Antineoplastic Agents. XVIII. N-(2-Haloethyl)benzylamines[1,2]

G. R. PETTIT,[3] S. K. GUPTA, AND P. A. WHITEHOUSE

Departments of Chemistry, Arizona State University, Tempe, Arizona 85281, and University of Maine, Orono, Maine 04473

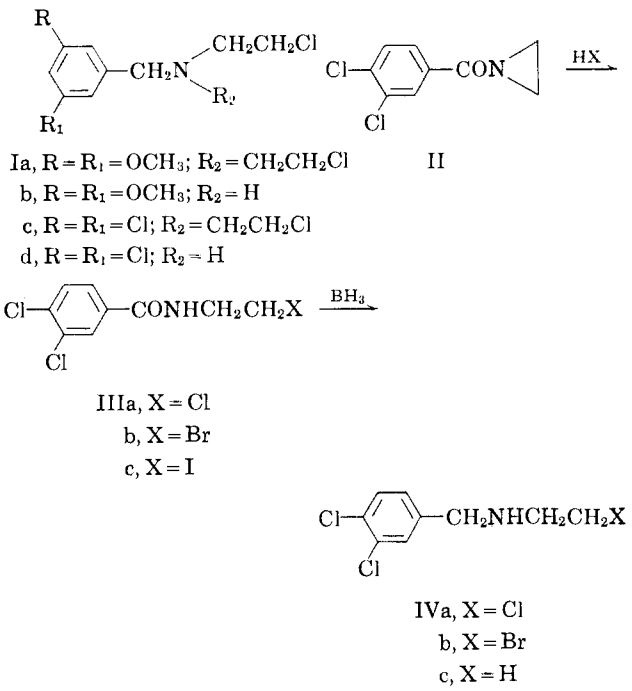
Received January 10, 1967

A series of N-benzyl-N-(2-haloethyl)amines have been synthesized for comparison of possible antineoplastic properties with those of the corresponding N-bis(2-chloroethyl)amines. Conversion of 3,4-dichlorobenzoylaziridine (II) with HCl or HBr to, respectively, amides IIIa and IIIb followed by a diborane reduction sequence yielding amines IVa and IVb outlines the synthetic methods employed. Several N-2-iodoethylamides of the type illustrated by structure IIIc were prepared from the corresponding aziridine amide employing HI or from a N-2-chloroethylamide precursor using NaI in acetone. Reaction between the N-2-iodoethylamides and diborane (in tetrahydrofuran) at approximately 60° for 2 hr or at room temperature (overnight) was shown to cause virtually complete hydrogenolysis of the C–I bond. Presently available biological results indicate the N-(2-chloroethyl)-benzylamines to be considerably less active than the corresponding N-bis(2-chloroethyl)benzylamines.

Based on an earlier study[4a] of the aromatic system of podophyllotoxin as a carrier group for nitrogen mustards, it became necessary to prepare a number of N-benzyl-N-bis(2-haloethyl)amines.[4b-d] Several of the resulting benzylamines displayed potentially useful antineoplastic properties.[4b,d] The present investigation was undertaken to evaluate the possibility of uncovering useful cancer chemotherapeutic properties among the corresponding N-benzyl-N-(2-haloethyl)-amines (*e.g.*, amine Ia *vs.* Ib).

Some N-(2-chloroethyl)amines such as 1,6-(2-chloroethylamino)-1,6-dideoxy-D-mannitol dihydrochloride have reached clinical trial[5] and others have given evidence of antineoplastic activity.[6] Generally these "one-armed" nitrogen mustards have been considered less useful. To determine the relative merits of certain benzylamine carrier groups for N-(2-haloethyl)-amines, synthesis of the substances summarized in Table III was undertaken. Scheme I illustrates the general route found most satisfactory for obtaining benzylamines of this type.[7] Selection of the aziridine benzamides as intermediates resided with their ready entry into ring-opening reactions and availability of the corresponding benzoic acids. In each case the amide was prepared from the corresponding aroyl chloride and aziridine in the presence of aqueous KOH.

