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## DERIVATIVES OF 3-AZABICYCLOHEPTANE

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This invention relates to organic chemo-therapeutic agents and methods of their preparation, and more particularly relates to compounds of value in the treatment of cardio-vascular and other diseases. More specifically the invention relates to azabicycloheptane (3:2:0) bases, and the simple and mono- and bis-quaternary salts thereof.

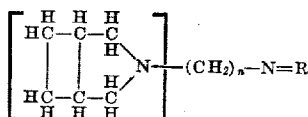
It is a basic objective of the present invention to provide novel organic compounds and methods for their preparation.

It is another object of the invention to provide novel, physiologically active compounds having chemotherapeutic or medicinal properties, particularly hypotensive activity.

It is a further object of the invention to provide novel compounds comprising N-dialkylaminoalkyl-3-azabicycloheptane (3:2:0) bases and the simple, mono- and bis-quaternary salts thereof, and methods of synthesizing these compounds.

These and other objects and the manner in which they are accomplished will become apparent to those conversant with the art from the following description of the general class of compounds and certain specific examples of particular members as well as general and specific methods for their synthesis.

Generally stated, the novel compounds discovered are obtained by forming the N-dialkylaminoalkyl imides from the anhydride of cis-1,2-cyclobutane dicarboxylic acid, the reduction of these imides by suitable means to obtain N-dialkylaminoalkyl-3-azabicycloheptane bases which may be converted by appropriate means into the simple, mono- and bis-quaternary salts.



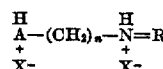
Formula 1

Formula 1 shows the general structural formula of compounds obtained by the methods hereafter more particularly described. This formula depicts the free bases, and for convenience in representation the azabicycloheptane nucleus (enclosed in parenthesis, Formula 1) will be designated by the letter A hereafter.

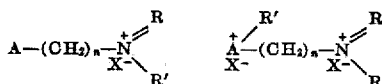
The simple salts of the bases illustrated by Formula 1 are shown by Formula 2 while the mono- and bis-quater-

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nary salts of these bases are shown by Formulae 3(a) and 3(b) respectively.



Formula 2



Formula 3(a)

Formula 3(b)

In these formulae A represents the azabicycloheptane nucleus and  $n$  a number from 1 to 6. R represents two alkyl groups with from 1 to 6 carbon atoms. R' represents an alkyl group with from 1 to 6 carbon atoms, an alkylene group containing 3 carbon atoms, or the structure (N=R) may represent a heterocyclic ring namely, morpholine, piperidine, pyrrolidine, piperazine or N-methyl piperazine. X<sup>-</sup> represents an anion namely, chloride, iodide, bromide, acetate or sulfate. The site of both simple and quaternary salt formation on the nucleus A is always the ring nitrogen at position 3. In the quaternary salts R' may be the same as or different from R in any of the formulae given.

The free bases, Formula 1, and their simple salts, Formula 2, possess varying degrees of antihistaminic and bronchodilatory activity. The quaternary salts of these bases, Formula 3(a), 3(b), and in particular the bis-quaternary salts, Formula 3(b), possess a marked hypotensive activity in mammals. For example the dimethiodide of Example I had a very favorable therapeutic ratio, at a total dosage level of 25 mg. I. M. there was a marked lowering of blood pressure and at the same time the toxicity has been determined to be 1250 mg./kg.

The following examples of specific compounds and methods will illustrate the manner in which the general synthesizing procedure may be applied to obtain particular members of the class of compounds discovered. It will be understood, however, that the following examples are merely illustrative and are not, nor are they intended to be, exhaustive of all the compounds embraced by the present invention.

### EXAMPLE I

#### N-dimethylaminoethyl-3-azabicycloheptane (3:2:0) simple salts and quaternary salts

*The free base.*—24.5 grams of the dimethylaminoethyl imide of 1,2-cis-cyclobutane dicarboxylic anhydride, dissolved in 200 ml. of anhydrous ether was added to a rapidly stirred solution of 15 g. of lithium aluminum hydride (LiAlH<sub>4</sub>) in 600 ml. of anhydrous ethyl ether. Addition was made so as to just maintain reflux. The mixture was stirred for 2 hours after all the imide solution had been added, allowed to stand overnight and then decomposed by the dropwise addition of water so that reflux was just maintained. When the evolution of hydrogen had ceased, a slight excess of water was added, the mixture stirred 1–3 hours, inorganic material filtered off and the residue washed several times with ether. The ethereal filtrate was dried over anhydrous sodium sulfate, the ether stripped off and the residue vacuum distilled to



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yield 17.7 grams of colorless liquid with an amine-like odor, B. P. 38–44° C./0.3 mm.:  $n_D^{20}=1.4766$ .

