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

Hypotensive Agents. V.[1] Hydrogenated Bis-isoindole Quaternary Salts[2]

BY LEONARD M. RICE, CHARLES H. GROGAN AND E. EMMET REID

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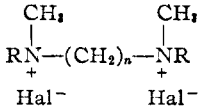
Seven series of bis-quaternary salts containing various isoindole ring systems have been prepared by reaction of the appropriate N-methylisoindoline base with α,ω-halogen disubstituted alkanes. When methylene diiodide or ethylene dibromide was used only one side of the molecule was quaternized. Many of these compounds are active hypotensive agents. The relatively large number of series studied permits some correlation between physiological response and structure to be drawn.

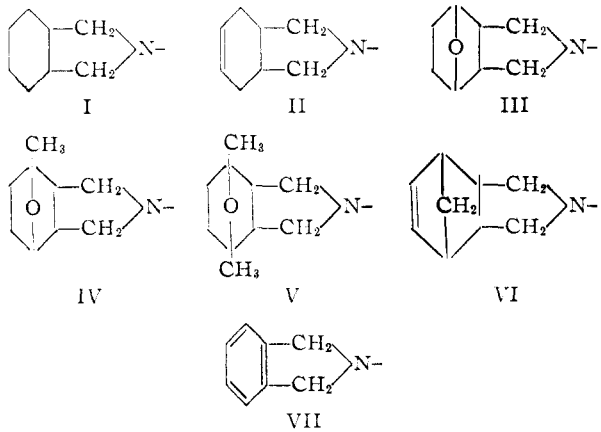
In a previous publication[1] it was shown that the isoindole nucleus is a very desirable ring system in the production of hypotensive agents. The use of such drugs as hexamethonium and decamethonium and the many papers on related species of α,ω-bis-quaternary compounds have stimulated us to report our researches in this field employing isoindole type ring systems. During our experiments on hydrogenated isoindole compounds we have prepared many N-alkylisoindoles in various states of hydrogenation[3] and here wish to report the N-methylisoindoline compounds and some derivatives.

By employing these N-methyl-*t*-amine bases we have prepared seven distinct series of α,ω-symmetrically substituted isoindole quaternary salts of the general formula



$n = 2$ to 10

In the above formula the ring systems, R, that were studied are shown in the figures below and will be designated by the corresponding Arabic number in all the tables which follow



I II III IV V VI VII

The starting points in our syntheses were the appropriate anhydrides which were either commercially available or were prepared by the way of the Diels–Alder reaction from substituted furans.[4] All the N-methylimides were made by the reaction of an aqueous 25% solution of methylamine on the appropriate anhydride followed by slowly raising the temperature to 240° where it was maintained for a short time. Following recrystallization from benzene the imides, which are listed in Table I,[5] were reduced with lithium aluminum hydride in ether solution to the corresponding N-methylisoindole bases in excellent yields.

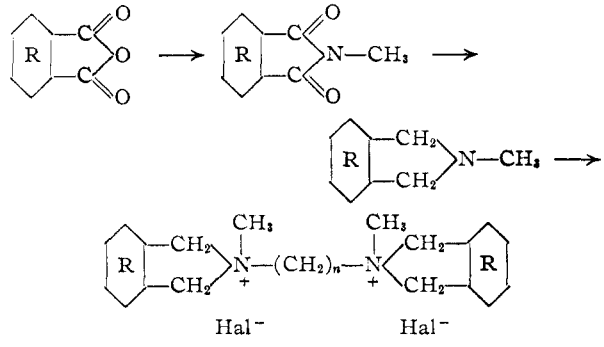
TABLE I

N-METHYLENDIOXYPERHYDROPHTHALIMIDES

Ring	Formula	M.p., °C.	Analyses, % Nitrogen Calcd.	Found
3	$C_9H_{11}NO_3$	135	7.73	7.93
4	$C_{10}H_{13}NO_3$	108	7.17	7.41
5	$C_{11}H_{15}NO_3$	128.5	6.69	6.66

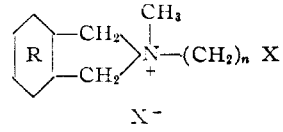
These new tertiary bases and their constants are listed in Table II and their picrates and methiodides in Table III. The only base previously reported is N-methylisoindoline by von Braun and Kohler[6] who prepared it by the action of methylamine on *o*-xylylene bromide.

Formation of the bis-quaternary salts was accomplished by the reaction of the N-methylisoindole type base with an α,ω-dihalogen substituted alkane in an inert solvent. The reaction sequence is



Reaction sequence A.

The quaternization proceeded readily in all cases where $n = 3$ or greater. In the cases where $n = 1$ or 2 and methylene diiodide or ethylene dibromide was employed in the reaction, the products were al-



(1) Hypotensive Agents, IV, L. M. Rice, C. H. Grogan and E. E. Reid, THIS JOURNAL, **75**, 4911 (1953).

