L-Thyroxine-C^{14}.—The method of Chalmers, *et al.*,[2] was followed. From 3,5-diiodo-L-thyronine-C^{14} (26 mg., 0.05 mmole), 33% aqueous ethylamine (0.26 ml.), and a 1.9 *N* solution (0.11 ml.) of iodine in concentrated potassium iodide, there was obtained crude L-thyroxine-C^{14}. Precipitation from a mixture of 95% ethanol (1 ml.) and 2 *N* sodium hydroxide (0.5 ml.) afforded pure white crystalline L-thyroxine-C^{14} (17 mg., 44%, based on 3,5-diiodo-L-thyronine-C^{14}; 2.6% based on phenol-C^{14}). It melted at 227–228° dec.,[15] specific activity 1.55 μc./mg.

Characterization of L-Thyroxine-C^{14}. A. Paper Chromatography.—The L-thyroxine-C^{14} was compared with nonradioactive and I^{131}-labeled L-thyroxine by descending technique in three different solvent systems: *t*-amyl alcohol saturated with 2 *N* ammonium hydroxide, *n*-butyl alcohol–*p*-dioxane–2 *N* ammonium hydroxide (4:1:5), and *n*-butyl alcohol–acetic acid–water (4:1:5). The R_f values were 0.26, 0.48, and 0.85, respectively. A single radioactive peak corresponding to nonradioactive L-thyroxine was observed in each case.

B. Biological Activity.—The L-thyroxine-C^{14} exhibited biological activity equivalent to authentic L-thyroxine when tested by the inhibition of propylthiouracil-induced goiters in rats[16] and the suppression of thyroidal iodine-131 uptake.[17]

Acknowledgment.—The authors wish to express appreciation for the valuable technical assistance of Eveline Bruenger.

(15) The sample was placed on hot stage preheated to 220° and heated at the rate of 4°/min. Ref.[2] m.p. 233–235° dec. The optical rotation as determined on a sample of nonradioactive L-thyroxine prepared in the same way from nonradioactive phenol was $[\alpha]_D^{27} -5.6°$ (*c*, 2.2 in a 1:2 mixture of *N* sodium hydroxide and ethyl alcohol).

(16) (a) E. W. Dempsey and E. B. Astwood, *Endocrinology*, **32**, 509 (1943); (b) C. A. Plamondon, H. A. Selenkow, J. G. Wiswell, and S. P. Asper, Jr., *Bull. Johns Hopkins Hosp.*, **102**, 88 (1958).

(17) W. C. Money, R. I. Meltzer, D. Feldman, and R. W. Rawson, *Endocrinology*, **64**, 123 (1959).

Bicyclic Imides and Isoindolines[1]

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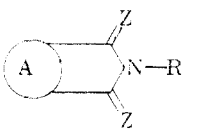
In view of our previous extensive work on isoindoles, isoindolines, the corresponding intermediate imides,[2,3] and other azabicyclic systems,[4] it was desired to screen representative types and derivatives of these systems in the primary rodent tumor and tissue culture screens of the Cancer Chemotherapy National Service Center.[5] Accordingly, a cooperative arrangement was worked out whereby sufficient quantities of these compounds could be made available for the anticancer primary screens.

During the course of this work a number of new derivatives of these ring systems were prepared in addition to those previously reported. Since previous work had shown a high physiological activity, accompanied by low toxicity,[6] in derivatives of the 4,7-epoxyisoindoline ring system, most of the new derivatives reported herein were derived from this nucleus. These derivatives, and some related imides and isoindolines, are listed in Table I together with pertinent physical data.

The imides were prepared by reaction of the appropriate primary amines, with or without solvent depending on the volatility and solubility of the amine, with the desired dicarboxylic acid anhydrides, followed by cyclization of the initially formed amic acid to the corresponding imide.[2] The isoindoline bases were obtained by reduction of the imides with lithium aluminum hydride in absolute ether. In all cases the reduction proceeded smoothly and gave good yields of the desired products except when the N substituent was hydrogen. In this case the yield was considerably reduced (from 80–95% to around 50%).