SCHEME I



Treating, for example, amide II in $CHCl_3$ with HCl readily opened the aziridine ring[8] to afford a quantitative yield of N-(2-chloroethyl)-3,4-dichlorobenzamide (IIIa). Several of the N-(2-chloroethyl)amides were also prepared using concentrated HCl to open the aziridine ring or by eliminating aqueous KOH from the initial aroyl chloride–aziridine condensation reaction. However, the latter procedure was considered less satisfactory than the hydrogen chloride technique. Similar reaction between amide II (Table I) and hydrogen bromide provided the corresponding bromo derivative IIIb. In several cases, the N-(2-bromoethyl)amides were obtained by displacing chloride from a N-(2-chloroethyl)amide precursor using LiBr

(1) For Part XVII refer to G. R. Pettit and M. R. Chamberland, *Can. J. Chem.*, **44**, 813 (1966).

(2) This investigation was aided by Grants No. T-79F and T-79G from the American Cancer Society.

(3) Department of Chemistry, Arizona State University.

(4) (a) G. R. Pettit and J. A. Settepani, *J. Org. Chem.*, **27**, 2962 (1962); (b) G. R. Pettit, M. R. Chamberland, D. S. Blonda, and M. Vickers, *Can. J. Chem.*, **42**, 1699 (1964); (c) G. R. Pettit and R. L. Smith, *ibid.*, **42**, 572 (1964); (d) G. R. Pettit, D. S. Blonda, and E. Harrington, *ibid.*, **41**, 2962 (1963).

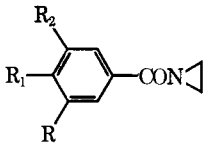
(5) L. F. Larionov, "Cancer Chemotherapy," Pergamon Press Inc., New York, N. Y., 1965, p 294.

(6) R. M. Peck, A. P. O'Connell, and H. J. Creech, *J. Med. Chem.*, **9**, 217 (1966); H. Z. Sommer, C. Scher, S. Bien, G. Olsen, J. K. Chakrabarti, and O. M. Friedman, *ibid.*, **9**, 84 (1966); P. Hebborn and D. J. Triggle, *ibid.*, **8**, 541 (1965); R. F. Pittillo, A. J. Narkates, and J. Burns, *Cancer Res.*, **24**, 1222 (1964); F. M. Schabel, Jr., T. P. Johnston, G. S. McCaleb, J. A. Montgomery, W. R. Laster, and H. E. Skipper, *ibid.*, **23**, 725 (1963); W. W. Lee, B. J. Berridge, Jr., L. O. Ross, and L. Goodman, *J. Med. Chem.*, **6**, 567 (1963); K. Sawatari, *Chem. Pharm. Bull.* (Tokyo), **10**, 390 (1962).

(7) For a recent review of synthetic routes to N-(2-haloethyl)amines see: J. N. Singh and A. B. Lal, *J. Indian Chem. Soc.*, **43**, 308 (1966); C-Y. Wu and R. E. Robertson, *Chem. Ind.* (London), 195 (1966); N. J. Leonard, R. Y. Ning, and R. L. Booth, *J. Org. Chem.*, **30**, 4357 (1965); G. F. Hennion and A. C. Hazy, *ibid.*, **30**, 2650 (1965); N. J. Leonard and J. V. Paukstelis, *ibid.*, **30**, 821 (1965); R. B. Moffett, *J. Med. Chem.*, **7**, 319 (1964); L. S. Yaguzhinskii and A. Ya. Berlin, *J. Gen. Chem. USSR*, **33**, 3004 (1963); N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 4835 (1963); N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963); see also ref 6.

(8) For a review of N-substituted aziridines consult: G. Allen, D. J. Oldfield, N. L. Paddock, F. Rallo, J. Serregi, and S. M. Todd, *Chem. Ind.* (London), 1032 (1965); D. Rosenthal, G. Brandrup, K. H. Davis, Jr., and M. E. Wall, *J. Org. Chem.*, **30**, 3689 (1965); A. T. Bottini and R. L. Van Etten, *ibid.*, **30**, 575 (1965); G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *ibid.*, **30**, 666 (1965); C. W. Woods, A. B. Borkovec, and F. M. Hart, *J. Med. Chem.*, **7**, 371 (1964); U. Harder, E. Pfeil, and K-F. Zenner, *Ber.*, **97**, 510 (1964); M. Beroza and A. B. Borkovec, *J. Med. Chem.*, **7**, 44 (1964); A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964); H. W. Heine, *J. Am. Chem. Soc.*, **85**, 2743 (1963); H. W. Heine, *Angew. Chem.*, **74**, 772 (1962).