(2) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

(3) L. M. Rice, E. E. Reid and C. H. Grogan, *J. Org. Chem.*, **19**, 884 (1954).

(4) K. Alder and H. Backendorf, *Ann.*, **535**, 101 (1938); O. Diels and S. Olsen, *J. prakt. Chem.*, [2] **156**, 285 (1940).

(5) Only those imides which have not been previously reported are included here.

(6) J. von Braun and Z. Kohler *Ber.*, **51**, 103 (1918).

TABLE II

N-METHYLISOINDOLINES

Ring	Formula	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	$n^{25}D$
1	$C_9H_{17}N$	72	20	77.63	77.50	12.31	12.14	10.06	10.16	1.4770
2	$C_9H_{15}N$	60–63	11	78.77	79.09	11.02	11.10	10.21	10.12	1.4849
3	$C_9H_{15}NO$	82–83	10	70.55	70.47	9.87	9.83	9.14	9.01	30–32[a]
4	$C_{10}H_{17}NO$	100–102	16	71.81	71.71	10.25	9.97	8.38	8.68	1.4782
5	$C_{11}H_{19}NO$	90–91	7	72.88	73.04	10.57	10.31	7.73	7.68	1.4743
6	$C_{10}H_{15}N$	70–74	10	80.45	80.32	10.13	10.02	9.39	9.55	1.5003
7	$C_9H_{11}N$	92–95	25[b]	...	...	...	...	...	...	....

[a] Melting point. [b] J. von Braun and Z. Kohler, *Ber.*, **51**, 103 (1918), reported b.p. 81–82° at 13 mm.

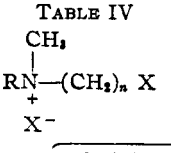
TABLE III

DERIVATIVES OF N-METHYLISOINDOLES

Ring	Picrate Formula	Picrate M.p., °C.	Picrate Nitrogen, % Calcd.	Picrate Nitrogen, % Found	Methiodide Formula	Methiodide M.p., °C.	Methiodide Ionic iodine, % Calcd.	Methiodide Ionic iodine, % Found
1	$C_{15}H_{20}N_4O_7$	225–227	15.21	14.96	$C_{10}H_{20}IN$	230–232	45.14	45.36
2	$C_{15}H_{18}N_4O_7$	206–208	15.30	15.49	$C_{10}H_{18}IN$	213–214	45.46	45.58
3	$C_{15}H_{18}N_4O_8$	208.5–210	14.66	14.34	$C_{10}H_{18}INO$	192–193	43.00	43.11
4	$C_{16}H_{20}N_4O_8$	209–211	14.14	14.24	$C_{11}H_{20}INO$	157–157.5	41.05	40.96
5	$C_{17}H_{22}N_4O_8$	196–197	13.65	13.82	$C_{12}H_{22}INO$	191–193	39.27	39.27
6	$C_{16}H_{18}N_4O_7$	224–225	14.81	14.71	$C_{11}H_{18}IN$	252.5–254	43.59	43.72
7	$C_{15}H_{14}N_4O_7$	128–129[a]	15.47	14.99	$C_{10}H_{14}IN$	253–255	46.13	45.72

[a] J. von Braun and Z. Kohler, *Ber* , **51**, 103 (1918), reported m.p. 126°.