Representative compounds were submitted to and screened under the auspices of the Cancer Chemotherapy National Service Center in the primary rodent tumor screens (consisting of murine sarcoma 180, adenocarcinoma 755, and lymphoid leukemia 1210). A number of the compounds were also assayed for growth inhibitory activity against the KB cell line in tissue culture.

Isoindolines and other azabicyclic compounds resynthesized for screening are shown by the general formula



wherein the following A ring systems were represented: (1) benzene; (2) cyclohexane; (3) *cis*-Δ^4-cyclohexene; (4) 3,4,5,6-tetrachlorobenzene; (5) 5-methyl-*cis*-Δ^4-cyclohexene; (6) 3,6-epoxycyclohexane; (7) 3,6-methano-Δ^4-cyclohexene; (8) 3-methyl-3,6-epoxycyclohexane; (9) cyclobutane; (10) 1,2,2-trimethylcyclopentane. Z was oxygen (intermediate imides) or 2H (isoindolines or other azabicyclic bases). R was varied to include hydrogen, alkyl groups from 1 to 10 atoms, dialkylaminoalkyl, and heterocyclic alkyl groups. In the latter two side-chain types, R was the composite grouping $-(CH_2)_nNR'R'$ wherein *n* was varied from 2 to 6; R′ alkyl groups containing from 1 to 6 atoms, or the grouping NR'_2 consisted of the heterocycles morpholine, piperidine, or pyrrolidine. In all cases the isoindolines and other azabicyclic structures were submitted in the form of their acid addition (usually hydrochlorides) salts, to ascertain if activity existed in the base itself, and as quaternary salts, usually as the methonium iodide. Where dialkylaminoalkyl or heterocyclic alkyl side chains existed, presenting a basic nitrogen atom in the side chain, the acid addition and quaternary salts of the imides were also submitted.

An analysis of the screening data for some 100 compounds of the type submitted showed that none had significant activity against leukemia L-1210 (a 25% increase in life span). The hydrogen imides of the various dicarboxylic anhydrides employed were prepared and submitted since tetrahydrophthalimide showed a 24% increase in life span. None of the other imides was as active as tetrahydrophthalimide. None of the alkylimides, dialkylaminoalkyl, or heterocyclic alkyl imides (their acid addition and quaternary salts) passed any of the stages in the assay against

(1) Supported in part by the Cancer Chemotherapy National Service Center, under contract SA-43-ph-2347, and the Gosebrickter Fund for Medical Research, Inc.

(2) L. M. Rice, E. E. Reid, and C. H. Grogan, *J. Org. Chem.*, **19**, 880 (1954).

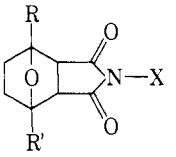
(3) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 3011 (1953).

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

(5) *Cancer Chemotherapy Rept.*, **1**, 63 (1959).

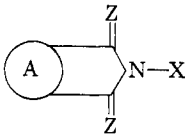
(6) C. H. Grogan and L. M. Rice, U. S. Patent 2,781,122 (1957).

