7.24	7.23	9.15	9.11
n-Propyl	$C_9H_{13}NO_2$	72–74	0.3	31–31.5[a]	64.65	64.59	7.84	7.75	8.38	8.68
n-Butyl	$C_{10}H_{15}NO_2$	86–92	0.3	1.4878	66.27	66.32	8.34	8.07	7.73	8.02
n-Amyl	$C_{11}H_{17}NO_2$	87–92	0.3	1.4860	67.66	67.85	8.78	8.68	7.17	7.12
n-Hexyl	$C_{12}H_{19}NO_2$	102–108	0.3	1.4844	68.86	68.81	9.15	9.15	6.69	6.79
n-Heptyl	$C_{13}H_{21}NO_2$	100–105	0.1	1.4825	69.92	70.06	9.48	9.65	6.27	6.53
n-Octyl	$C_{14}H_{23}NO_2$	110–113	0.1	1.4814	70.85	70.98	9.77	9.93	5.90	6.10
n-Nonyl	$C_{15}H_{25}NO_2$	118–122	0.2	1.4805	71.67	71.50	10.03	9.89	5.57	5.51
n-Decyl	$C_{16}H_{27}NO_2$	135–139	0.3	1.4807	72.41	72.30	10.25	10.13	5.28	5.14
n-Hexadecyl	$C_{22}H_{39}NO_2$	160–165	0.04	53–54[a]	75.59	75.44	11.25	11.08	4.01	4.18

[a] Melting point.

TABLE II

N-ALKYL-3-AZABICYCLO[3.2.0]HEPTANES

N-Substituent	Formula	B.p., °C.	Mm.	n_D^{20}	Analysis					
					Carbon		Hydrogen		Nitrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1. Methyl	$C_7H_{13}N$	123–133	760	1.4583	75.61	75.76	11.79	11.69	12.60	12.58
2. Butyl	$C_{10}H_{19}N$	112–115	75	1.4599	78.36	78.38	12.50	12.54	9.14	9.39
3. Hexyl	$C_{12}H_{23}N$	100–105	15	1.4672	79.49	79.70	12.78	12.74	7.73	7.88
4. Decyl	$C_{16}H_{31}N$	117–125	2	1.4648	80.94	80.94	13.16	13.10	5.90	6.15

DERIVATIVES OF ABOVE BASES

	Hydrochloride				Methiodide			
	Formula	M.p., °C.	Analysis Ionic Chloride		Formula	M.p., °C.	Analysis Ionic Iodide	
			Calcd.	Found			Calcd.	Found
1.	$C_7H_{14}ClN$	167–168	24.01	24.19	$C_8H_{16}IN$	197–198	50.14	50.20
2.	$C_{10}H_{20}ClN$	208–209	18.69	18.85	$C_{11}H_{22}IN$	189–190	42.99	43.04
3.	$C_{12}H_{24}ClN$	170–171.5	16.28	16.31	$C_{13}H_{26}IN$	101–102	39.26	39.39
4.	$C_{16}H_{32}ClN$	161–162	12.95	13.10	$C_{17}H_{34}IN$	146–147	33.45	33.63

1. Picrate, m.p. 178–179°: Calcd. for $C_{13}H_{16}N_4O_7$: N, 16.47. Found: N, 16.43.
2. Picrate, m.p. 102–103°: Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.66. Found: N, 14.83.
3. Picrate, m.p. 62–63.5°: Calcd. for $C_{18}H_{26}N_4O_7$: N, 13.65. Found: N, 13.66.
4. Picrate, oil.

ported in the literature is the *N*-phenyl imide of cyclobutane dicarboxylic acid which was prepared by Perkin[8] from aniline and the anhydride.

By reaction of primary alkyl amines with *cis*-1,2-cyclobutane dicarboxylic anhydride we have prepared the corresponding imides from methyl through decyl. The reaction was carried out in all cases in the flask from which the imide was to be distilled by reacting the anhydride with a slight excess of the amine. The mixture of cyclobutane amic acid and imide obtained in all cases, from the exothermic reaction on mixing, was then heated at 160–180° for 2 hr. to complete cyclization of all amic acid to the imide. The *N*-alkyl imides thus obtained, Table I, were isolated by distillation *in vacuo* in a good state of purity and in yields greater than 80% when prepared in quantities of 25 grams or more.

The reduction of representative members of this series of imides by means of lithium aluminum hydride in ether solution proceeded smoothly to yield the corresponding *N*-alkyl-3-azabicyclo[3.2.0] heptane bases in yields of 80% or better when prepared in quantities of 25 grams or more. These bases are all typical tertiary amines and were readily characterized as methiodides, hydrochlorides, and picrates. The methyl, butyl, hexyl, and decyl members of this series, their derivatives, and pertinent characteristics are listed in Table II.