TABLE I



R	R_1	R_2	Yield,[b] %	Solvent[c]	Mp,[d] °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
	CH_3O		85.5	1	76.5	$C_{10}H_{11}NO_2$	67.79	67.99	6.26	6.24	7.90	8.02
CH_3O	CH_3O		72	1	86	$C_{11}H_{13}NO_3$	63.76	63.56	6.32	6.46	6.76	6.90
—OCH_2O—			75	1	62.5	$C_{10}H_9NO_3$	62.82	62.67	4.74	4.72	7.33	7.66
CH_3O	CH_3O	CH_3O	90	2	61–62	$C_{12}H_{15}NO_4$[e]	60.75	60.87	6.32	6.42	5.90	5.84
CH_3O	CH_3O	CH_3O[a]	75	2	70.5–71	$C_{13}H_{17}NO_4$	62.15	62.36	6.82	6.95		
	F		35	3	42.5–43	C_9H_8FNO	65.44	65.00	4.72	5.25		
Cl	Cl		80	2	97.5–98	$C_9H_7Cl_2NO$[f]	50.00	50.03	3.24	3.45	6.48	6.33
CH_3		CH_3	60	..	Oil[g]	$C_{11}H_{13}NO$	75.40	75.35	7.48	7.63	7.99	7.93

[a] Represents 3,4,5-trimethoxyphenethyl. [b] Over-all yield from the corresponding acid and based on recrystallized amide. [c] The amide was recrystallized from (1) benzene–hexane, (2) benzene–petroleum ether, (3) petroleum ether. [d] Melting point of the colorless analytical sample. [e] *Anal.* Calcd: O, 27.00. Found: O, 27.20. [f] *Anal.* Calcd: Cl, 32.87. Found: Cl, 32.67. [g] Purified by chromatography (eluted with benzene) on silica gel, $n^{29}D$ 1.5464.

n acetone. Again, the HBr technique was considered superior. The N-(2-iodoethyl)amides such as IIIc were easily obtained from the N-(2-chloroethyl)amides using NaI in acetone solution or by treating the corresponding aziridine amide with hydriodic acid.

The N-(2-haloethyl)amides summarized in Table II did not display the great sensitivity to moisture exhibited by the corresponding N-bis(2-haloethyl)-amides prepared earlier.[4c] In fact, the amide → ester rearrangement reaction generally observed with N-bis(2-haloethyl)amides was not encountered in the present study. Although this point was not pursued, prolonged heating in H_2O might cause rearrangement of these N-(2-haloethyl)amides, since Fry[9] has reported rearrangement of α-benzoylamino-β-chloropropionic acid to O-benzoylserine in hot H_2O.

The previously reported[10] successful reduction of various amides to amine derivatives by diborane combined with our own experience (*e.g.*, ref 11) with this mild and versatile reagent clearly indicated that diborane should be the reagent of choice for converting the N-(2-haloethyl)amides to the corresponding benzylamines (III → IV). The chloro- and bromoethylamide reduction to the respective benzylamines was easily achieved using commercially available 1 *M* diborane in THF solution at room temperature. Under the same conditions, the N-(2-iodoethyl)amides (*e.g.*, IIIc) underwent hydrogenolysis of the carbon–iodine bond. When the reduction reaction was repeated at approximately 60° for 2 hr, hydrogenolysis again constituted the major reaction pathway. By this means amide IIIc was converted in nearly quantitative yield to N-ethylamine IVc. As the N-(2-iodoethyl)benzylamines were considered of much less interest than the chloro and bromo derivatives, further effort in this direction was discontinued.[12] All but one of the substances summarized in each of Tables II and III have nitrogen one carbon removed from the aromatic system. For comparison purposes, synthesis of N-(2-chloroethyl)-3,4,5-trimethoxyphenethylamine hydrochloride, a two-carbon system characteristic of mescaline,[4d] was included.