TABLE I
7-Oxabicyclo[2.2.1]heptane-2,3-dicarboximides



					Analyses, %							
					Carbon		Hydrogen		Nitrogen		Oxygen	
X	R	R′	M.p., °C	Empirical formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1. Hydrogen	H	H	185	$C_8H_9NO_3$	57.48	57.60	5.43	5.34	8.38	8.63	28.72	28.69
2. Hydrogen	CH_3	H	160–161	$C_9H_{11}NO_3$	59.66	59.65	6.12	5.96	7.73	7.75	26.49	26.38
3. Hydrogen	CH_3	H	171–172[a]	$C_9H_{11}NO_3$	59.66	59.46	6.12	6.12	7.73	7.57	26.49	26.72
4. Hydrogen	CH_3[j]	CH_3[j]	205–206	$C_{10}H_{13}NO_3$	61.52	61.61	6.71	6.66	7.18	6.99		
5. Methyl	H	H	135	$C_9H_{11}NO_3$	59.66	59.56	6.12	6.08	7.73	7.83	26.49	26.63
6. Methyl	CH_3	H[o]	54–56	$C_{10}H_{13}NO_3$	61.52	61.54	6.71	6.65	7.18	7.09		
7. Methyl	CH_3	H	108	$C_{10}H_{13}NO_3$	61.52	61.48	6.71	6.54	7.18	7.41		
8. Methyl	CH_3	CH_3	128.5	$C_{11}H_{15}NO_3$	63.14	63.02	7.23	7.34	6.69	6.66		
9. Ethyl	H	H	165–166	$C_{10}H_{13}NO_3$	61.52	61.65	6.71	6.54	7.18	7.28	24.59	24.65
10. Ethyl	CH_3	H	95–96	$C_{11}H_{15}NO_3$	63.14	63.25	7.23	7.39	6.69	6.78	22.94	23.13
11. Propyl	H	H	78–79	$C_{11}H_{15}NO_3$	63.14	63.05	7.23	7.09	6.69	6.76	22.94	22.90
12. Butyl[a]	H	H	80–81	$C_{12}H_{17}NO_3$	64.55	64.44	7.68	7.78	6.27	6.44	21.50	21.62
13. Amyl[b]	H	H	66–67	$C_{13}H_{19}NO_3$	65.80	65.98	8.07	7.88	5.90	6.15	20.23	20.33
14. Hexyl[c]	H	H	30–31	$C_{14}H_{21}NO_3$	66.90	67.18	8.42	8.23	5.57	5.66	19.10	19.26
15. Heptyl[d]	H	H	66–67	$C_{15}H_{23}NO_3$	67.89	67.73	8.74	8.57	5.28	5.30	18.10	18.09
16. Octyl[e]	H	H	33–34	$C_{16}H_{25}NO_3$	68.78	68.78	9.02	8.91	5.01	4.98	17.18	17.40
17. Nonyl[f]	H	H	41–42	$C_{17}H_{27}NO_3$	69.59	69.65	9.28	9.15	4.77	4.83	16.36	16.48
18. Decyl[g]	H	H		$C_{18}H_{29}NO_3$	70.32	70.40	9.51	9.48	4.56	4.55	15.61	15.50
19. 2-Hydroxyethyl	H	H	159–160	$C_{10}H_{13}NO_4$	56.86	57.04	6.20	6.13	6.63	6.52		
20. 3-Methoxypropyl[h]	H	H	52–53	$C_{12}H_{17}NO_4$	60.23	60.45	7.16	7.24	5.85	5.73		
21. 3-Isopropoxypropyl[i]	H	H		$C_{14}H_{21}NO_4$	62.90	63.01	7.92	7.80	5.24	5.37		
22. Benzyl	H	H	114–115	$C_{15}H_{15}NO_3$	70.05	70.02	5.88	6.00	5.44	5.29		
23. 4-Methoxyphenyl	H	H	189–190	$C_{15}H_{15}NO_4$	65.92	65.95	5.53	5.71	5.13	5.30		
24. Homoveratryl	H	H	106–107	$C_{18}H_{21}NO_5$	65.24	65.24	6.39	6.24	4.23	4.37		
25. 2-Pyridyl	H	H	162–163	$C_{13}H_{12}N_2O_3$	63.92	63.88	4.95	5.00	11.47	11.56		
26. 4-Carboxyphenyl	H	H	265–266	$C_{15}H_{13}NO_5$	62.71	62.58	4.56	4.73	4.88	4.51		

Related Imides and Isoindolines



				Analyses, %					
				Carbon		Hydrogen		Nitrogen	
A	X	Z	Empirical formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
3-Methyl-3,6-epoxycyclohexane-1,2-	Ethyl	2H	$C_{11}H_{19}NO$[k]	72.88	72.93	10.56	10.85	7.73	8.02[p]
Cyclohexane-1,2-	Octadecyl	O	$C_{24}H_{43}NO_2$[l]	76.34	76.38	11.48	11.71	3.71	3.99
Cyclohexane-1,2-	Octadecyl	2H	$C_{24}H_{47}N$[m]	82.44	82.60	13.55	13.65	4.01	4.20[q]
3,4,5,6-tetrachlorophenyl-1,2-	Methyl	O	$C_9H_3Cl_4NO_2$[n]	36.16	36.12	1.01	1.13	4.68	4.82[r]

