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

Hypotensive Agents. IX. 3-Azabicyclo[3.3.1]nonane Derivatives[1]

LEONARD M. RICE[2] AND CHARLES H. GROGAN[3]

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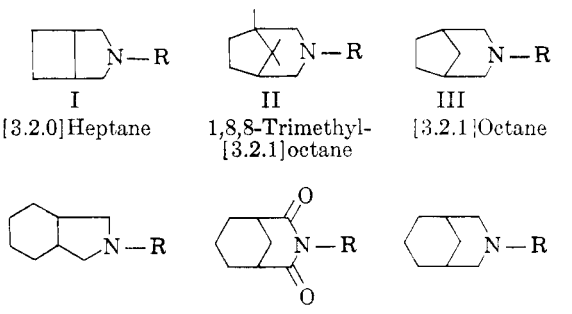
Series of 3-alkyl and 3-dialkylaminoalkyl-3-azabicyclo[3.3.1]nonane-2,4-diones have been prepared from *cis*-hexahydroisophthalic anhydride and the corresponding alkyl and dialkylaminoalkylamines. These imides have been reduced to the corresponding 3-alkyl and 3-dialkylaminoalkyl-3-azabicyclo[3.3.1]nonanes and hydrochloride and mono- and bis-quaternary salts prepared for screening as hypotensive agents. These compounds exhibited only a low degree of hypotensive activity or were inactive. When compared to the very active compounds encountered in the closely related isoindole, 2-azabicyclo-[4.3.0]nonane series, this was quite an unexpected result and illustrates again the difficulties and pitfalls frequently encountered in structural-physiological activity predictions and correlation. In this case just changing the bridging in the bicyclic ring from the [4.3.0] to the [3.3.1] structure resulted in marked reduction or almost complete loss of hypotensive activity.

In continuation of our investigations of various bicyclic nitrogen heterocycles for use as one or both of the bridgehead groups in the formation of *alpha, omega* symmetrical and unsymmetrical bis-ammonium salts for screening in our hypotensive chemotherapy program, we have prepared derivatives in which the 3-azabicyclo[3.3.1]nonane nucleus is thus employed. Previous studies of this type of chemical structure have been concerned with such derivatives containing the 3-azabicyclo[3.2.0]heptane nucleus[4] (I), the 3-azabicyclo[3.2.1]octane nucleus[5,6] (II and III), and several variations including ring substitution and bridged modifications, of the 2-azabicyclo[4.3.0]nonane nucleus(IV).[7,8] This is the basic isoindole nucleus.

In these series of unsymmetrical bis-ammonium salts, the most effective combination was found to be either the dimethylaminoethyl or dimethylaminopropyl side chain in which the quaternizing group was also methyl. Not only the size of the bicyclic nucleus as well as ring substituents thereon but also the shape was found to affect the degree and duration of the hypotensive response obtained. This is reflected in the variation in response obtained by substituting on the bicyclic nucleus or by keeping the same number of atoms in the nucleus and changing the position of the bridging in the ring. This important factor, in addition to ring size, has also been noted by Cavallito *et al.*[9] in their review of hypotensive activity versus structural relationship of a large number of unsymmetrical bis-ammonium salts. It has been noted by them and by us that compounds having the same number of atoms comprising the entire bicyclic nucleus, and the common property of producing a good hypotensive response, but having different ring bridging (shape), differed greatly in toxicity, therapeutic index, and effectiveness by oral and parenteral routes.



I
[3.2.0]Heptane

II
1,8,8-Trimethyl-[3.2.1]octane

III
[3.2.1]Octane

IV
[4.3.0]Nonane (Isoindole)

V
[3.3.1]Nonane-2,4-dione
R = H alkyl or dialkylaminoalkyl

VI
[3.3.1]Nonane
VIa, R = Alkyl
VIb, R = Di-alkylaminoalkyl

Unsymmetrical as well as symmetrical *alpha, omega* bis-ammonium salts containing the isoindole nucleus, IV, 2-azabicyclo[4.3.0]nonane, and the many modifications of it prepared and screened by us, in general possessed hypotensive properties as a nucleus type. However, the degree and duration of this effect, toxicity and therapeutic index, as well as the therapeutic value in humans, of these compounds varied quite widely with variations in ring substituents and additional bridging of the basic isoindole nucleus to form tricyclic rings with an additional oxygen[10] or methylene bridge.