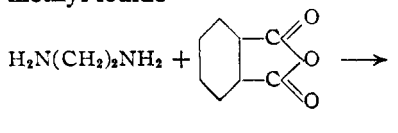
TABLE IV

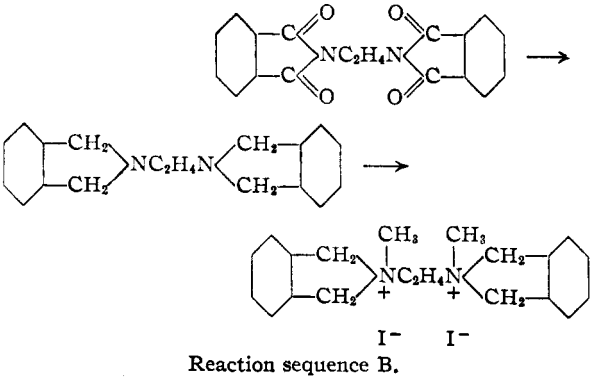


Ring	X	n	Formula	M.p., °C.	Analyses, % Ionic halogen Calcd.	Ionic halogen Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	I	1	$C_{10}H_{19}I_2N$	151–152	31.18	31.26	29.50	29.91	4.70	4.73
1	Br	2	$C_{11}H_{21}Br_2N$	181–182	24.43	24.43	40.39	40.59	6.47	6.52
2	I	1	$C_{10}H_{17}I_2N$	147–149	31.33	30.99	29.65	30.03	4.23	4.29
2	Br	2	$C_{11}H_{19}Br_2N$	166–168	24.58	24.76	40.64	40.90	5.89	6.02
3	I	1	$C_{10}H_{17}I_2NO$	177–178	30.14	30.26	28.52	28.56	4.07	4.18
3	Br	2	$C_{11}H_{19}Br_2NO$	210–212	23.43	23.64	38.73	39.28	5.61	5.56
4	I	1	$C_{11}H_{19}I_2NO$	167–167.5	29.17	29.30	30.36	30.29	4.40	4.48
4	Br	2	$C_{12}H_{21}Br_2NO$	205–207	22.50	22.62	40.58	40.53	5.96	5.99
5	I	1	$C_{12}H_{21}I_2NO$	180–181	28.26	27.96	32.09	32.33	4.71	4.83
5	Br	2	$C_{13}H_{23}Br_2NO$	194–195	21.65	21.74	42.30	41.94	6.28	6.47
6	I	1	$C_{11}H_{17}I_2N$	197–200	30.42	29.92	31.67	32.03	4.11	4.11
6	Br	2	$C_{12}H_{19}Br_2N$	207–209	23.71	24.08	42.75	43.18	5.68	5.99
7	I	1	$C_{10}H_{13}I_2N$	161–162	31.65	32.00	29.95	29.96	3.27	3.46
7	Br	2	$C_{11}H_{15}Br_2N$	223–224	24.89	25.00	41.15	40.88	4.71	4.96

ways of the type in which only one half of the molecule was quaternized. This was the result in all the series investigated under the conditions employed. It made no difference whether the reactants were refluxed or allowed to interact at room temperature in solvents such as alcohol or acetone. These products were crystalline substances which melted sharply with decomposition. They are listed in Table IV together with appropriate data.

When $n = 2$ in the general formula the bis-quaternary compounds were produced by the reaction of ethylenediamine with hexahydrophthalic anhydride followed by the reduction with lithium aluminum hydride and quaternization by means of methyl iodide





Reaction sequence B.

In addition the compound in which $n = 6$, bis-1,6-(3,3′-perhydroisoindolyl)-hexane dimethiodide, was produced by the above reaction sequence B. This same compound was also made by means of

TABLE V

BIS-α,ω-(N,N'-PERHYDROISOINDOLYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING I

			Analysis, % Ionic iodine				Analysis, % Ionic bromine	
n	Formula	M.p., °C.[a]	Calcd.	Found	Formula	M.p., °C.	Calcd.	Found
2	$C_{20}H_{38}I_2N_2$	270–271	45.29	45.23	.....	.....	...	...
3	$C_{21}H_{40}I_2N_2$	264–265	44.19	43.97	$C_{21}H_{40}Br_2N_2$	284–285	33.27	33.24
4	$C_{22}H_{42}I_2N_2$	266–267	43.14	43.07	$C_{22}H_{42}Br_2N_2$	290–291	32.33	32.00
5	$C_{23}H_{44}I_2N_2$	290–291	42.14	42.19	$C_{23}H_{44}Br_2N_2$	284–285	31.44	31.17
6	$C_{24}H_{46}I_2N_2$	250–252	41.18	41.27	$C_{24}H_{46}Br_2N_2$	264–264.5	30.59	30.45
9	$C_{27}H_{52}I_2N_2$	224.5–225.5	38.55	38.33	$C_{27}H_{52}Br_2N_2$	234–235	28.31	28.04
10	$C_{28}H_{54}I_2N_2$	217–218	37.74	38.09	$C_{28}H_{54}Br_2N_2$	237–238	27.63	27.44
C_8H_8[b]		.....	...	...	$C_{26}H_{42}Br_2N_2$	269–270	29.46	29.12

[a] Many melted with decomposition. [b] *p*-Xylylene.

TABLE VI

BIS-α,ω-(N,N'-4,7,8,9-TETRAHYDROISOINDOLINYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING II

			Analysis, % Ionic iodine				Analysis, % Ionic bromine	
n	Formula	M.p., °C.[a]	Calcd.	Found	Formula	M.p., °C.[a]	Calcd.	Found
3	$C_{21}H_{36}I_2N_2$	256–257.5	44.51	44.60	$C_{21}H_{36}Br_2N_2$	250–251	33.55	33.70
4	$C_{22}H_{38}I_2N_2$	242–243	43.44	43.22	$C_{22}H_{38}Br_2N_2$	260–261	32.59	32.73
5	$C_{23}H_{40}I_2N_2$	253–254	42.42	42.56	$C_{23}H_{40}Br_2N_2$	241–241.5	31.69	31.25
6	$C_{24}H_{42}I_2N_2$	232–233	41.45	41.65	$C_{24}H_{42}Br_2N_2$	236–238	30.83	30.59
9	$C_{27}H_{48}I_2N_2$	185.5–187	38.78	38.80	$C_{27}H_{48}Br_2N_2$	195–196	28.52	28.36
10	$C_{28}H_{50}I_2N_2$	218–219	37.97	37.66	$C_{28}H_{50}Br_2N_2$	201–203	27.82	28.00
C_8H_8[b]		.....	...	...	$C_{26}H_{38}Br_2N_2$	252–253	29.69	29.33

[a] Many melted with decomposition. *p*-Xylylene.

reaction sequence A. The products obtained from both reactions were identical as evidenced by their individual and mixed melting points, solubility and infrared spectra.