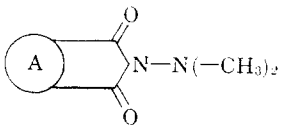
[a] B.p. 115–125° (0.3 mm.). [b] B.p. 130–140° (0.3 mm.). [c] B.p. 137–145° (0.2 mm.). [d] B.p. 153–160° (0.2 mm.). [e] B.p. 155–165° (0.3 mm.). [f] B.p. 163–170° (0.3 mm.). [g] B.p. 166–176° (0.3 mm.). [h] B.p. 130–143° (0.2 mm.). [i] B.p. 144–154° (0.2 mm.). [j] 1,2-Dimethyl, from Cantharidin. [k] B.p. 86–87° (3.5–4 mm.). [l] B.p. 188–194° (0.2.3 mm). [m] B.p. 164–166° (0.25 mm.). [n] M.p. 208–210°. [o] *endo-cis* configuration. All others, *exo-cis* configuration. [p] Hydrochloride, m.p. 139–140°. *Anal.* Calcd. for $C_{11}H_{20}ClNO$: Cl, 16.28. Found: Cl, 16.19. Methiodide, m.p. 120–121°. *Anal.* Calcd. for $C_{12}H_{22}INO$: I, 39.26. Found: I, 38.90. [q] Hydrochloride, m.p. 184–185°. *Anal.* Calcd. for $C_{24}H_{48}ClN$: Cl, 9.18. Found: Cl, 9.09. Methiodide, m.p. 221–222°. *Anal.* Calcd. for $C_{25}H_{50}IN$: I, 25.82. Found: I, 26.09. Allyliodide, m.p. 172–173°. *Anal.* Calcd. for $C_{27}H_{52}IN$: I, 24.52. Found: I, 24.68. Butiodide, m. p. 199–202°. *Anal.* Calcd. for $C_{28}H_{56}IN$: I, 23.78. Found: I, 23.87. Dodeciodide, m.p. 231–232°. *Anal.* Calcd. for $C_{34}H_{68}IN$: I, 20.54. Found: I, 20.47. [r] *Anal.* Calcd.: Cl, 47.44. Found: Cl, 47.20.

S-180 and CA-755 except the methyl imide of ring system 4. The dimethylhydrazine imides (Table II) were inactive.

Compounds which passed one or more stages in the sequential screening procedure against S-180 or Ca-755 are listed in Table III, together with values for a few "near misses" of closely related structural types, for comparison. In general the methyl, butyl (or hexyl), and decyl derivatives were tested and activity was discovered in the longer alkyl chains, primarily the quaternary salts, except in the case of ring 7 in which little difference between base and quaternary configuration

TABLE II

Derivatives of N,N-Dimethylhydrazine



A	M.p., °C.	B.p., °C. (mm.)	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Cyclohexane-1,2-	73–74	105–115 (0.25)	$C_{10}H_{16}N_2O_2$	61.20	61.45	8.22	8.08	14.28	14.16
Δ^4-Cyclohexene-1,2-	76–77	105–110 (0.2)	$C_{10}H_{14}N_2O_2$	61.84	62.05	7.27	7.30	14.42	14.31
5-Methyl-Δ^4-cyclohexene-1,2-	...	108–112 (0.23)	$C_{11}H_{16}N_2O_2$	63.44	63.59	7.74	7.78	13.45	13.66
3,6-Epoxycyclohexane-1,2-	185–186		$C_{10}H_{14}N_2O_4$	57.13	57.37	6.71	6.90	13.33	13.23
3-Methyl-3,6-epoxycyclohexane-1,2-	135–136		$C_{11}H_{16}N_2O_3$	58.92	59.03	7.19	7.34	12.49	12.39
Δ^4-3,6-Methanocyclohexene-1,2-	138–139		$C_{11}H_{14}N_2O_2$	63.44	63.36	7.74	7.78	13.45	13.22
1,2,2-Trimethylcyclopentane-1,3-	46–47	95–100 (0.23)	$C_{12}H_{26}N_2O_2$	64.25	64.31	8.99	9.08	12.49	12.31
3,4,5,6-Tetrachlorophenyl-1,2-	252–253		$C_{10}H_8Cl_4N_2O_2$[a]	36.62	36.51	1.84	1.95	8.54	8.70

