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3-Amino-4-halosydnone Imines. A New Type of Antihypertensive Agent

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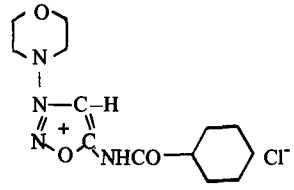
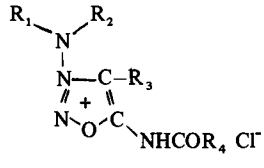
The preparation, some spectral data, and the antihypertensive properties of 3-amino-4-halosydnone imines are described. These compounds are closely related to the previously discovered 3-aminosydnone imines and show a similar, if not a more pronounced, blood pressure lowering effect on oral administration to hypertensive rats.

The discovery of the pronounced blood pressure lowering effects of 3-aminosydnone imines,[1-5] as exemplified by N^6-cyclohexylcarbonyl-3-morpholinosydnone imine hydrochloride (PR-G-138),[3] provided an incentive for further modification of this mesoionic system. It was found[3] that



PR-G-138



I

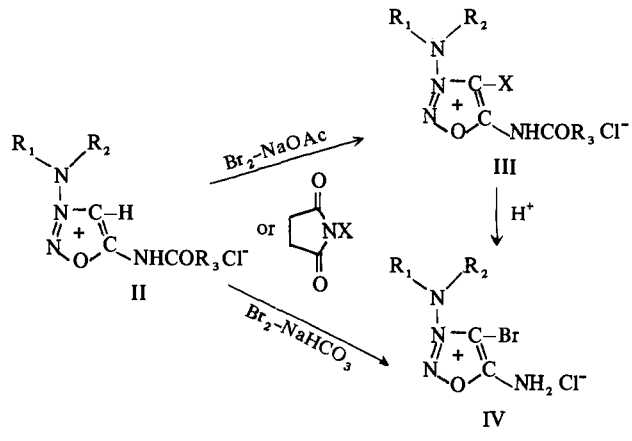
$R_3 = CH_3, CH_2CH_3, CH_2CH_2Ph$

the presence of hydrogen in the 4 position of the sydnone imine ring was of crucial importance for the antihypertensive activity. Replacement of this hydrogen by a methyl, ethyl, or aralkyl group as in I decreased the blood pressure lowering effect dramatically. The inactivation caused by the substituent R_3 could be due to its bulk, which inhibits the approach to the receptor, or to rapid oxidation of the additional alkyl group, a metabolic pathway commonly encountered with drugs containing an alkyl group attached to an aromatic ring.[6] To distinguish between these two alternatives, chlorine, bromine, and iodine were introduced into the 4 position. The halogen atoms provided considerable bulk and were at the same time not prone to metabolic changes.

Pharmacological investigation of the halogenated compounds of formula III and IV (Table I) showed that most of them retained the antihypertensive activity of N^6-cyclohexylcarbonyl-3-morpholinosydnone imine hydrochloride and related substances or caused an even more pronounced fall in blood pressure.

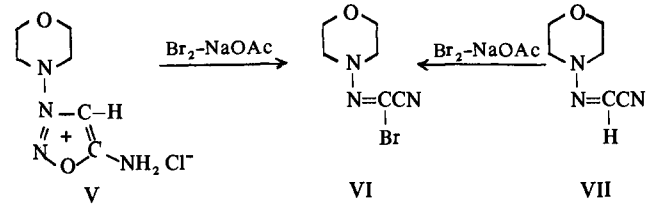
Chemistry. The use of elemental bromine for the preparation of acylated 4-bromosydnone imines has been described previously,[7,8] but the process has not been applied to acylated 3-aminosydnone imines. Bromination of II in the presence of sodium bicarbonate led to concomitant loss of the acyl group (IV, Scheme I) which could be avoided by employing sodium acetate as a buffer. Deacylation of III occurred also under mildly acidic conditions. Elemental chlorine and iodine proved unsuitable for the synthesis of the desired 4-chloro and iodo derivatives III. The use of *N*-halosuccinimide was therefore investigated and was found satisfactory for the introduction of all three halides. Bromination of compounds without an acyl group (V, Scheme II) gave the unexpected VI. The structure of VI was confirmed through its preparation by bromination of VII previously obtained by basic hydrolysis of 3-aminosydnone imines.[9,†] The presence of halide in the 4 position surprisingly gave rise to only minor changes in the ir, uv, and nmr spectra, compared to the starting material (Table II).

