TABLE I

No.	R	X	Method	Yield, %	Mp, °C	Bp (mm), °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Hydrochloride Mp, °C	Hydrochloride Formula	Hydrochloride Calcd, % C	Hydrochloride Calcd, % H	Hydrochloride Found, % C	Hydrochloride Found, % H
1	2-Pyridyl	O	A	63	123–124[a]		$C_{13}H_{16}N_2O$	72.11	7.46	72.18	7.41	180–181	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	61.42	7.07
2	3-Pyridyl	O	A	78	103–104[a]		$C_{13}H_{16}N_2O$	72.11	7.46	72.09	7.43	201–203	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	61.61	6.42
3	4-Pyridyl	O	A	72	101–102.5[a]		$C_{13}H_{16}N_2O$	72.11	7.46	72.21	7.16	234–235	$C_{13}H_{16}N_2O \cdot HCl$	61.77	6.78	62.14	6.70
4	2-Piperidyl	O	B	81	94–96[b]	150–155 (1)	$C_{13}H_{22}N_2O$	70.22	9.93	70.09	9.67	286–287	$C_{13}H_{22}N_2O \cdot HCl$	60.33	8.96	59.99	8.79
5	3-Piperidyl	O	B	69	102–103[b]	170–178 (2)	$C_{13}H_{22}N_2O$	70.22	9.93	70.69	9.81	263–264	$C_{13}H_{22}N_2O \cdot HCl$	60.33	8.96	60.56	9.30
6	4-Piperidyl	O	B	70	113–115[a]	173–178 (3)	$C_{13}H_{22}N_2O$	70.22	9.93	69.96	9.89	326–327	$C_{13}H_{22}N_2O \cdot HCl$	60.33	8.96	60.39	9.15
7	N-Me-2-piperidyl	O	C	74	62–63[c]	164–168 (3)[d]	$C_{14}H_{24}N_2O$	71.14	10.24	71.21	10.16	279–281	$C_{14}H_{24}N_2O \cdot HCl$	61.63	9.24	61.96	9.19
8	N-Me-3-piperidyl	O	C	76	63–65[e,f]	155–157 (0.5)	$C_{14}H_{24}N_2O$	71.14	10.24	71.48	10.40	240–242	$C_{14}H_{24}N_2O \cdot HCl \cdot H_2O$	57.82	9.36	57.92	9.32
9	N-Me-4-piperidyl	O	C	72	66–68[g]	150–157 (2)	$C_{14}H_{24}N_2O$	71.14	10.24	71.16	10.35	275–278	$C_{14}H_{24}N_2O \cdot HCl$	61.63	9.24	61.40	9.38
10	2-Pyridyl	H_2	D	40		140–143 (5)[h]	$C_{13}H_{18}N_2$	77.18	8.97	77.28	9.01	263–264	$C_{13}H_{18}N_2 \cdot 2HCl$	56.73	7.33	57.13	7.19
11	3-Pyridyl	H_2	D	38		114–119 (2)[i]	$C_{13}H_{18}N_2$	77.18	8.97	76.86	9.40	231–233	$C_{13}H_{18}N_2 \cdot 2HCl$	56.73	7.33	56.38	7.14
12	4-Pyridyl	H_2	D	50		125–127 (3)[j]	$C_{13}H_{18}N_2$	77.18	8.97	77.25	8.91	233–234	$C_{13}H_{18}N_2 \cdot 2HCl$	56.73	7.33	56.70	7.66
13	2-Piperidyl	H_2	B	51		140–150 (10)[k]	$C_{13}H_{24}N_2$	74.94	11.61	74.52	10.92	202–204	$C_{13}H_{24}N_2 \cdot 2HCl$	55.49	9.32	55.35	9.25
14	N-Me-2-piperidyl	H_2	D	73		132–135 (6)[l]	$C_{14}H_{26}N_2$	75.61	11.79	75.58	11.71						
15	3-Piperidyl	H_2	B[m]	46								277–278	$C_{13}H_{24}N_2 \cdot 2HCl$	55.49	9.32	55.81	9.55
16	4-Piperidyl	H_2	B[m]	43								263–265	$C_{13}H_{24}N_2 \cdot 2HCl \cdot H_2O$	52.17	9.43	52.52	9.68

[a] From isopropyl acetate. [b] From benzene–petroleum ether (bp 30–60°). [c] From ether. [d] $n^{25}D$ 1.5216. [e] $n^{29}D$ 1.5205. [f] From hexane. [g] From petroleum ether. [h] $n^{27}D$ 1.5422. [i] $n^{31}D$ 1.5370. [j] $n^{31}D$ 1.5340. [k] $n^{25}D$ 1.5072. [l] $n^{25}D$ 1.5008. [m] Isolated as the hydrochloride salt.