[a] *Anal.* Calcd.: Cl, 43.24. Found: Cl, 43.19.

was seen. Accordingly, an octadecyl derivative was made and a group of quaternary salts prepared from it. Toxicity was increased, as expected, and activity decreased. All possible permutations of the dialkylaminoalkyl and heterocyclic alkyl side chains and ring systems were not studied as this would involve thousands of compounds. However, representative members studied revealed activity against S-180 and Ca-755 in the bis-quaternary salts of the lower dialkyl (methyl, ethyl)aminoalkyl ($n=2,3$) isoindolines. The basic structures (as hydrochlorides) apparently, on the basis of limited data, undergo a reversal with the longer R′ groups and n values >3, as the diethylaminohexyl derivative of ring 2 is more active than its bis-quaternary ion. The morpholinopropyl derivatives were the most active of the side chains studied.

TABLE III

ANTITUMOR ACTIVITIES

Ring System	R	S-180 (T/C)[a]	Ca-755 (T/C)[a]	KB tissue culture, ED_{50}, μg./ml.
1	Diethylaminoethyl·2MeI	0.57	...	...
1	Morpholinopropyl·2MeI	...	0.33; 0.22	...
2	Morpholinopropyl·MeI	.62	...	...
2	Morpholinopropyl·2MeI	.53; 0.29	...	...
2	Dimethylaminopropyl·2MeI	.48; 0.38	...	...
2	Dimethylaminopropyl·2HCl	.68	...	...
2	Diethylaminohexyl·2HCl	...	.41; 0.38	...
2	Diethylaminohexyl·2MeI	...	.61	...
2	Diethylamino-2-pentyl·2MeI	...	2.01; 1.98	...
2	Decyl·MeI	.49; 0.31	...	2.4
2	Octadecyl·MeI	.62	...	...
2	Piperidinoethyl·2HCl	...	...	6.8
3	Diethylaminoethyl·2MeI	.59; 0.58	...	...
3	Morpholinopropyl·2MeI	.53; 0.29	...	...
4	Methylimido	.43; 0.41	0.56	...
5	Dimethylaminoethyl·2HCl	...	...	2.6
7	Morpholinopropyl·2MeI	.50; 0.16; 0.0009	...	...
7	Decyl·MeI	.59	...	...
7	Decyl·HCl	.47; 0.48	...	...

[a] *T/C* limiting values for the three stages of the sequential analysis for synthetics are ≦0.53; 0.19; 0.07. Blanks in these columns represent negative data while those in the KB column represent no screening data available.

The tissue culture data permit no conclusions except that compounds within the basic structure studied are capable of producing growth inhibition at ED_{50} values within the areas of interest (≦10 μg./ml. at the time of submittal, since revised to ≦ 6 μg./ml.). It would be most helpful to have tissue culture screening data on compounds screened in animal systems for purposes of comparison and possible intercorrelation of the data obtained by *in vivo* and *in vitro* techniques. If we are ever to learn what the screening data from the various screening systems mean, this is one of the necessary preliminary steps. Since negative screening data are published periodically,[7] no attempt has been made to include any more of these data than was necessary for structure–activity discussion.

Pharmacological screening of these compounds (other than anticancer) showed that the hydrogen imides possessed in varying degrees central nervous stimulant and antibarbiturate activity. Again the oxygen bridged rings provided the most active and least toxic compounds.[8] None was superior to 4-ethyl-4-methylglutarimide (Bemegride)[8,9a–c] Substitution of hydrogen by alkyl diminished or abolished this activity.

The amidoximinopropylepoxyisoindoline derivative, because of its structural similarity to certain guanidinoalkyl heterocycles known to possess hypotensive activity,[10] was screened for hypotensive activity in the dog prepared by the external carotid artery cannulation technique[11] and by measurements by femoral artery puncture in the intact unanesthetized animal.[12] Its hypotensive activity was mild and of short duration.

Various derivatives of *unsym*-dimethylhydrazine were prepared and are listed in Table II. These compounds possessed mild local anesthetic, sedative, and tranquilizing properties. All except the ring-halogenated derivatives were remarkably soluble. Most are soluble in cold water as well as hydrocarbon solvents; *i.e.*, ligroin, hexane, and petroleum ether (b.p. 30–60°). The Experimental section gives detailed preparations of those compounds not listed in the tables or previously reported in the literature.