Scheme I



X = Cl, Br, I

Scheme II



Antihypertensive Activity. The antihypertensive activity was determined after oral administration of the substance to either Skelton hypertensive rats[10] or to spontaneously hypertensive rats (SHR, NIH strain). The blood pressure was measured indirectly from the tail artery using a Narco electrosphygmomanometer. The changes in blood pressure are the averages obtained in groups of six animals (Table I). The hypotensive response occurred within minutes and was maintained for at least 3 hr.

The structure-activity relationships closely followed those observed in the nonhalogenated series[3] (X = H). Again the nature of R_1 and R_2 was not very critical for activity, even the dimethyl derivative **1** showed a pronounced blood pressure lowering effect. If R_1 was benzyl (**19**), only high doses produced a blood pressure depression and branching of R_1 as in **20** and **21** completely abolished activity, as was the case in the nonhalogenated series. No clear-cut activity pattern evolved on comparing acylated and nonacylated compounds. Remarkable and unexpected was the finding of complete lack of antihypertensive effect of the acetylated substances **4**, **8**, and **22**. The corresponding compounds in the nonhalogenated series were all active. The decrease in blood pressure caused by the chloro and bromo derivatives **12** and **13** was quite similar to that produced by the starting

†M. Götz and K. Grozinger, unpublished results.

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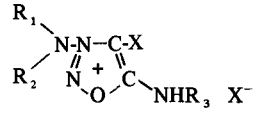
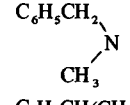
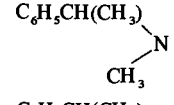
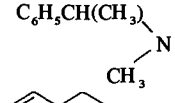
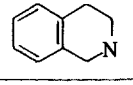
Table I