I, X = O
IV, X = H_2

II, R = H; X = O
III, R = CH_3; X = O
V, R = H; X = H_2

Experimental Section[3]

N-Nicotinoylisoquinuclidine. Method A.—A solution of 100 g (0.66 mole) of ethyl nicotinate, 73 g (0.66 mole) of isoquinuclidine, and 700 ml of hexane was dried by azeotropic distillation using a Dean–Stark trap. After 2 hr, 4 g of commercial anhydrous sodium methoxide was added and heating was continued for 20 hr. The solvent was removed by vacuum distillation on the steam bath. Water was added and the product was extracted with chloroform. After removal of the solvent the residue was recrystallized.

N-Nipecotoylisoquinuclidine. Method B.—A solution of 30 g (0.14 mole) of N-nicotinoylisoquinuclidine, 2 g of PtO_2, 11.7 ml of concentrated HCl, and 200 ml of absolute ethanol was reduced in a Parr hydrogenator at 4.2 kg/cm². The reduction was complete in about 3 hr. The catalyst was filtered and the filtrate was concentrated *in vacuo* to a residue, which was dissolved in water, made basic with NH_4OH, and extracted with chloroform. The product was purified by the method given in Table I.

N-(1-Methylnipecotoyl)isoquinuclidine. Method C.—A mixture of 18 g (0.08 mole) of N-nipecotoylisoquinuclidine, 30 g of formic acid (98%), and 24 ml of 37% formaldehyde was heated on the steam bath for 48 hr. The colorless solution was concentrated to dryness *in vacuo*, the residue was suspended in water, made basic with NH_4OH, and extracted with chloroform.

N-(3-Picolyl)isoquinuclidine. Method D.—A suspension of N-nicotinoylisoquinuclidine (40 g, 0.185 mole) in 300 ml of ether was added to a refluxing suspension of 15 g (0.4 mole) of $LiAlH_4$ in 1 l. of anhydrous ether, and the reaction mixture was heated under reflux with stirring for 15–20 hr. After the usual decomposition, the product was distilled.

(3) All melting points are corrected. Microanalysis was performed by Mr. Edwin Connor of these laboratories.

Substitution in the Hydantoin Ring. IV. N-3-*p*-Bromoanilinomethyl Derivatives

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The condensation of primary and secondary aliphatic or aromatic amines with formaldehyde and phthalimide or succinimide has been shown in previous studies in this laboratory to produce phthalimidomethyl and succinimidomethyl derivatives of amines which are particularly useful for identification purposes.[1] More recently a series of N-3-aryl- (and alkyl-) aminomethylhydantoins prepared by condensing various hydantoins with formaldehyde and amines has been reported.[2] In the present study this condensation is extended to include the preparation of a number of N-3-*p*-bromoanilinomethylhydantoins. The hydantoins used in this investigation were prepared from the corresponding ketone, ammonium carbonate, and potassium cyanide according to

(1) (a) H. W. Heine, M. B. Winstead, and R. P. Blair, *J. Am. Chem. Soc.*, **78**, 672 (1956); (b) M. B. Winstead, and H. W. Heine, *ibid.*, **77**, 1913 (1955); (c) M. B. Winstead, K. V. Anthony, L. L. Thomas, R. G. Strachan, and H. J. Richwine, *J. Chem. Eng. Data*, **7**, 414 (1962).

(2) M. B. Winstead, D. E. Barr, C. R. Hamel, D. J. Renn, H. I. Parker, and R. M. Neumann, *J. Med. Chem.*, **8**, 117 (1965).