Because of the broad general hypotensive activity encountered with many series of compounds containing this ring system, we were interested in varying the bridging in the compound to ascertain its effect on physiological activity. To this end we

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(2) Present address: The Celanese Corp. of America, Summit, N. J.

(3) Present address: National Institutes of Health, Bethesda 14, Md.

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(6) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).

(7) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

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TABLE I

3-DIALKYLAMINOALKYL-3-AZABICYCLO[3.3.1]NONANE-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}
1	Dimethylaminoethyl	$C_{12}H_{20}N_2O_2$	95–105	0.1	64.25	64.43	8.99	8.82	12.49	12.47	1.5030
2	Dimethylaminopropyl	$C_{13}H_{22}N_2O_2$	112–117[a]	0.07	65.51	65.55	9.31	9.11	11.76	12.06	1.5019
3	Diethylaminoethyl	$C_{14}H_{24}N_2O_2$	105–115	0.1	66.63	66.77	9.59	9.63	11.10	11.30	—
4	Diethylaminopropyl	$C_{15}H_{26}N_2O_2$	118–124	0.1	67.63	67.74	9.84	9.84	10.52	10.69	—

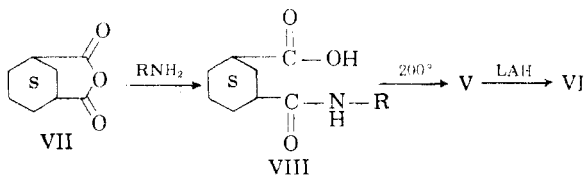
DERIVATIVES OF COMPOUNDS ABOVE

	Hydrochloride Formula	Hydrochloride M.P., °C.	Hydrochloride Chlorine, % Calcd.	Hydrochloride Chlorine, % Found	Methiodide Formula	Methiodide M.P., °C.	Methiodide Iodine, % Calcd.	Methiodide Iodine, % Found
1	$C_{12}H_{21}ClN_2O_2$	195–196	13.60	13.49	$C_{13}H_{23}IN_2O_2$	213–214	34.65	34.52
2	$C_{13}H_{23}ClN_2O_2$	183–184	12.90	13.14	$C_{14}H_{25}IN_2O_2$	224–225	33.37	33.65
3	$C_{14}H_{25}ClN_2O_2$	145–147	12.28	12.20	$C_{15}H_{27}IN_2O_2$	163–164	32.18	32.40
4	$C_{15}H_{27}ClN_2O_2$	118–119	11.71	11.83	$C_{16}H_{29}IN_2O_2$	114–116	31.08	30.95

[a] M.P., °C. 34–35. From ligroin.

have now prepared unsymmetrical bis-ammonium salts containing the 3-azabicyclo[3.3.1]nonane nucleus, VI, which contains the exact number of total atoms in the bicycle as the isoindoles, IV, but differs only in the bridging in the bicycle. The results of this study were quite unexpected since it was found that by simply changing the bridging from [4.3.0] to [3.3.1] in the azabicyclononane nucleus there resulted compounds that were either inactive or possessed a very low activity when administered either orally or parenterally. The toxicities of these compounds did not differ greatly from some of the corresponding members of the perhydroisoindoline series.

The synthesis of compounds containing the 3-azabicyclo[3.3.1]nonane nucleus was achieved by employing *cis*-hexahydroisophthalic anhydride as the key starting material. Hexahydroisophthalic acid was prepared by catalytic hydrogenation of dimethyl isophthalate followed by separation of the calcium salts of the *cis* and *trans* isomers according to the method of Skita *et al.*[11] The acid was converted to the anhydride by treatment with acetyl chloride. Hexahydroisophthalic anhydride, VII, was treated with various primary alkyl and dialkylaminoalkylamines to obtain the corresponding amic acids, VIII, which readily yielded the corresponding 3-azabicyclo[3.3.1]-2,4-diones (imides), V, on cyclization at 200° for 4 hr. All imides thus prepared were readily isolated as colorless oils by distillation *in vacuo*, with the exception of the imide in which R was hydrogen. Typical examples of the dialkylaminoalkyl imides and their hydrochloride and methonium salts are given in Table I.