Structures assigned each of the amides (Table II) and the amine hydrohalides (Table III) were supported by results of infrared spectral analysis and nmr studies. The pmr survey of these substances was carried out as part of another study and experimental results will be reported in a future communication.[13] The number of similar compounds available for infrared spectral study led to some observations which can now be recorded. A summary of these results appears in Table IV.

Biological evaluations are being performed under guidance of the Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service, and results available at present indicate that, in general, the N-(2-haloethyl)benzylamines will be less active than the N-bis(2-haloethyl)benzylamines against Walker 256 (subcutaneous) in randomly bred albino rats. Comparison of two of the more promising N-bis(2-chloroethyl)benzylamines prepared in our laboratory, namely, Ia[4b] and Ic,[14] with the respective one-armed derivatives Ib and Id reported here provide support (at present) for such a conclusion. At a dose of 4.8 mg/kg tertiary amine Ia completely inhibited tumor growth while the corresponding secondary amine Ib at 50 mg/kg led to only about 10% inhibition of tumor growth. Similarly, tertiary amine Ic·HCl at 50 mg/kg gave approximately 96% inhibition of growth, whereas secondary amine Id·HCl at the same dose level was ineffectual; raising the dose of amine Id hydrochloride to 100 mg/kg afforded only 15% inhibition of growth. Doubling the dose to 200 mg/kg resulted in approximately 17% mortality and, in the survivors, 52% inhibition of tumor growth. In each case, the substance was given intraperitoneally in saline solution on the first day of tumor transplant and continued for 5 days. Evaluation of tumor growth was made on the tenth day.

(9) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).

(10) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964); Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, **29**, 2870 (1964); and W. V. Curran and R. B. Angier, *ibid.*, **31**, 3867 (1966).

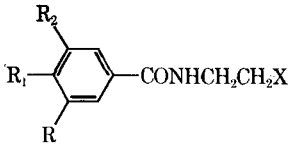
(11) G. R. Pettit and W. J. Evers, *Can. J. Chem.*, **44**, 1293 (1966).

(12) The 2-iodoethylamines should be easily obtainable by treating the N-2-chloroethylamines with NaI–acetone (*cf.* ref 4d).

(13) The mass spectrum of each substance was also found consistent with the assigned structure and for the reason just noted, the spectra will be discussed in a future contribution.

(14) The chemistry of this substance will be described in a subsequent paper by G. R. Pettit, P. A. Whitehouse, and M. A. Sciaraffa, in preparation.