	Carbon	Hydrogen	Nitrogen
Calculated, Percent.....	71.37	11.98	16.65
Found, Percent.....	71.64	11.89	16.80

*The dihydrochloride.*—The base was dissolved in anhydrous isopropanol and an excess of an alcoholic solution of HCl gas was added. On cooling and adding anhydrous ethyl ether, the dihydrochloride separated as crystalline white material with a melting point over 305° C.

Ionic chloride: Calculated—29.40%; found—29.30%.

*The dimethiodide.*—When the base was mixed with an excess of methyl iodide in anhydrous methanol and allowed to stand, the crystalline material crystallizing or precipitated out on adding anhydrous ether was generally a mixture of the mono- and di-methiodides. In order to obtain the dimethiodide free of monomethiodide, it was necessary to reflux the base with an excess of methyl iodide in anhydrous methanol for 2–4 hours. The material that crystallized on cooling or on the addition of ether to the cooled reaction mixture melted at 215–219° C. On recrystallization from ethanol it melted at 219–221° C.

Ionic iodide: Calculated—56.14%; found—55.94%.

*The monomethiodide.*—This was obtained free from the dimethiodide by mixing molar equivalents of the free base and methyl iodide in methanol and letting the mixture stand a day at room temperature and adding ether to the cooled mixture. It had a melting point of 203–205° C. On recrystallization from isopropanol it crystallized in rectangular plates of melting point 204–206°.

Ionic iodide: Calculated—40.91%; found—41.16%.

#### EXAMPLE II

##### *N*-diethylaminoethyl-3-azabicycloheptane (3:2:0) simple and quaternary salts

*The free base.*—On reduction of the diethylaminoethyl imide with lithium aluminum hydride ( $\text{LiAlH}_4$ ) in a manner similar to that described under Example I, 26 grams of the imide yielded 20.2 grams of the title base of Example II, with B. P. 64–65°/0.8 mm.:  $n_D^{20}=1.4717$ .

	Carbon	Hydrogen	Nitrogen
Calculated, Percent.....	73.41	12.32	14.27
Found, Percent.....	73.23	12.19	14.46

*The dihydrochloride.*—Addition of an excess of a saturated solution of HCl in ethanol to the base dissolved in isopropanol, cooling and addition of ether produced the white crystalline dihydrochloride, M. P. 214–216° C. Recrystallization from isopropanol gave M. P. 215–216° C.

Ionic chloride: Calculated—26.34%; found—26.10%.

*The dimethiodide.*—The dimethiodide can be obtained directly by reacting the base with an excess of methyl iodide in acetone and allowing the mixture to stand 1 day. On refrigeration the dimethiodide separated in crystalline form, M. P. 230–233° C. decomposition. Recrystallization from absolute ethanol sharpened the M. P. to 230–231° C. decomposition. Decomposition may set in lower than the melting point if the material is heated very slowly.

Ionic iodide: Calculated—52.86%; found—52.79%.

#### EXAMPLE III

##### *N*-dimethylaminopropyl-3-azabicycloheptane (3:2:0) simple and quaternary salts

*The free base.*—Reduction of 28 grams of the appropriate imide with 15 g. of lithium aluminum hydride

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( $\text{LiAlH}_4$ ) as detailed under Example I yielded 22 grams of the title base, B. P. 53–55° C./0.3 mm.,  $n_D^{20}=1.4702$ .

	Carbon	Hydrogen	Nitrogen
Calculated, Percent.....	72.47	12.16	15.37
Found, Percent.....	72.63	12.27	15.66

*The dihydrochloride.*—Addition of excess alcoholic HCl to the base in isopropanol and precipitation with ether yielded the salt with M. P. 265–268° C. Recrystallization from isopropanol-ether gave M. P. 265° C.

Ionic chloride: Calculated—27.78%; found—27.53%.

*The dimethiodide.*—The dimethiodide formed readily with excess methyl iodide and the base in acetone at room temperature on standing 1 day. M. P. 235–238° C. Recrystallization from isopropanol-ether gave M. P. 242–243° C.

Ionic iodide: Calculated—54.45%; found—54.48%.

#### EXAMPLE IV

##### *N*-diethylaminopropyl-3-azabicycloheptane (3:2:0) salts and quaternary salts

*The free base.*—Reduction of the corresponding imide (14 grams) with lithium aluminum hydride ( $\text{LiAlH}_4$ ) (6 grams) as detailed in Example I yielded 11 grams of the title base, B. P. 75–77° C./0.7 mm.,  $n_D^{20}=1.4696$ .

	Carbon	Hydrogen	Nitrogen
Calculated, Percent.....	74.22	12.46	13.32
Found, Percent.....	74.38	12.35	13.55

*The dihydrochloride.*—This was formed analogous to Example III, M. P. 191–192° C., with no change on recrystallization from isopropanol-ether.