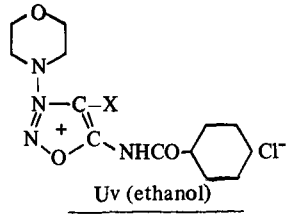


III and IV

Compd	R_1R_2N	R_3	X	Method[a]	Yield, %	Mp, °C dec	Crystn solvent	Formula	Analyses	mg/kg[b] po	Δbp, mm
1	$(CH_3)_2N$	H	Br	C	63	159	MeOH–petroleum ether	$C_4H_9BrN_4O \cdot HBr$	H, N; C[c]	10	−40
2	$(CH_3)_2N$	Nicotinoyl	Br	B	28	171	MeOH–Et_2O	$C_{10}H_{10}BrN_5O_2 \cdot HBr$	C, H, N	10	−30
3	Piperidino	H	Br	B	85	140	IPA–Et_2O	$C_7H_{11}BrN_4O \cdot HBr$	C, H, N	10	−35
4	Piperidino	$COCH_3$	Br	B	51	98	MeOH–Et_2O	$C_9H_{13}BrN_4O_2 \cdot HBr$	C, H, N	25	0
5	Piperidino	$COOC_2H_5$	Br	A	17	137	EtOH–Et_2O	$C_{10}H_{15}BrN_4O_2 \cdot HCl$	C, H, N, Br, Cl	10	−30 (SHR)
6	Piperidino	$COOC_2H_5$	Cl	A	13	131	EtOH–Et_2O	$C_{10}H_{15}ClN_4O_3 \cdot HCl$	C, H, Cl, N	10	−20 (SHR)
7	Azepino	H	Br	A	31	142	IPA–Et_2O	$C_8H_{13}BrN_4O \cdot HCl$	C, H, N, Br, Cl	10	−20 (SHR)
8	Azepino	$COCH_3$	Cl	A	15	147	CH_3CN	$C_{10}H_{15}ClN_4O_2 \cdot HCl$	C, H, Cl, N	10	0 (SHR)
9	Azepino	$COOC_4H_9$	Br	A	41	109–110	IPA–Et_2O	$C_{13}H_{21}BrN_4O_3 \cdot HBr$	H, Br, N; C[d]	100	−30 (SHR)
10	Morpholino	H	Br	A	38	170	MeOH–Et_2O	$C_6H_9BrN_4O_2 \cdot HBr$	C, H, N	10	−30
				B	10						
11	Morpholino	H	Cl	A	52	160	MeOH–Et_2O	$C_6H_9ClN_4O_2 \cdot HCl$	C, H, Cl, N	10	−30 (SHR)
12	Morpholino	Cyclohexylcarbonyl	Cl	A	81	135	MeOH–Et_2O	$C_{13}H_{19}ClN_4O_3 \cdot HCl$	C, H, Cl, N	10	−40
13	Morpholino	Cyclohexylcarbonyl	Br	B	74	150	MeOH–Et_2O	$C_{13}H_{19}BrN_4O_3 \cdot HCl$	C, H, N	10	−40
14	Morpholino	Cyclohexylcarbonyl	I	A	8	158–160	MeOH–Et_2O	$C_{13}H_{19}IN_4O_3 \cdot HCl$	C, H, N	20	−35
15	Morpholino	$COOC_2H_5$	Cl	A	19	165	MeOH–Et_2O	$C_9H_{13}ClN_4O_4 \cdot HCl$	C, H, Cl, N	10	−25 (SHR)
16	Morpholino	$COOC_2H_5$	Br	A	65	168	MeOH–Et_2O	$C_9H_{13}BrN_4O_4$	C, H, Br, N	10	−30 (SHR)
17	Morpholino	$COOC_2H_5$	I	A	72	165	MeOH–Et_2O	$C_9H_{13}IN_4O_4$	C, H, I, N	10	−20 (SHR)
18	c-$N(CH_2CH_2)_2N$-CH_3	COO-C_6H_5	Br	A	63	106–108	MeOH–Et_2O	$C_{14}H_{16}BrN_5O_3 \cdot 2HBr \cdot H_2O$	C, N; H,[e] Br[f]	10	−35 (SHR)
19		CO-C_6H_4-*o*-Cl	Br	B	40	98–99	MeOH–Et_2O	$C_{17}H_{14}BrClN_4O_2 \cdot HBr$	C, H, N	30	0 (SHR)
20		$COCH_3$	Br	B	36	104–105	MeOH–Et_2O	$C_{13}H_{15}BrN_4O_2 \cdot HBr \cdot H_2O$	C, H, N	100	0
21		$COOCH_3$	Br	A	35	94–95	IPA–Et_2O	$C_{13}H_{15}BrN_4O_3 \cdot HBr$	C, H, Br, N	100	0 (SHR)
22		$COCH_3$	Br	B	10	124	MeOH–Et_2O	$C_{13}H_{13}BrN_4O_2 \cdot HBr$	C, H, N	100	0

[a] A, halo succinimide; B, Br_2–NaOAc; C, Br_2–$NaHCO_3$. [b] Six rats were used in the control group. Blood pressure increased at 1 hr by 3 mm with a standard error of the mean of ±2 mm. [c] C: calcd, 16.68; found, 16.19. [d] C: calcd, 35.31; found, 34.88. [e] H: calcd, 3.58; found, 4.06. [f] Br: calcd, 42.66; found, 43.12.

Table II



	X	Ir (KBr), cm^{-1}	Uv (ethanol) λ_{max}, mμ	ε	Nmr (DMSO), τ
PR-G-138	H	1725, 1625	325 243	11,400 9,100	3N-CH_2, 3.83 4C-H, 9.22
12	Cl	1727, 1625	348 254	10,500 10,000	3N-CH_2, 3.97
13	Br	1720, 1620	348 250	9,500 9,000	3N-CH_2, 3.88
14	I	1720, 1600	350 253	6,000 7,800	3N-CH_2, 4.01

material PR-G-138 (10 mg/kg po, –40 mm, SHR). The iodo compound **14** appeared slightly less active, as did the iodo compound of the series **15–17**. The pharmacological profile‡ and a favorable therapeutic index make the 3-amino-4-halosydnone imines promising candidates for further evaluation.

Experimental Section§

The nmr spectra were determined on a Varian A-60; uv spectra were recorded on a Bausch and Lomb 505 and the ir spectra on a Perkin-Elmer Infracord 237B.

Method A. Halosuccinimide. The acylated 3-aminosydnone imine hydrochloride was dissolved in H_2O, basified with excess Na_2CO_3 solution, and extracted into $CHCl_3$. The solution was dried and evaporated. To 0.05 mol of free base dissolved in 150 ml of CCl_4, 0.15 mol of *N*-halosuccinimide was added.# The mixture was heated to 75° for 3 hr,** cooled and mixed with 100 ml of H_2O, and worked up as usual. The residue was dissolved in MeOH and acidified with HCl–Et_2O and crystallized.