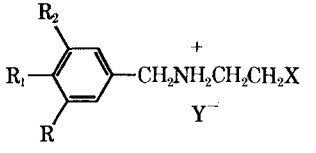
TABLE II



R	R_1	R_2	X	Yield,[b] %	Method[d]	Solvent[e]	Mp,[f] °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
			I	55	1	1	110.5	$C_9H_{10}INO$	39.27	39.39	3.63	3.83	46.18	46.32	5.09	5.20
CH_3	CH_3		Cl	80	2	1	143.5–144	$C_{11}H_{14}ClNO$	62.40	62.43	6.63	6.71	16.75	16.67	6.63	6.61
CH_3	CH_3		Br	50	3	1	139–140	$C_{11}H_{14}BrNO$	51.56	51.72	5.50	5.51	31.20	31.07	5.44	5.40
CH_3	CH_3		I	65	1	1	137.5–138	$C_{11}H_{14}INO$	43.56	43.67	4.62	4.83	41.86	42.02	4.62	4.53
CH_3		CH_3	Cl	80	4	1	103–104, 109.5–110	$C_{11}H_{14}ClNO$	62.40	62.61	6.63	6.73			6.63	6.89
CH_3		CH_3	I	65	1	1	88–88.5	$C_{11}H_{14}INO$	43.56	43.65	4.62	4.72			4.62	4.80
CH_3O		CH_3O	Cl	95	2	2	94–94.5	$C_{11}H_{14}ClNO_3$	54.21	54.23	5.79	5.86	14.54	14.55	5.74	5.61
	CH_3O		Cl	85	4	1	132–132.5	$C_{10}H_{12}ClNO_2$	56.20	56.23	5.62	5.82	16.59	16.70	6.55	6.70
	CH_3O		Br	80	5	2	165–166.5	$C_{10}H_{12}BrNO_2$	46.51	46.59	4.60	4.89	30.96	30.76	5.42	5.26
—OCH_2O—			Cl	95	4	1	98–99	$C_{10}H_{10}ClNO_3$	52.74	52.35	4.42	4.43	15.57	15.35	6.15	5.95
—OCH_2O—			Br	90	5	1	159–160	$C_{10}H_{10}BrNO_3$	44.13	44.18	4.37	3.83	29.36	29.69	5.14	5.34
—OCH_2O—			I	60	6	1	196–197.5[g]	$C_{10}H_{10}INO_3 \cdot H_2O$	35.60	35.80	3.56	3.73	37.68	37.87	4.15	4.22
CH_3O	CH_3O		Cl	80	2	1	129–130	$C_{11}H_{14}ClNO_3$	54.20	54.04	5.74	5.78			5.74	5.98
CH_3O	CH_3O		Br	75, 55	3, 5	1, 2	193–194	$C_{11}H_{14}BrNO_3$	45.83	45.71	4.89	4.99	27.77	27.64		
CH_3O	CH_3O		I	50	6	2	179–180	$C_{11}H_{14}INO_3$	39.40	39.63	4.21	4.25	37.86	37.95	4.18	4.05
CH_3O	CH_3O	CH_3O	Cl	70	2	1	137–137.5[h]	$C_{12}H_{16}ClNO_4$	52.65	52.76	5.86	5.96	13.00	12.86	5.15	5.24
CH_3O	CH_3O	CH_3O	I	80	6	1	144.5–145	$C_{12}H_{16}INO_4$	39.45	39.50	4.38	4.46	34.79	34.92	3.83	3.58[i]
CH_3O	CH_3O	CH_3O[c]	Cl	80	2	1	101.5–102[j]	$C_{13}H_{18}ClNO_4$	54.26	54.45	6.30	6.42	12.35	12.27	4.87	4.97
F			Cl	75	2	3	95–95.5	C_9H_9ClFNO[k]	53.61	54.05	4.50	4.82	17.59	17.67[l]	6.94	7.21
	F		Cl	80	4	1	113–113.5	C_9H_9ClFNO[k]	53.61	54.12	4.50	4.63	17.66	17.57[l]	6.94	6.98
CF_3			Cl	78	2	3	64–65	$C_{10}H_9ClF_3NO$	47.72	47.65	3.60	3.41	14.08	14.03	5.56	5.59
CF_3		CF_3	Cl	80	2	3	102.5–103	$C_{11}H_8ClF_6NO$	41.33	41.25	2.52	2.50	11.09	11.06[l]	4.32	4.42
Cl			Cl	85	2	3	85–85.5	$C_9H_9Cl_2NO$	49.56	49.57	4.15	4.43	32.51	32.33	6.42	6.25
Cl	Cl		Cl	100	2	1	100–100.5	$C_9H_8Cl_3NO$	42.77	42.42	3.16	3.32	42.17	41.68	4.71	4.76
Cl	Cl		Br	90	3	1	99.5–100	$C_9H_8Cl_2BrNO$	36.36	37.13	2.69	2.94				
Cl	Cl		I	60	1	1	111.5–112[g]	$C_9H_8Cl_2INO$	31.39	31.59	2.32	2.46	20.60	20.42[l]	4.06	3.84
Cl		Cl	Cl	68[c]	2	3	134.5–135	$C_9H_8Cl_3NO$	42.80	42.86	3.19	3.21	42.12	42.20	5.54	5.45

[a] Corresponds to 3,4,5-trimethoxyphenethyl. [b] Yield based on recrystallized amide. [c] Over-all yield from the acid chloride precursor. [d] Employing (1) III, (2) HCl, (3) HBr, (4) HCl, (5) LiBr, (6) NaI. [e] A pure specimen recrystallized from (1) benzene, (2) ethanol, (3) benzene–hexane. [f] Melting point of the colorless analytical sample unless otherwise noted. [g] Pale yellow. [h] Lit.[5] mp 132–134.5°. [i] *Anal.* Calcd: CH_3O, 25.40. Found: CH_3O, 25.80. [j] *Anal.* Calcd: F, 9.42. Found: F, 9.60. [k] *Anal.* Calcd: F, 9.42. Found: F, 9.23. [l] % chlorine.