(7) J. Leiter, A. R. Rourke, D. B. Fitzgerald, S. A. Schepartz, and I. Wolinsky, *Cancer Res.* (Supplement), **22**, 221 (1962).

(8) L. F. Sancilio, Ph.D. Thesis, Department of Pharmacology, Georgetown University Medical School (1959).

(9) (a) W. S. Benica and C. O. Wilson, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 451 (1950); (b) *ibid.*, **39**, 454 (1950); (c) J. F. Fazekas and T. Koppanyi, *Anesthesia Analgesia Current Res.*, **33**, 58 (1954).

(10) I. H. Page and H. P. Dustan, *J. Am. Med. Assoc.*, **170**, 1265 (1959).

(11) W. Dameshek and J. Loman, *Am. J. Physiol.*, **101**, 140 (1932).

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

Experimental

All melting points are corrected. Elemental microanalyses were performed at the microanalytical laboratory of the National Institutes of Health, Bethesda, Md., or at Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

1-Methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide.—To 90.5 g. (0.5 mole) of 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride was added 150 ml. of a saturated aqueous solution of ammonia. After the vigorous reaction had subsided, the mixture was stirred and heated until homogeneous. The water was boiled off and the residue heated at 160–180° for 2 hr. On cooling the mass solidified to give a quantitative yield of product melting at 160–162°. On recrystallization from chloroform–ligroin, it melted at 161–162°.

4-Methyl-4,7-epoxyhexahydroisoindoline.—1-Methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide (60 g., 0.3 mole) was placed in a Soxhlet apparatus and extracted overnight into a stirred solution of 25 g. of lithium aluminum hydride in 1.5 l. of absolute ether. The addition complex was decomposed by slow dropwise addition of water, and the mixture was stirred 4 hr. The inorganic precipitate was filtered, pressed tightly on the filter, and washed with two 100-ml. portions of ether. The ethereal filtrate and washings were dried over anhydrous sodium sulfate and filtered. The ether was stripped and the residue was distilled to yield 26 g. (56%) of product, b.p. 123–125° (35 mm.), $n^{25}D$ 1.4926.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.26; H, 9.73; N, 8.98.

The **hydrochloride** was formed by bubbling anhydrous hydrogen chloride gas through an ether solution of the base, m.p. 148.5–149.5°. On recrystallization from methanol–ether, it melted at 150–151°.

Anal. Calcd. for $C_9H_{16}ClNO$: Cl, 18.69. Found: Cl, 18.81.

4-Methyl-4,7-epoxy-2-(2-cyanoethyl)hexahydroisoindoline.—4-Methyl-4,7-epoxyhexahydroisoindoline (19 g., 0.125 mole) was refluxed with a large excess of acrylonitrile (0.5 mole) for 2 hr. and the excess acrylonitrile was distilled. The residual oil was distilled under reduced pressure to give 24.5 g., 93%, of the compound, b.p. 158–160° (6 mm.).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 68.92; H, 8.54; N, 13.31.

The **methiodide** was obtained as a tacky yellow material by refluxing the base with a 10% excess of methyl iodide in ethyl acetate and diluting with ether. Vacuum drying for several days at room temperature gave a solid material, m.p. 156–157°, which on recrystallization from methanol–ether and methylene chloride–ether, melted at 165–166°.

Anal. Calcd. for $C_{13}H_{21}INO$: I, 36.45. Found: I, 36.56.

4-Methyl-4,7-epoxy-2-(3-amidoximinopropyl)hexahydroisoindoline Dihydrochloride.—To a solution of 14 g. of hydroxylamine hydrochloride in 300 ml. of absolute ethanol was added 41.2 g. (0.2 mole) of 4-methyl-4,7-epoxy-2-(2-cyanoethyl)hexahydroisoindoline. When a homogeneous solution was obtained, a solution of 4.6 g. (0.2 mole) of sodium in 150 ml. of absolute ethanol was added with stirring. The mixture was refluxed 3 hr. and let stand overnight. The next day, the mixture was filtered and gaseous hydrogen chloride bubbled in until precipitation was complete. After adding an equal volume of ether, mixing, and allowing the precipitate to settle, the product was filtered, washed with cold ethanol, and dried. It melted at 162–164° and on recrystallization from alcohol–ether at 163–165°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N_3O_2$: C, 46.15; H, 7.37; Cl, 22.71. Found: C, 45.88; H, 7.01; Cl, 23.32.