All the bis-(isoindolyl)-alkane methonium salts derived from the various ring systems are listed in Tables V through XI, together with their appropriate constants.

Following the methods outlined in our previous paper[1] we would like to report also at this time six

TABLE VII

BIS-α,ω-(N,N'-4,7-ENDOXYPERHYDROISOINDOLYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING III

			Analysis % Ionic halogen	
n	Formula	M.p., °C.[a]	Calcd.	Found
3	$C_{21}H_{36}I_2N_2O_2$	255–256	42.14	42.18
4	$C_{22}H_{38}I_2N_2O_2$	294–295	41.18	41.05
5	$C_{23}H_{40}I_2N_2O_2$	233–234	40.27	40.32
6	$C_{24}H_{42}I_2N_2O_2$	263–264	39.39	39.38
9	$C_{27}H_{48}I_2N_2O_2$	227–229	36.98	37.02
10	$C_{28}H_{50}I_2N_2O_2$	235–236	36.24	36.01
C_8H_8[b]	$C_{26}H_{38}Br_2N_2O_2$	267–268	28.02	27.84

[a] Many melted with decomposition. [b] *p*-Xylylene.

TABLE VIII

BIS-α,ω-(N,N'-4-METHYL-4,7-ENDOXYPERHYDROISOINDOLYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING IV

			Analysis, % Ionic halogen	
n	Formula	M.p., °C.[a]	Calcd.	Found
3	$C_{23}H_{40}I_2N_2O_2$	265–267	40.27	40.09
4	$C_{24}H_{42}I_2N_2O_2$	255–256	39.39	38.94
5	$C_{25}H_{44}I_2N_2O_2$	257–258	38.55	38.39
6	$C_{26}H_{46}I_2N_2O_2$	232–233	37.75	37.58
9	$C_{29}H_{52}I_2N_2O_2$	210–211	35.52	35.72
10	$C_{30}H_{54}I_2N_2O_2$	223–224	34.84	34.69

[a] Many melted with decomposition.

TABLE IX

BIS - α,ω - (N,N' - 4,7 - DIMETHYL - 4,7 - ENDOXYPERHYDROISOINDOLYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING V

			Analysis, % Ionic halogen	
n	Formula	M.p., °C.[a]	Calcd.	Found
3	$C_{25}H_{44}I_2O_2N_2$	261–262	38.55	38.38
4	$C_{26}H_{46}I_2N_2O_2$	217–219	37.75	37.91
5	$C_{27}H_{48}I_2N_2O_2$	257–259	36.98	36.73
6	$C_{28}H_{50}I_2N_2O_2$	234–235	36.24	35.98
9	$C_{31}H_{56}I_2N_2O_2$	215–217	34.18	34.30
10	$C_{32}H_{58}I_2N_2O_2$	238–239	33.55	33.24

[a] Many melted with decomposition.

TABLE X

BIS - α,ω - (N,N' - 4,7,8,9 - TETRAHYDRO - 4,7 - ENDOMETHANOISOINDOLINYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING VI

			Analysis, % Ionic halogen	
n	Formula	M.p., °C.[a]	Calcd.	Found
3	$C_{23}H_{36}I_2N_2$	301–303	42.71	42.84
4	$C_{24}H_{38}I_2N_2$	294–296	41.72	41.72
5	$C_{25}H_{40}I_2N_2$	291–292	40.78	41.10
6	$C_{26}H_{42}I_2N_2$	260–261	39.88	39.48
9	$C_{29}H_{48}I_2N_2$	222–223	37.41	37.24
10	$C_{30}H_{50}I_2N_2$	225–226	36.65	36.40

[a] Many melted with decomposition.

TABLE XI

BIS-α,ω-(N,N'-ISOINDOLINYL)-ALKANE DIMETHONIUM SALTS, BIS-METHONIUM SALTS OF RING VII

			Analysis, % Ionic halogen	
n	Formula	M.p., °C.[a]	Calcd.	Found
3	$C_{21}H_{28}I_2N_2$	240–241	45.14	45.15
4	$C_{22}H_{30}I_2N_2$	224–226	44.05	43.58
5	$C_{23}H_{32}I_2N_2$	227–228	43.00	42.93
6	$C_{24}H_{34}I_2N_2$	251–253	42.00	41.86
9	$C_{27}H_{40}I_2N_2$	215–216	39.27	39.05
10	$C_{28}H_{42}I_2N_2$	217–218	38.43	38.29

[a] Many melted with decomposition.