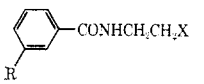
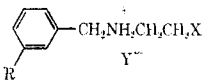
TABLE III



R	R_1	R_2	X	Y	Yield,[b] %	Solvent[d]	Mp,[e] °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Bromine, % Calcd	Bromine, % Found	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found
			Cl	Br	85	1	181–182.5	$C_9H_{13}BrClN$	43.11	43.21	5.18	5.24	31.93	31.83	14.16	13.99	5.58	5.46
CH_3	CH_3		H	Br	60	1	144–144.5	$C_{11}H_{18}BrN \cdot H_2O$[i]	50.38	50.32	7.63	6.97					5.34	5.18
CH_3	CH_3		Cl	Cl	90	1	210.5–211.5	$C_{11}H_{17}Cl_2N$	56.41	56.73	7.26	7.39			30.39	30.15	5.98	5.77
CH_3	CH_3		Br		70	2	178–180	$C_{11}H_{16}BrN \cdot 0.5H_2O$	52.59	53.03 53.09	6.82	7.33 7.57	31.81	32.03			5.57	5.54
CH_3		CH_3	H	Br	63	1	91.5–92	$C_{11}H_{18}BrN \cdot H_2O$[i]	50.38	50.59	7.63	6.83					5.24	5.35
CH_3		CH_3	Cl	Br	75	1	206–210, 222.5–223.5	$C_{11}H_{17}BrClN$	47.38	47.33	6.10	6.14	28.72	28.68	12.75	12.59	5.02	5.13
	CH_3O		Cl	Cl	70	1	180–188, 203–204.5	$C_{10}H_{15}Cl_2NO$	50.89	50.97	6.35	6.43			30.00	29.78	5.93	5.72
R = R_1 = OCH_2O			Cl	Cl	90	1	170–172, 208–210, 260[f]	$C_{10}H_{13}Cl_2NO_2$	48.00	48.09	5.20	5.35			28.40	28.21	5.60	5.81
R = R_1 = OCH_2O			Br		83	1	136–137[g]	$C_{10}H_{12}BrNO_2 \cdot H_2O$[i]	43.47	43.60	5.07	5.02	28.98	28.76				
CH_3O	CH_3O		Cl	Cl	80	1	183–185[h]	$C_{11}H_{17}Cl_2NO_2$	49.62	49.63	6.39	6.43					5.26	5.20
CH_3O	CH_3O		Br		65	2	154.5–155[g]	$C_{11}H_{16}BrNO_2 \cdot H_2O$[i]	45.20	44.98	6.16	6.11	27.36	27.19			4.79	4.69
CH_3O		CH_3O	Cl	Cl	52	2	180–181	$C_{11}H_{17}Cl_2NO_2$	49.63	49.74	6.43	6.44			26.63	26.56	5.26	5.07
CH_3O	CH_3O	CH_3O	Cl	Cl	90	1	165–165.5	$C_{12}H_{19}Cl_2NO_3$	48.64	48.64	6.41	6.51						
CH_3O	CH_3O	CH_3O[a]	Cl		98	1	181.5–182.5	$C_{13}H_{21}Cl_2NO_3$	50.32	50.58	6.77	6.90			22.90	22.64	4.51	4.54
F			Cl	Cl	55	2	184–186	$C_9H_{12}Cl_2FN$	48.24	48.64	5.38	5.54			31.68	31.97		
	F		Cl	Cl	75	1	219–220	$C_9H_{12}Cl_2FN$	48.21	48.42	5.35	5.44			31.69	31.45	6.25	6.05
CF_3			Cl	Cl	57	2	194–195	$C_{10}H_{12}Cl_2F_3N$	43.81	43.93	4.41	4.50			25.86	25.85	5.11	5.24
CF_3		CF_3	H	Cl	52[c]	2	183[f]	$C_{11}H_{12}ClF_6N$	42.94	43.01	3.93	4.00			11.52	11.86	4.55	4.46
CF_3		CF_3	Cl	Cl	50	2	199–200	$C_{11}H_{11}Cl_2F_6N$	38.61	38.42	3.24	3.30			20.73	20.47	4.92	4.91
Cl			Cl	Cl	53	2	199–200	$C_9H_{12}Cl_3N$	44.93	45.03	5.02	4.96			44.21	44.16	5.82	5.72
Cl	Cl		H	Br	80	1	183–185	$C_9H_{11}BrCl_2N \cdot H_2O$	35.45	35.64	3.95	4.62					5.06	4.62
Cl	Cl		Cl	Cl	75	1	191–192	$C_9H_{10}Cl_4N$	39.27	39.41	4.00	4.20			51.64	51.56	5.09	4.94
Cl	Cl		Br	Cl	75	1	199–202	$C_9H_{11}BrCl_3N$	33.80	34.15	3.44	3.53					4.38	4.19
Cl		Cl	Cl	Cl	48	2	174[f]	$C_9H_{11}Cl_4N$	39.31	39.43	4.00	3.90			51.42	51.40	5.08	4.91