Ionic chloride: Calculated—25.03%; found—25.20%.

*The dimethiodide.*—This was also formed analogous to Example III, M. P. 185–187° C. Recrystallization from isopropanol-ether, M. P. 189–190° C.

Ionic iodide: Calculated—51.36%; found—51.25%.

#### EXAMPLE V

##### *N*-morpholinoethyl-3-azabicycloheptane (3:2:0) salts and quaternary salts

*The free base.*—15 grams of the imide reduced with 6 grams of lithium aluminum hydride ( $\text{LiAlH}_4$ ) as detailed under Example I, yielded 11 grams of the base, B. P. 84–86° C./0.2 mm.,  $n_D^{20}=1.4935$ .

	Carbon	Hydrogen	Nitrogen
Calculated, Percent.....	69.59	10.78	12.49
Found, Percent.....	69.78	10.63	12.41

*The dihydrochloride.*—This was formed analogous to Example III, M. P. 271–273° C., with no change on recrystallization.

Ionic chloride: Calculated—23.85%; found—24.00%.

*The dimethiodide.*—This was formed analogous to Example III, M. P. 223–230° C. decomposition. Recrystallization from ethanol, M. P. 230–231.5° C., decomposition.

Ionic iodide: Calculated—49.94%; found—50.06%.

From the foregoing description of a novel class of compounds, and the detailed preparation and characterization of exemplary members of the class, it will be understood that, on the basis of the discovery and knowledge disclosed herein, other specific compounds can be made and variations in the methods of synthesis resorted to. The appended table contains additional examples of bases prepared by the procedures detailed herein. Therefore, the specific compounds and methods disclosed herein are to be considered in all respects as illustrative and not restrictive, the scope of the discovery being indicated by



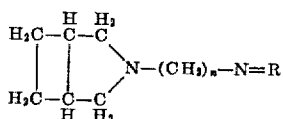
the appended claims rather than the foregoing descriptive detailed examples, and all specific compounds and variations and methods which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

# N-DIETHYLAMINOETHYL-3-AZABICYCLOHEPTANE (3:2:0)

N-substituent	B. P., °C.	mm.	Analysis, Percent					
			Carbon		Hydrogen		Nitrogen	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
diethylaminobutyl...	63-68	0.3	74.94	-----	12.58	-----	12.49	-----
diethylaminoamyl...	77-83	0.3	75.56	-----	12.68	-----	11.75	-----
diethylaminoethyl...	84-96	0.3	76.12	-----	12.78	-----	11.10	-----
dibutylaminoethyl...	84-96	0.1	76.12	-----	12.78	-----	11.10	-----
dibutylaminoethyl...	115-122	0.08	77.65	-----	13.07	-----	9.08	-----
morpholinoethyl...	72-76	0.3	68.53	-----	10.54	-----	13.32	-----
piperidinoethyl...	80-84	0.2	74.94	-----	11.61	-----	13.45	-----

We claim:

1. As a novel composition of matter, a compound selected from the group consisting of (1) compounds having the formula



where, in said formula,  $n$  is a number from 1 to 6,  $\text{R}$  is selected from the group consisting of two alkyl groups each alkyl group having 1 to 6 carbon atoms and radicals which form, together with the nitrogen atom to which they are attached, heterocyclic groups consisting of morpholino, piperidino and pyrrolidino and (2) acid addition salts and mono and di-quaternary salts of (1).

2. As a novel composition of matter, a dimethonium salt of N - dimethylaminoethyl - 3 - azabicycloheptane (3:2:0).

3. As a novel composition of matter, a dimethonium

salt of N - diethylaminoethyl - 3 - azabicycloheptane (3:2:0).

4. As a novel composition of matter, a dimethonium salt of N - dimethylaminopropyl - 3 - azabicycloheptane (3:2:0).

5. As a novel composition of matter, a dimethonium salt of N - diethylaminopropyl - 3 - azabicycloheptane (3:2:0).

6. As a novel composition of matter, a dimethonium salt of N - morpholinopropyl - 3 - azabicycloheptane (3:2:0).

7. As a novel composition of matter, N-dimethylaminoethyl-3-azabicycloheptane (3:2:0).

8. As a novel composition of matter, the dimethonium chloride of N-dimethylaminoethyl - 3 - azabicycloheptane (3:2:0).

9. As a novel composition of matter, N-dimethylaminopropyl-3-azabicycloheptane (3:2:0).

10. As a novel composition of matter, the dimethonium chloride of N-dimethylaminopropyl-3-azabicycloheptane (3:2:0).

11. As a novel composition of matter, the dimethonium chloride of N-diethylaminoethyl - 3 - azabicycloheptane (3:2:0).

No references cited.