TABLE XII

N-DIALKYLAMINOALKYL-3,6-ENDOXYHEXAHYDROPHTHALIMIDES

N-Substituent	Formula	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	HCl, m.p., °C.	Analyses, % Ionic chloride Calcd.	Ionic chloride Found
Diethylaminoethyl	$C_{14}H_{22}N_2O_3$	141–146	0.4	63.13	63.27	8.33	8.27	10.52	10.50	199–200	11.71	11.78
Dimethylamino-propyl	$C_{13}H_{20}N_2O_3$	134–140	.1	61.88	61.95	7.99	7.88	11.10	11.06	212–213	12.28	12.34
Diethylaminopropyl	$C_{15}H_{24}N_2O_3$	159–163	.5	64.26	64.18	8.63	8.36	9.99	10.07	160–161	11.19	11.45
Morpholinoethyl	$C_{14}H_{20}N_2O_4$	168–173[a]	.1	59.98	60.10	7.19	7.07	9.99	9.81	250–252	11.19	11.28
3-Dibutylamino-propyl	$C_{19}H_{32}N_2O_3$	185–190	.4	67.82	68.10	9.59	9.76	8.33	8.46	158–159	9.51	9.58
Morpholinopropyl	$C_{15}H_{22}N_2O_4$	175–185	.2	61.21	61.31	7.53	7.27	9.52	9.45	233	10.72	10.77

[a] M.p. 120–122°.

TABLE XIII

N-DIALKYLAMINOALKYL-4,7-ENDOXYPERHYDROISOINDOLES

N-Substituent	Formula	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Diethylaminoethyl	$C_{14}H_{26}N_2O$	88–93	0.1	70.54	70.55	10.99	11.11	11.75	11.65
Dimethylaminopropyl	$C_{13}H_{24}N_2O$	87–94	.1	69.60	69.40	10.78	10.98	12.49	12.31
Diethylaminopropyl	$C_{15}H_{28}N_2O$	93–97	.2	71.38	71.07	11.18	11.11	11.10	11.32
Morpholinoethyl	$C_{14}H_{24}N_2O_2$	117–122[a]	.3	66.63	66.90	9.59	9.72	11.10	11.12
3-Dibutylaminopropyl	$C_{19}H_{36}N_2O$	126–130	.1	73.97	74.20	11.76	12.06	9.08	8.91
Morpholinopropyl	$C_{15}H_{26}N_2O_2$	128–133	.1	67.63	67.41	9.84	9.64	10.52	10.40

[a] M.p. 76–78°.

TABLE XIV

DERIVATIVES OF COMPOUNDS OF TABLE XIII

Formula	M.p., °C.[a]	Analysis, % Ionic chloride Calcd.	Ionic chloride Found	Formula	M.p., °C.	Analysis, % Ionic iodine Calcd.	Ionic iodine Found
	Hydrochloride				Dimethiodide		
$C_{14}H_{28}Cl_2N_2O$	207–208	22.78	22.89	$C_{16}H_{32}I_2N_2O$	234–236	48.60	48.41
$C_{13}H_{26}Cl_2N_2O$	241–243	23.86	23.91	$C_{15}H_{30}I_2N_2O$	264–266	49.94	49.58
$C_{15}H_{30}Cl_2N_2O$	.....	21.80	21.92	$C_{17}H_{34}I_2N_2O$	217–219	47.33	47.43
$C_{14}H_{26}Cl_2N_2O_2$	261–263	21.80	21.68	$C_{16}H_{30}I_2N_2O_2$	229–230[b]	47.34	47.20
$C_{19}H_{38}Cl_2N_2O$	.....	...	...	$C_{21}H_{42}I_2N_2O$	166–168	42.85	42.59
$C_{15}H_{28}Cl_2N_2O_2$	249–250	20.90	20.68	$C_{17}H_{32}I_2N_2O_2$	231–233	46.13	45.67

[a] Many melted with decomposition. [b] Monomethiodide, m.p. 161–163°. *Anal.* Calcd. for $C_{15}H_{27}IN_2O_2$: iodine, 32.18. Found: iodine, 31.85.

new dialkylaminoalkyl-3,6-endoxyhexahydrophthalimides together with their reduction products and dimethonium salts. These compounds are tabulated in Tables XII, XIII and XIV, together with pertinent data.

For such a large group of compounds of closely allied structures it is possible to draw some conclusions as to the relation of structure to activity. In dimethonium salts of the compounds in which a dialkylamino-alkyl group is substituted on the isoindole nitrogen the following general trends were noted.

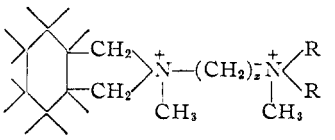
In Table XV is shown the toxicity trend in rats with a change in the dialkylaminoalkyl side chain. Here it can be seen that while keeping the central methylene carbon chain at 2 and increasing the size of the alkyl groups attached to the nitrogen that there is an increase in the toxicity of the compounds. The most favorable group is the methyl. The introduction of morpholine or piperidine as in 4 or 5 seems to be intermediate. Number 7 is the hydrochloride of the free amine base and not a quaternary salt.