[a] Refers to 3,4,5-trimethoxyphenethyl. [b] Yield based on recrystallized hydrohalide derivative. [c] Over-all yield from the acid chloride precursor. [d] A pure sample recrystallized from (1) ethanol, (2) ethanol–diethyl ether. [e] Melting point of the colorless analytical sample unless otherwise noted. [f] Decomposition point. [g] Melting point of the free base monohydrate. [h] C. W. Soudern and P. J. Breivogel [U. S. Patent 2,639,285 (May 19, 1953); *Chem. Abstr.*, **48**, 8265 (1954)] report mp 187–188.5°. [i] Iodine, found 0.00. [j] Free base monohydrate.

TABLE IV
INFRARED ABSORPTION FREQUENCIES (cm^{-1})

Compd type	Bond type	Stretching[a]	Deformation	Skeletal	Out of plane
 (Table II)	C—CH	3050–3000 w		1610–1500 m–s	950–830 s
	CH_2CH_2	3280–3200 s	1440–1420 m–s		
	C=O[b]	1650–1625 s			
	NH[c]	3440–3340 w	1554–1520 (amide II) s		
	CONH			1315–1292 w–m	
 (Table III)	C—CH				840–820 s
	CH_2CH_2	2940–2950 s	1440–1410 m–s		
	CN	1420–1400 w			
		1220–1200 w			
	NH[d]	3400 w–m	1580–1560 w		
	NH_2^+	2800–2750 s	816–790 m–s		

[a] w = weak, m = medium, s = strong. [b] The majority were near 1640 cm^{-1} with 1700 cm^{-1} found for N-(2-iodoethyl)-3,4-methylenedioxybenzamide. In general, the C=O absorption was shifted to a higher frequency as the β-halo substituent varied from iodine to bromine to chlorine. [c] Highest value (1577 cm^{-1}) for the deformation vibration occurred with the compound noted in footnote *b*. [d] With dimethyl and dimethoxy ring substituents, the stretching vibration occurs between 3340–3310 cm^{-1} and the deformation vibration between 1609–1605 cm^{-1}.

Experimental Section

The experiments summarized below illustrate general techniques employed to obtain the substances summarized in Tables I–III. Diborane (1 *M*) in THF was employed as received from Metal Hydrides Division, Ventron Corp. Melting points were recorded using a Kofler melting point apparatus and purity was confirmed by thin layer chromatography on silica gel G. Both $CHCl_3$ and benzene-$CHCl_3$ mixtures proved suitable solvents for the amides. A solvent composed of 1:9 H_2O–EtOH was found generally useful for both the amides and amine hydrohalide salts. After drying, the thin layer plates were sprayed with either ninhydrin (violet to blue spots with the amides) or phosphomolybdic acid solution (Baker Analyzed 10% test solution). The latter reagent proved most useful for the amides and amine hydrohalide salts. Thin layer plates were developed by heating at 110–120° for 3–5 min.

Elmental microanalyses were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Infrared spectra were determined in KBr by Dr. R. A. Hill, University of Maine.