Hypotensives. VI.[1] Disubstituted Alkylenediamines and Related Compounds

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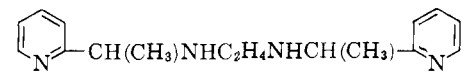
In an earlier report on studies of substituted alkylenediamines as diuretic agents we described a fleeting hypotensive action for some of the compounds.[3] These findings led directly to a related and orally effective adrenolytic agent, N,N′-bis[α-(2-pyridyl)ethyl]-ethylenediamine (I). The pharmacologic properties of



I

this material were the subject of a recent report by Halliday, *et al.*[4] Since compound I offered some promise, a structure–activity study was undertaken to determine the requirements for optimal activity. A few substituted alkylenediamines not closely related to the compounds discussed here are reported by Schusteritz, *et al.*,[5] and Short, *et al.*,[6] to possess adrenolytic or antihypertensive properties.

Compound I and most of the analogs reported here were prepared by condensing 2 equiv. of a carbonyl compound with an alkylenediamine to afford symmetrical Schiff bases. Catalytic reduction of the crude Schiff bases usually proceeded in good yield to the expected products, which were isolated by distillation. A similar method was utilized by Lacoste[7] to prepare VI (Table I) and by Szabo[8] for the synthesis of related alkylenediamines. All of the compounds listed in Table I except IV, VII, VIII, and XIII, were prepared in this manner and converted to the indicated salts. Compound IV was isolated and purified as a salt since the base was thermally unstable. Compound VII was generated by addition of ethylenediamine to 2-vinylpyridine under acid catalysis. Compound VIII resulted from the catalytic reduction over platinum of the commercially available azine in acetic acid followed by isolation and purification as the diacetate. Catalytic reduction of I over rhodium-on-alumina in the presence of acid provided XIII.

Another group of allied materials is listed in Table II. Displacement reactions on 2-(α-bromoethyl)pyridine[10] with *t*-butylamine, piperidine, trimethylamine, ethylenediamine, and 1-(*o*-methoxyphenyl)piperazine gave XIV, XV, XVI, XVII, and XVIII, respectively. The possibility of dehydrobromination of 2-(α-bromoethyl)-pyridine to 2-vinylpyridine followed by amine addition to the corresponding 2-(β-aminoethyl)pyridine was investigated. Piperidine was condensed with 2-vinylpyridine to afford XIX which was not identical with XV. Reductive aminations with 2-acetylpyridine and the appropriate amines were tried but found less satisfactory as a preparative route to some of these materials

(1) Paper V: J. E. Robertson, J. H. Biel, and F. DiPierro, *J. Med. Chem.*, **6**, 381 (1963).

(2) Central Research Laboratories, Minnesota Mining and Manufacturing Co., St. Paul, Minn.

(3) J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.*, **81**, 2527 (1959).

(4) R. P. Halliday, W. J. Kinnard, and J. P. Buckley, *Pharmacologist*, **4**, 148 (1962).

(5) L. Schusteritz, G. Stille, M. Walter, and V. Wolf, *Arzneimittel-Forsch.*, **9**, 628 (1959).

(6) J. H. Short, W. L. Chan, M. Freifelder, D. G. Mikolasek, J. L. Schmidt, H. G. Schoepke, C. Shannon, and G. R. Stone, Abstracts of Papers, 144th National Meeting, American Chemical Society, Los Angeles, California, April, 1963, p. 10-L.

(7) R. G. Lacoste, Ph.D. Thesis, Clark University, Worcester, Mass., 1957.

(8) J. L. Szabo, D. Hill, and W. F. Bruce, U. S. Patents 2,627,491, 2,739,981, and 2,876,236.

(9) Aldrich Chemical Co., Milwaukee, Wis.

(10) B. H. Walker, *J. Org. Chem.*, **25**, 1047 (1960).