In compounds 8, 9 and 10 are shown the large increase in toxicity by going from only methyl to butyl. The most striking effect on the toxicity is seen when the carbon chain between the two nitrogens is expanded. Here with only 2 carbons we have a toxicity as shown in the table of 1250 mg./kg. When the number is increased to 3 the toxicity is increased to 500 as shown in 8. When increased to 4, and 6 as in 12, and 13, the toxicity is 200 and 25 mg./kg., respectively. This same general trend was also noted in the bis-isoindole series and when substituents were introduced into the central chain as in compounds 14 and 15.

In Table XVI is shown the trend in acute toxicity with a change in ring structure where the side chain is kept constant at dimethylaminoethyl. The least toxic compound here seemed to be derived from tetrahydrophthalic and then hexahydrophthalic and 3-methyltetrahydrophthalic. Here also is shown some of the endo-oxygen analogs which are of very low toxicity. The 3-methyl seemingly being the least toxic. Here the toxicity is at least one fourth as much as when an endomethylene bridge ring is used. The unbridged compounds are intermediate. These trends also are carried over into the bis-isoindole quaternary compounds. The good hypotensive activity of these compounds in dogs follows the same trend as does the toxicity; that is, that the short central carbon

TABLE XV

TOXICITY TREND IN DIALKYLAMINOALKYL HEXAHYDROISOINDOLINE DIMETHIODIDE SERIES



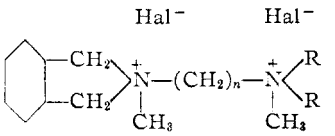
	x	R	Mg./kg.
1	2	CH_3	1250
2	2	C_2H_5	1000
3	2	C_6H_{13}	350
4	2	C_6H_{10}	650
5	2	C_4H_8O	750
6	2	Hexahydroisoindoline	800
7	2	H	500
8	3	CH_3	500
9	3	C_2H_5	400
10	3	C_4H_9	250
11	3	C_4H_8O	1000
12	4	C_2H_5	200
13	6	C_2H_5	25
14	6	Hexahydroisoindoline	25
15	Propanol-2	C_2H_5	200
16	Pentyl-2	C_2H_5	200

TABLE XVI

TREND IN TOXICITY WITH RING STRUCTURE CHANGE

Ring system	Mg./kg.
Isoindoline	400
4,7,8,9-Tetrahydroisoindoline	1500
Perhydroisoindole	750
5-Methyl-4,7,8,9-tetrahydroisoindoline	750
4,6-Dimethyl-4,7,8,9-tetrahydroisoindoline	350
4,7,8,9-Tetrahydro-4,7-endomethanoisoindoline	400
4,7-Endoxyperhydroisoindole	1000
4-Methyl-4,7-endoxyperhydroisoindole	1500
4,7-Dimethyl-4,7-endoxyperhydroisoindole	1000
8,9-Dimethyl-4,7-endoxyperhydroisoindole	1000

chain on the various endoxy bridged compounds are the most active.



In summary the following conclusions may be drawn for most favorable toxicity and activity relationship in the isoindole series studied: 1, n should be a small number such as 2 or 3; 2, R should be methyl or ethyl; 3, the ring system should be of an oxygen bridged type isoindole; 4, in the bis-isoindole series the first and third statements also hold true.

Experimental

General Method for the Preparation of N-Methylimides and their Reduction.—The preparation of N-methyl-3-methyl-3,6-endoxyhexahydrophthalimide and its reduction and quaternization will illustrate the procedure followed.

(a) **N-Methyl-3-methyl-3,6-endoxyhexahydrophthalimide.**—Into a 500-ml. flask was placed 118.4 g. (0.65 mole) of finely powdered 3-methyl-3,6-endoxyhexahydrophthalic anhydride. With cooling and intermittent shaking 100 g. of a 25% aqueous solution of methylamine was added (excess). When the initial reaction had subsided the solution was heated to boiling. After all the water had boiled off the temperature was slowly raised to 240–250°. The crude product solidified on cooling and was recrystallized from benzene, m.p. 107–109°. An additional recrystallization from benzene–petroleum ether yielded 102 g. of colorless crystals melting at 108° (83%).

(b) **N-Methyl-4-methyl-4,7-endoxyperhydroisoindole.**—In a three-liter, three-necked flask, fitted with a mechanical stirrer, dropping funnel and a Soxhlet extractor was placed 36 g. of lithium aluminum hydride and 1500 ml. of anhydrous ether. When solution had been effected 60 g. of N-methyl-3-methyl-3,6-endoxyhexahydrophthalimide was placed in the thimble of the extractor. After about 6 hours of reflux all of the imide was transferred to the reaction flask by means of the circulating ether. The Soxhlet extractor was then replaced with a long condenser and the reaction mixture was stirred an additional 2 hours. The flask was cooled in an ice-bath and with vigorous stirring, the reaction mixture was decomposed by the dropwise addition of water. The addition of the water was regulated so that reflux was just maintained, and then an excess of 20 cc. was added. After decomposition the mixture was stirred an additional hour and filtered with suction. The inorganic precipitate was well pressed and washed with three portions of ether. After drying over sodium sulfate, the ether was distilled off and the residue distilled in vacuum. There was obtained 53 g. (68%) of material boiling at 100–102° at 16 mm.