3,4-Dichlorobenzoylaziridine (II).—A solution of 3,4-dichlorobenzoyl chloride prepared (see ref 4d for an alternative method using PCl_5) from the corresponding benzoic acid (19.2 g) and $SOCl_2$ (75 ml) in benzene (50 ml) was added dropwise during 30 min to a stirred mixture (ice–salt bath cooling) composed of benzene (200 ml), diethyl ether (20 ml), aziridine (7.5 ml), and 10% aqueous KOH (30 ml). The reaction mixture was maintained at approximately 0° while stirring was continued 2 hr. The organic phase was separated and washed with cold 1% aqueous NaOH and H_2O. Following drying ($MgSO_4$), solvent was removed *in vacuo*. The residue weighed 20 g and crystallized from benzene–petroleum ether (bp 30–60°) as needles melting at 97–98°. Three recrystallizations from benzene gave a pure specimen (Table I).

N-(2-Chloroethyl)-3,4-dichlorobenzamide (IIIa).—HCl was passed into a solution of aziridine II (2.5 g) in $CHCl_3$ (10 ml) for 5 min. The ensuing reaction was exothermic. Solvent was removed *in vacuo* at approximately 50° and the residue was collected and washed with water. Recrystallization from benzene–hexane gave 3.0 g of crystals melting at 100°. Three recrystallizations from benzene afforded an analytical sample (Table II).

The preceding route to amide IIIa proved general and useful. Allowing the aziridine amides to react with concentrated HCl as noted below (using HI to obtain amide IIIc), or by eliminating KOH from the initial aroyl chloride–aziridine reaction proved less satisfactory for obtaining the 2-chloroethylamides.

N-(2-Bromoethyl)-3,4-dichlorobenzamide (IIIb).—A solution of aziridine II (2.0 g) in $CHCl_3$ (25 ml) was treated with HBr as summarized in the preceding experiment using HCl. Recrystallization of the crude product from benzene–petroleum ether gave 2.2 g melting at 99° (Table II).

N-(2-Iodoethyl)-3,4-dichlorobenzamide (IIIc). Method A. Aziridine II (5.0 g) was added to 57% HI (25 ml). Upon mixing an exothermic reaction commenced and when the heat effect became nominal the mixture was warmed at approximately 60° for 10 min. After dilution with ice–water (100 g) the product was extracted with $CHCl_3$. The combined extract was washed with H_2O and dried ($MgSO_4$). Following removal of solvent, the yellow residue was recrystallized from benzene to yield long yellow needles (5.0 g) melting at 111–112° (Table II).

Method B.—A mixture composed of acetone (200 ml), amide IIIa (5.0 g), and NaI (25 g) was heated at reflux 40 hr. Solvent was removed *in vacuo* and the solid residue was collected and washed well with H_2O. Recrystallization from benzene gave 5.0 g melting at 111–112°. Mixture melting point determination and comparison of infrared spectra (in KBr) of the products obtained from methods A and B established their mutual identity.

N-(2-Chloro- and -Bromoethyl)benzylamine Hydrohalides. Diborane reduction of the 2-chloroethyl and 2-bromoethyl amides was performed using an overnight reaction period at room temperature. The general technique was as described in the following experiment involving N-(2-iodoethyl)benzamide except that excess diborane was removed using concentrated HCl at ice-bath temperature in place of aqueous KOH. Following removal of the THF *in vacuo* the aqueous solution was cooled and adjusted to pH 10–11 with aqueous KOH. The base was extracted with diethyl ether and converted to the hydrohalide salt (as summarized below).

N-Ethyl-3,4-dichlorobenzylamine (IVc) Hydrobromide.—A solution of N-(2-iodoethyl)-3,4-dichlorobenzamide (IIIc, 2.0 g) in THF (50 ml) was cooled (ice bath) and treated (in a N_2 atmosphere with stirring) with 1 *M* diborane (15 ml). The solution was warmed at approximately 60° for 2 hr. After cooling, excess diborane was eliminated using cold 40% aqueous KOH solution (5 ml). The product was extracted with diethyl ether and washed with H_2O. The ethereal solution was dried ($MgSO_4$) and treated with HBr. The HBr salt (IVc) which separated weighed 1.5 g and melted at 182–184°. The analytical sample recrystallized from EtOH as colorless crystals (Table III).

When the above experiment was conducted using an overnight reaction period at room temperature, similar results were obtained.