These imides were all readily reduced by means of lithium aluminum hydride in ether solution to yield the corresponding bicyclic bases, VI, in good yields. These bases and their dihydrochloride and bis-methonium salts are listed in Table II. Conversion of the bases to their dihydrochlorides and monomethiodides occurred readily at room temperature. The monomethiodides are also listed in Table II. However, as in the case of the 3-azabicyclo[3.2.1]octanes, the introduction of the second methonium group could only be achieved with difficulty. It was necessary to heat the bases in a bomb tube at 100° in order to effect bisquaternization.

The hypotensive activity of these compounds was evaluated on dogs by both the cannulation technique and femoral artery puncture in the intact animal.[12] When the dialkylaminoalkyl hexahydroisophthalimides were employed as either the hydrochloride or methiodide, no activity was encountered. The dihydrochlorides of the 3-dialkylaminoalkyl-3-azabicyclo[3.3.1]nonanes were also inactive. The mono- and bis-quaternary methonium salts of these bases surprisingly were either inactive or showed only a low order of activity. Thus, by bringing about such a simple change in structure as that reported herein, changing the bridging from [4.3.0] to [3.3.1] in the azabicyclononane nucleus, while retaining identical N substituents, resulted in a change in hypotensive activity from very great and therapeutically useful in humans to practically inactive in the present series of compounds.

EXPERIMENTAL

3-Methyl-3-azabicyclo[3.3.1]nonane-2,4-dione. A total of 30.0 grams of a 25% aqueous solution of methylamine

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(12) W. E. O'Malley, G. Winkler, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc., Sci. Ed.*, 46, 346 (1957),

TABLE II

3-DIALKYLAMINOALKYL-3-AZABICYCLO[3.3.1]NONANES

	Substituent	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
1	Dimethylaminoethyl	$C_{12}H_{24}N_2$	59–62	0.3	73.41	73.56	12.32	12.24	14.27	14.20	1.4870
2	Dimethylaminopropyl	$C_{13}H_{26}N_2$	68–70	0.2	74.22	74.32	12.46	12.54	13.32	12.91	1.4843
3	Diethylaminoethyl	$C_{14}H_{28}N_2$	73–76	0.1	74.94	75.18	12.58	12.44	12.48	12.74	—
4	Diethylaminopropyl	$C_{15}H_{30}N_2$	75–78	0.1	75.56	75.80	12.68	12.86	11.76	11.93	—

DERIVATIVES OF COMPOUNDS ABOVE

	Dihydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Monomethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found	Dimethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
1	$C_{12}H_{26}Cl_2N_2$	275–276	26.33	26.17	$C_{13}H_{27}IN_2$	218–220	37.52	37.41	$C_{14}H_{30}I_2N_2$	239–240	52.86	52.95
2	$C_{13}H_{28}Cl_2N_2$	278–279	25.03	25.05	$C_{14}H_{29}IN_2$	213–214	36.02	36.20	$C_{15}H_{32}I_2N_2$	257–258	51.36	51.70
3	$C_{14}H_{30}Cl_2N_2$	197–198	23.85	23.56	$C_{15}H_{31}IN_2$	174–175	34.65	34.38	$C_{16}H_{34}I_2N_2$	221–222	49.89	49.94
4	$C_{15}H_{32}Cl_2N_2$	205–207	22.55	22.78	$C_{16}H_{33}IN_2$	133–134	33.37	33.43	$C_{17}H_{36}I_2N_2$	214–216	48.60	48.81

(excess) was added with cooling and stirring to 30.8 g. (0.2 mole) of *cis*-hexahydroisophthalic anhydride contained in a 250-ml. round-bottom flask. When the initial reaction had subsided, the solution was heated to boiling. After all water had boiled off the temperature was slowly raised to 240°. The product was distilled *in vacuo* at 82–86° at 0.5 mm., and melted at 59–60°, yield 18 g. (54%).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.88; H, 7.87; N, 8.58.

3-Butyl-3-azabicyclo[3.3.1]nonane-2,4-dione. The butyl homolog was prepared in essentially the same manner except that the reaction mixture was heated at 180° for several hours and then distilled *in vacuo*, b.p. 95–104° at 0.1 mm., m.p. 34–36°.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.57; H, 9.06; N, 6.90.