The N-methylimides from hexahydrophthalic and tetrahydrophthalic anhydride were distilled and added in ether solution for reduction. The N-methylimides from endoxyphthalic and endomethylene tetrahydrophthalic anhydrides were prepared as in (a) above and added in the form of a benzene or benzene–ether solution. All others were prepared as in (a) and (b) above.

All the methiodides and picrates of the N-methylisoindoles were prepared in the usual way employing alcohol as a solvent.

(c) **Bis-α,ω-(N,N'-4-methyl-4,7-endoxyperhydroisoindolyl)-pentane Dimethonium Diiodide.**—To 0.03 mole (5.01 g.) of N-methyl-4-methyl-4,7-perhydroisoindole dissolved in 20 ml. of acetone was added 0.015 mole (4.86 g.) of pentamethylene diiodide. The mixture was allowed to stand at room temperature for one hour, then heated to boiling and allowed to stand an additional 4 hours. The crude product was filtered, washed with alcohol ether mixture and dried, m.p. 255–257°. One recrystallization from methanol ether gave white crystals, m.p. 257–258°.

(d) **β-(4-Methyl-4,7-endoxyperhydroisoindolyl)-ethyl Bromide Methonium Bromide.**—This was prepared as in (a) above employing 0.03 mole of N-methyl-4-methyl-4,7-endoxyperhydroisoindole and 0.03 mole of ethylene bromide in acetone. If a large excess of the base was used the same product was obtained. The mixture was refluxed in acetone for 15 minutes and allowed to cool. The product was completely precipitated with ether and after recrystallization from methanol melted with decomposition at 205–207°.

Preparation of Bis-1,6-(hexahydrophthalimido)-hexane.—Into a flask was placed 0.2 mole (30.8 g.) of hexahydrophthalic anhydride dissolved in the minimum amount of benzene. After solution 0.1 mole (11.6 g.) of hexamethylenediamine dissolved in a small amount of benzene was added. The mixture was heated in an oil-bath until all the benzene had distilled off and then the temperature was raised to 190° where it was maintained for one hour. The product which solidified on cooling was recrystallized from benzene–petroleum ether and melted at 81–82.5°.

Anal. Calcd. for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.16; H, 8.52; N, 7.14.

Preparation of Bis-1,2-(hexahydrophthalimido)-ethane.—This was prepared in a manner analogous to the hexane compound above and recrystallized from ethanol, m.p. 147–148°.

Anal. Calcd. for $C_{18}H_{24}N_2O_4$: N, 8.43. Found: N, 8.27.

Preparation of Bis-1,2-(perhydroisoindolyl)-ethane.–The above imide dissolved in tetrahydropyran was added to an ether solution of lithium aluminum hydride with rapid stirring in the usual way. After decomposition with water, filtering, drying and stripping, the residue was fractionated. The fraction boiling at 120–132° at 0.1 mm. was collected.

Anal. Calcd. for $C_{18}H_{32}N_2$: C, 78.20; H, 11.67; N, 10.13. Found: C, 77.52; H, 11.35; N, 9.83.

The hydrochloride was prepared in the usual way employing alcoholic hydrogen chloride and after recrystallization melted at 300–301°.

Anal. Calcd. for $C_{18}H_{34}N_2Cl_2$: Cl, 20.30. Found: Cl, 20.25.

The dimethiodide was prepared employing a large excess of alcohol in the usual way with methyl iodide, and after recrystallization from methanol melted 269.5–271°.

Anal. Calcd. for $C_{20}H_{38}N_2I_2$: I, 45.29; Found: I, 45.23.

Preparation of Bis-1,6-(perhydroisoindolyl)-hexane.—This was prepared in a manner analogous to that of the ethane base above. The free base was collected at 160–165° at 0.05 mm.

Anal. Calcd. for $C_{22}H_{40}N_2$: C, 79.45; H, 12.12; N, 8.42. Found: C, 79.63; H, 12.01; N, 8.15.

The hydrochloride was prepared in the usual way and melted at 203–204°.

Anal. Calcd. for $C_{22}H_{42}N_2Cl_2$: Cl, 17.49. Found: Cl, 17.54.

The dimethiodide prepared as above melted at 249° on recrystallization from methanol.

Anal. Calcd. for $C_{24}H_{46}N_2I_2$: I, 41.18. Found: I, 41.10.