Following the study of the behavior of simple alkyl amines we next employed the dialkylaminoalkylamines and similarly obtained the imides in straightforward manner and in yields of 70% or better on runs of 25 grams or more. Some of the dialkylaminoalkyl imides thus obtained are listed

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TABLE III

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.0]HEPTANE-2,4-DIONES

N-Substituent	Formula	B.p., °C.	Mm.	n_D^{20}	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1. Dimethylaminoethyl	$C_{10}H_{16}N_2O_2$	86–94	0.08	1.4938	61.20	61.32	8.22	8.24	14.28	14.32
2. Diethylaminoethyl	$C_{12}H_{20}N_2O_2$	93–100	0.2	1.4910	64.25	64.44	8.99	8.83	12.49	12.60
3. Dimethylaminopropyl	$C_{11}H_{18}N_2O_2$	87–97	0.2	1.4942	62.83	62.75	8.63	8.71	13.32	13.22
4. Diethylaminopropyl	$C_{13}H_{22}N_2O_2$	100–103	0.1	1.4918	65.51	65.63	9.31	9.21	11.76	12.01
5. Morpholinopropyl	$C_{13}H_{20}N_2O_3$	150–155	0.3	1.5130	61.88	61.97	7.99	7.84	11.10	11.32

DERIVATIVES OF ABOVE IMIDES

Monohydrochloride: Formula	M.p., °C.	Analysis Ionic Chloride: Calcd.	Found	Monomethiodide: Formula	M.p., °C.	Analysis Ionic Iodide: Calcd.	Found
1. $C_{10}H_{17}ClN_2O_2$	204–205	15.24	15.23	$C_{11}H_{19}IN_2O_2$	259–260	37.53	37.31
2. $C_{12}H_{21}ClN_2O_2$	204–205	13.69	13.60	$C_{13}H_{23}IN_2O_2$	125–126	34.81	34.65
3. $C_{11}H_{19}ClN_2O_2$	238–239	14.37	14.51	$C_{12}H_{21}IN_2O_2$	258–259	36.03	36.10
4. $C_{13}H_{23}ClN_2O_2$	148–149	12.90	13.10	$C_{14}H_{25}IN_2O_2$	184–184.5	33.37	33.43
5. $C_{13}H_{21}ClN_2O_3$	185–186	12.28	12.31	$C_{14}H_{23}IN_2O_3$	239.5–240	32.19	32.12

TABLE IV

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.2.0]HEPTANE

N-Substituent	Formula	B.P., °C.	Mm.	n_D^{20}	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1. Dimethylaminoethyl	$C_{10}H_{20}N_2$	38–44	0.3	1.4766	71.37	71.64	11.98	11.89	16.65	16.80
2. Diethylaminoethyl	$C_{12}H_{24}N_2$	64–65	0.8	1.4717	73.41	73.23	12.32	12.19	14.27	14.46
3. Dimethylaminopropyl	$C_{11}H_{22}N_2$	53–55	0.3	1.4702	72.47	72.63	12.16	12.27	15.37	15.66
4. Diethylaminopropyl	$C_{13}H_{26}N_2$	75–77	0.7	1.4696	74.22	74.38	12.46	12.35	13.32	13.55
5. Morpholinopropyl	$C_{13}H_{24}N_2O$	84–86	0.2	1.4935	69.59	69.78	10.78	10.63	12.49	12.41

DERIVATIVES OF ABOVE BASES

Dihydrochloride: Formula	M.P., °C.	Analysis Ionic Chloride: Calcd.	Found	Dimethiodide: Formula	M.P., °C.	Analysis Ionic Iodide: Calcd.	Found
1. $C_{10}H_{22}Cl_2N_2$	>305 dec.	29.40	29.30	$C_{12}H_{26}I_2N_2$	219–221	56.14	55.94
2. $C_{12}H_{26}Cl_2N_2$	215–216	26.34	26.10	$C_{16}H_{30}I_2N_2$	230–231	52.86	52.79
3. $C_{11}H_{24}Cl_2N_2$	264–265	27.78	27.53	$C_{13}H_{28}I_2N_2$	242–243	54.45	54.48
4. $C_{13}H_{28}Cl_2N_2$	191–192	25.03	25.20	$C_{16}H_{32}I_2N_2$	189–190	51.36	51.25
5. $C_{13}H_{26}Cl_2N_2O$	271–272	23.85	24.00	$C_{15}H_{30}I_2N_2O$	230–231	49.94	49.45

with derivatives and characteristics in Table III. Reduction of the dialkylaminoalkyl imides with lithium aluminum hydride proceeded in a manner analogous to that of the alkyl imides and yielded the expected bases, Table IV. These bases were also stable to vacuum distillation and were conveniently isolated in this way. Yields in this case were 70% or better on runs of 25 grams or more.

Both the simple alkyl bases and dialkylaminoalkyl bases quaternized readily to form mono- and bis-quaternary salts as was the case in the isoindole series.[9] In the azabicyclooctane series[1] derived from camphoric anhydride, some of the dialkylaminoalkyl bases, particularly those with short methylene side chain between the nitrogen atoms, had to be heated for protracted periods in a bomb tube with excess methyl iodide in methanol to effect bis-quaternization.

In both the *N*-alkyl and *N*-dialkylaminoalkyl series of imides no evidence of cleavage of the cyclobutane ring was observed on reduction of the diones to the bases. All compounds prepared in these series were stable and colorless.