Method B. Br_2–NaOAc. To 0.05 mol of 3-aminosydnone imine hydrochloride suspended in 350 ml of Et_2O, 16 g of NaOAc was added. At reflux temperature 16 g (0.1 mol) of Br_2 in 25 ml of $CHCl_3$ was dropped in and refluxed 5 hr. The mixture was cooled and filtered and filtrate evaporated to dryness. The residue was dissolved in EtOH, acidified with HCl, and crystallized.

Method C. Br_2–$NaHCO_3$. 3-Aminosydnone imine hydrochloride (0.05 mol) suspended in 20 ml of $CHCl_3$ and 300 ml of Et_2O were refluxed with 25 g of $NaHCO_3$ under stirring. Br_2 (12 g, 0.75 mol) was dropped in. The mixture was refluxed for 3 hr, cooled, and filtered and the filtrate evaporated. The residue was crystallized.

Hydrolysis of Acylated 3-Amino-4-halosydrone Imines (III → IV). III (0.01 mol) dissolved in 50 ml of H_2O was left at room temperature for 1 week. The clear solution was repeatedly extracted with Et_2O to remove the organic acid. The aqueous layer was evaporated to dryness and crystallized. Compounds 8, 12, 15, and 16 were obtained by this method.

Bromo(morpholinoimino)acetonitrile from 3-Morpholinosydnone Imine Hydrochloride (VI from V). To 0.1 mol of V and 32 g of NaOAc suspended in 600 ml of Et_2O, 32 g (0.2 mol) of Br_2 in 50 ml of $CHCl_3$ was added under reflux. The mixture was heated for 4 hr and filtered and filtrate concentrated to dryness. The residue was crystallized from Et_2O–petroleum ether: yield 5.0 g (23%); mp 54–56°; ir (KBr) 2200, 1575 cm^{-1}; uv (EtOH) λ_{max} 282, 230 nm (ε 8700, 3500).

Bromo(morpholinoimino)acetonitrile from (Morpholinoimino)-acetonitrile (VI from VII). To a solution of 0.1 mol of VII in 200 ml of Et_2O, 23 g of NaOAc was added. The mixture was refluxed and 24 g (0.15 mol) of Br_2 in 50 ml of $CHCl_3$ was dropped in, refluxed 2 hr, cooled, and filtered and filtrate evaporated: yield 6.0 g (25%); mp 54–55° (Et_2O–petroleum ether); ir, uv, and tlc identical with VI from V.

‡The detailed pharmacology will be published separately: J. T. Oliver, unpublished results.

§Where analyses are indicated only by symbols of the elements, analytical results were obtained within ±0.4% of the theoretical values.

#For chlorinations a trace of benzoyl peroxide was added.

**Occasionally the reaction proceeded satisfactorily also at room temperature.

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Potential Antitumor Agents. 13. Bisquaternary Salts

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Forty-two variants of bisquaternary salts of 4-[*p*-(*p*-(4-pyridylamino)phenylcarbamoyl)anilino]-quinoline have been synthesized for evaluation in the L1210 system. The N^1-alkyl-4-pyridylamino cationic function could be replaced by N^1-alkyl-4-pyridyl-, N^1-alkyl-5-(2,4-diaminopyrimidinyl)-, or amidinohydrazone and L1210 activity retained. Congeners substituted in the quinoline ring (Cl, CH_3, OCH_3, NO_2, NH_2) were screened and when the log *P* contribution of the quinoline substituent to antileukemic activity was compensated for, it appeared that electron-donor substituents provided the most L1210 active compounds. Reversal of the central –CONH– bond or replacement by –NHCONH– or –CH=CH– provided L1210 active molecules. 6- or 7-aminoquinoline variants were highly active and provided numbers of indefinite survivors in early ip L1210 tests. The 7-NO_2 quinoline congeners showed anomalously high activity while all 6-NO_2 variants proved inactive.

Series of bisquaternary ammonium heterocycles prepared earlier showed very high apparent activity in L1210 tests, some examples producing *T/C* values of greater than 300%.[1-8] In leukemic test groups treated for five consecutive days with certain of these agents (*e.g.*, I, R′ = H; R = C_2H_5), it was found that the animals dying later than 30 days after the start of dosing were free of leukemia. Such findings could have been predicted by extrapolating the