WASHINGTON 7, D. C.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

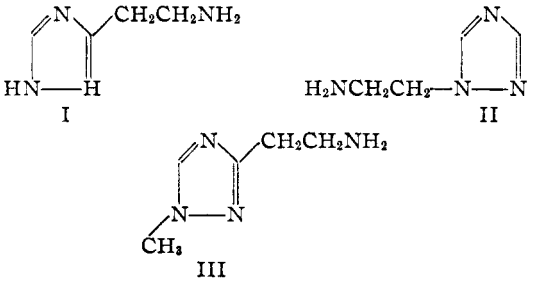
Isomeric and Nuclear-substituted β-Aminoethyl-1,2,4-triazoles

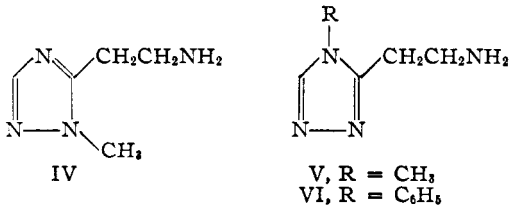
BY C. AINSWORTH AND R. G. JONES

RECEIVED AUGUST 13, 1954

1β-Aminoethyl-1,2,4-triazole (II), 1γ-aminopropyl-1,2,4-triazole (XIV), 3β-aminoethyl-1-methyl-1,2,4-triazole (III), 5β-aminoethyl-1-methyl-1,2,4-triazole (IV), 3β-aminoethyl-4-methyl-1,2,4-triazole (V) and 3β-aminoethyl-4-phenyl-1,2,4-triazole (VI) have been synthesized and tested pharmacologically. Only III and IV possessed histamine-like activity. An improved method for the synthesis of 1,2,4-triazole is described. Alkylation of a 3-alkyl-1,2,4-triazole (3β-phthalimidoethyl-1,2,4-triazole) with methyl iodide was found to give both the 3-alkyl-1-methyl and the 5-alkyl-1-methyl compounds.

3β-Aminoethyl-1,2,4-triazole (I) possessed unusually high histamine-like activity when tested on isolated muscle strips, on blood pressure and on gastric secretion.[1] Branching, shortening or lengthening of the side chain or alkylation of the amino group generally decreased or abolished activity.[2] Several additional variations of the basic structure I have been made with the hope of finding compounds having improved hypotensive action. The purpose of this communication is to describe the synthesis and preliminary pharmacology of a structural isomer of I, 1β-aminoethyl-1,2,4-triazole (II), and compounds III-VI in which the ring-nitrogen atoms carry substituents.





The starting material for the preparation of II was 1,2,4-triazole. This has been synthesized in low yields by heating hydrazine salts with formamide.[3] Better yields (up to 30%) were obtained by mixing one mole of hydrazine hydrate with two moles of formamide and distilling rapidly at atmospheric pressure. During this process, however, a large quantity of ammonia was evolved and diformylhydrazine was obtained as a by-product. In fact, if the mixture was heated slowly, all the ammonia was lost and diformylhydrazine was the only product. In order to avoid this loss of ammonia the reactants were heated in an autoclave. Thus 70–80% yields of 1,2,4-triazole were obtained by heating diformylhydrazine with excess ammonia or by heating a mixture of hydrazine, formamide and ammonia in an autoclave at 200° for 24 hours.[4]

Alkylation of 1,2,4-triazole has been shown to give exclusively the 1-substituted compounds.[5] Accordingly, ethyl 1,2,4-triazole-1-acetate (VII) was synthesized from ethyl bromoacetate and the sodium derivative of 1,2,4-triazole. Compounds VIII, IX and X were prepared from VII. Although VII readily underwent reduction with lithium aluminum hydride to give X, attempts to reduce the amide IX to the amine II were without success.

The condensation of the sodium derivative of 1,2,4-triazole with N-bromomethyl-, β-bromoethyl- and γ-bromopropylphthalimides gave, respectively, compounds XI, XII and XIII. Hydrolysis of XII afforded the desired 1β-aminoethyl-1,2,4-triazole (II), and hydrolysis of XIII gave XIV, the next higher homolog of II.

Alkylation of the sodium derivative of 3β-phthalimidoethyl-1,2,4-triazole with methyl iodide gave two products. After hydrolysis to remove the phthalyl group, the products were separated through their picrates and were found to be 3β-aminoethyl-1-methyl-1,2,4-triazole (III) and 5β-aminoethyl-1-methyl-1,2,4-triazole (IV). The ratio of III to IV was about 1 to 2, and none of the

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(2) C. Ainsworth and R. G. Jones, *ibid.*, **76**, 5651 (1954).

(3) (a) G. Pellizzari, *Gazz. chim. ital.*, **24**, 222 (1894); *Ber.*, **27(R)**, 801 (1894); (b) H. H. Strain, THIS JOURNAL, **49**, 1995 (1927).

(4) This method was developed by Dr. D. E. Morrison and J. J. Traverso.

(5) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954).