The compounds were screened for hypotensive activity by intravenous injection into dogs prepared for continuous kymographic or intermittent recording of blood pressure by insertion of a cannula into the carotid artery of the animal while under Nembutal anesthesia. When screened by this method the information obtained may be summarized as follows. The dialkylaminoalkyl imide hydrochloride salts were inactive. The dihydrochlorides

of the bicyclic bases were inactive. The bis-quaternary salts of the bicyclic bases were active agents in lowering blood pressure.

The acute toxicities, determined by intraperitoneal injection into rats, showed that the *N*-dimethylaminopropyl bis-methonium salt, one of the most effective in hypotensive properties, had an LD_{50} greater than 1000 mg./kg. With increase in length of the methylene side chain the acute toxicities of the methonium or ethonium salts increased. On keeping a constant side chain length and increasing the length of the dialkyl substituents the toxicity was also increased.

In this series, as in previous series,[1,9] the most active and least toxic compounds were those in which the quaternizing group was methyl or ethyl and the methylene chain between the two positive centers consisted of 2 or 3 carbon atoms.

An interesting observation of the structural relationship of this series of compounds to barbituric acid prompted us to prepare the simple imide, Figure I, II, in which R was hydrogen for testing as a respiratory stimulant and possible anti-barbiturate. These investigations are continuing.

EXPERIMENTAL

The following examples will illustrate the general synthesizing procedures employed.

N-Butyl-3-azabicyclo[3.2.0]heptane-2,4-dione. To 51.2 g. (0.40 mole) of powdered *cis*-1,2-cyclobutane dicarboxylic anhydride, 32.0 g. (10% excess) of *n*-butyl amine was added with cooling and intermittent shaking. The flask was weighed and any *n*-butyl amine lost was replaced. The reaction mixture was then heated slowly in an oil bath to 160–180° and maintained at this temperature for 2 hr. The crude product was allowed to cool and fractionated *in vacuo*. The product distilled at 86–92°/0.3 mm. and weighed 58 g. (80%), n_D^{20} 1.4878.

N-Butyl-3-azabicyclo[3.2.0]heptane. A solution of 18 g. of lithium aluminum hydride was prepared in a 2-liter, 3-necked reaction flask fitted with a dropping funnel, reflux condenser, and Hershberg stirrer. A solution of 36 g. of *n*-butyl-3-azabicyclo[3.2.0]heptane-2,4-dione in 300 ml. of anhydrous ether was added at such a rate so as to just maintain gentle reflux. After all the imide had been added stirring was continued for an additional 2 hr. With vigorous stirring water was added to decompose the mixture, at a rate just sufficient to maintain gentle reflux. An excess of 10 ml. of water was added, stirring continued for an hour, the inorganic material filtered off with rapid suction, the filter cake well pressed, and washed with 3 portions of ether. After drying over sodium sulfate, the ether was stripped off and the residue distilled *in vacuo* to yield 26 g. (85%) of the base, b.p. 112–115°/75 mm., n_D^{20} 1.4599.

The *Hydrochloride* was readily obtained in isopropyl alcohol with alcoholic HCl and precipitated with dry ether. On recrystallization from dry ether-isopropyl alcohol or methanol it melted at 208–209°. The *methiodide* was prepared in isopropyl alcohol with a slight excess of methyl iodide and precipitated with dry ether. Recrystallization from isopropyl alcohol-ether gave a pure white material with m.p. 189–190°. Addition of a saturated solution of picric acid in methanol to the base dissolved in methanol, cooling, and addition of small amounts of water yielded the *picrate* with m.p. 102–103°.

N-Dialkylaminoalkyl-3-azabicyclo[3.2.0]heptane-2,4-diones. These were obtained in a manner analogous to that employed to prepare the *N*-alkyl derivatives. The hydrochlorides and monomethiodides were obtained without difficulty as outlined under the *N*-butyl derivative.

N-Dialkylaminoalkyl-3-azabicyclo[3.2.0]heptanes. These bases were obtained by reduction of the corresponding imides with lithium aluminum hydride in a manner analogous to that outlined for the *N*-butyl base. The hydrochlorides were obtained in the usual manner. The bis-quaternary salts were obtained by refluxing the base in methanol or acetone with a slight excess of alkyl iodide. They were recrystallized from either isopropyl alcohol-ether or methanol-ether.

3-Azabicyclo[3.2.0]heptane-2,4-dione. Thirty-two g. (0.25 mole) of *cis*-1,2-cyclobutane dicarboxylic anhydride were placed in a 125 ml. flask and 45 g. of a 10% aqueous solution ammonia was slowly added with shaking. The anhydride dissolved and the resulting solution was heated to boiling on a hot plate. When all the water had boiled off the temperature was slowly raised to 240°. On cooling the crude product solidified. It was crystallized from methanol, m.p. 130-131.5°. Recrystallization from water yielded a pure product with melting point of 134.5–135°.

Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.78; H, 5.47; N, 11.44.

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