3-Azabicyclo[3.3.1]nonane-2,4-dione (*hexahydroisophthalimide*) was prepared as with the methyl analog except that concentrated aqueous ammonia was employed and the crude product recrystallized from petroleum ether or water-acetone. The product sublimed on heating to 80°.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.89; H, 7.19; N, 9.07.

3-Dimethylaminopropyl-3-azabicyclo[3.3.1]nonane-2,4-dione. A total of 31 g. (0.3 mole) of dimethylaminopropylamine was added in one lot to 46.2 g. (0.3 mole) of *cis*-hexahydroisophthalic anhydride contained in a 100-ml. round bottom flask. There was an immediate exothermic reaction and a homogeneous melt was obtained on stirring. After the initial reaction had subsided, the temperature was slowly raised to 180–200° and maintained for 4 hr. The product was distilled *in vacuo* to yield 43 g. (60%), b.p. 127–140° at 0.5 mm. Redistillation of the crude material yielded analytically pure material, 35 g. (49%), b.p. 112–117° at 0.07 mm., m.p. 34–35° from ligroin, n_D^{20} 1.5019.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.55; H, 9.11; N, 12.06.

The *hydrochloride* was formed in isopropyl alcohol with alcoholic-HCl and precipitated with dry ether, m.p. 183–184°.

The *methiodide* was readily formed in isopropyl alcohol at room temperature on treatment with excess methyl iodide, m.p. 224–225°.

3-Dimethylaminopropyl-3-azabicyclo[3.3.1]nonane. Lithium aluminum hydride, 16 g., was dissolved in 800 ml. of anhydrous ether in a two-liter, three-necked reaction flask equipped with dropping funnel, stirrer, and condenser, and protected from atmospheric moisture. A solution of 32 g. (0.13 mole) of 3-dimethylaminopropyl-3-azabicyclo[3.3.1]-nonane-2,4-dione in 400 ml. of anhydrous ether was dropped in just fast enough to maintain gentle reflux of the ether. The reaction mixture was stirred an additional hour and then decomposed by dropwise addition of water added so as to maintain reflux of the ether. A 10-ml. excess of water was added and the mixture stirred for one hour and filtered with rapid suction. The inorganic precipitate was washed with three portions of ether which were combined with the filtrate and dried over anhydrous sodium sulfate. The ether was stripped off and the residue distilled *in vacuo* to yield 23 g. (81%) of product boiling at 68–70° at 0.2 mm., n_D^{20} 1.4843. The *dihydrochloride* was prepared in the usual manner, m.p. 278–279°.

The *monomethiodide* was prepared by allowing the base to stand at room temperature overnight with slightly more than one equivalent of methyl iodide in absolute methanol. Precipitation with dry ether and recrystallization from methanol-ether gave a product with m.p. 213–214°. The *dimethiodide* was prepared by heating 8 ml. of methyl iodide, 20 ml. of methanol, and 4 ml. of the base in a bomb tube in a boiling water bath for 4 hrs. After cooling the product was precipitated by adding acetone and refrigeration. Recrystallization from either isopropyl alcohol or ethanol gave a product with m.p. 257–258°.

3-Methyl-3-azabicyclo[3.3.1]nonane. This compound was prepared in a manner analogous to that employed for the dimethylaminopropyl derivative. Employing 14 g. (0.084 mole) of 3-methyl-3-azabicyclo[3.3.1]nonane-2,4-dione there was obtained 9 g. (77%) of product, b.p. 85° at 38 mm. or 175° at 760 mm.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.67; H, 12.49; N, 10.20.

The *hydrochloride* was prepared in the usual way and recrystallized from isopropyl alcohol–ethyl acetate and melted at 211–213°.

Anal. Calcd. for $C_9H_{18}ClN$: Cl, 20.18. Found: Cl, 19.92.

The *methiodide* was prepared in refluxing acetone with an excess of methyl iodide and recrystallized from methanol–ethyl acetate, m.p. 234–235°.

Anal. Calcd. for $C_{10}H_{20}IN$: I, 45.14. Found: I, 45.07.

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