TABLE I

N-3-*p*-BROMOANILINOMETHYLHYDANTOINS

Substituted hydantoin	Mp, °C[a]	% yield[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5,5-Dicyclopropyl[d]	210.5–212[e]	89	$C_{16}H_{18}BrN_3O_2$	52.76	4.98	11.54	52.98	5.11	11.46
5,5-Diethyl	121–123[f]	70	$C_{14}H_{18}BrN_3O_2$	49.42	5.33	12.35	49.63	5.49	11.95
5,5-Dimethyl	196–196.5	76	$C_{12}H_{14}BrN_3O_2$[g]						
5,5-Diphenyl	190–192[h]	77	$C_{22}H_{18}BrN_3O_2$[i]	60.56	4.16	9.63	60.36	4.40	9.81
5,5-Di-*n*-propyl	154.5–155[h]	82	$C_{16}H_{22}BrN_3O_2$	52.18	6.02	11.41	52.48	6.20	11.25
5-Ethyl-5-phenyl	160–160.5[h]	85	$C_{18}H_{18}BrN_3O_2$	55.68	4.67	10.82	55.79	4.88	10.63
5,5-Hexamethylene	200–200.5[i]	42	$C_{16}H_{20}BrN_3O_2$	52.47	5.50	11.47	52.41	5.59	11.45
Hydantoin[d]	178.5–179[j]	90	$C_{10}H_{10}BrN_3O_2$	42.27	3.55	14.79	42.36	3.74	14.94
Menthonespiro[d]	246–246.5[j]	85	$C_{19}H_{26}BrN_3O_2$	55.89	6.42	10.29	55.87	6.23	10.11
5-*p*-Methoxyphenyl	168–168.5[h]	87	$C_{17}H_{16}BrN_3O_3$	52.32	4.13	10.77	52.40	4.29	10.88
5-Methyl-5-*p*-chlorophenyl[k]	199[j]	74	$C_{17}H_{15}BrClN_3O_2$	49.96	3.70	10.28	50.16	3.75	10.27
5-Methyl-5-isobutyl	166–166.5[h]	86	$C_{15}H_{20}BrN_3O_2$	50.86	5.69	11.86	51.16	5.92	11.93
5-Methyl-5-pentyl	134[h]	86	$C_{16}H_{22}BrN_3O_2$	52.18	6.02	11.41	52.18	5.99	11.42
5-Methyl-5-phenyl	152.5–153[h]	50	$C_{17}H_{16}BrN_3O_2$	54.56	4.31	11.23	54.37	4.53	11.31
5-Methyl-5-(2-thienyl)	155–156[h]	89	$C_{15}H_{14}BrN_3O_2S$	47.38	3.71	11.05	47.26	3.96	11.06
5,5-Pentamethylene[d]	223.5–224.5[h]	84	$C_{15}H_{18}BrN_3O_2$	51.15	5.15	11.93	51.16	5.37	11.53
5-Phenyl[d]	186–186.5	82	$C_{16}H_{14}BrN_3O_2$	53.35	3.92	11.67	53.61	4.13	11.51
5,5-Tetramethylene[d]	190.5–191[j]	77	$C_{14}H_{16}BrN_3O_2$	49.72	4.77	12.42	49.93	5.03	12.55
5-(*p*-Tolyl)	181–182[j]	81	$C_{17}H_{16}BrN_3O_2$	54.56	4.31	11.23	54.58	4.53	11.08

[a] All melting points were determined using a Mel-Temp apparatus and are corrected. [b] The products as obtained from the reaction mixture were of high purity, and the percentage yield reported is of unrecrystallized product. [c] Carbon and hydrogen analyses were conducted by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Nitrogen analyses were by the semimicro Kjeldahl method and were determined by Victor Krimsley and Eric Steinberg of this laboratory. [d] The product precipitated out of solution shortly after refluxing had begun, and the reaction mixture was refluxed for 30 min. [e] Recrystallized from aqueous acetone. [f] Recrystallized from aqueous ethanol. [g] This compound was reported.[2] [h] Recrystallized from ethanol. [i] Lit.[2] mp 194.5–195.5°, after repeated recrystallizations. [j] Recrystallized from ethanol–dimethylformamide. [k] A mixture of ethanol and dimethylformamide was used as the reaction solvent.

the method described by Goodson and co-workers.[3] Equimolar quantities of the hydantoin, *p*-bromoaniline, and formaldehyde were refluxed for 1 hr or less in ethanol solvent following the procedure previously described.[2] The products were obtained upon filtering and cooling the filtrate and are reported in Table I.

Acknowledgment.—The author wishes to thank the members of his 1964–1965 organic chemistry class who prepared the compounds reported herein as part of a special laboratory exercise.

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Quinoxaline Studies. XIII. N-(2-Quinoxaloyl)-α-amino Acids[1,2]

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Several physiologically active polypeptides, such as levomycin,[3] actinoleukin,[4] echinomycin,[5] and quinomycin,[6,7] have been shown to possess one or more quinoxaloyl moieties. This prompted the preparation of a series of N-(2-quinoxaloyl)-α-amino acids (Table I) for testing as antitumor agents.

(1) We gratefully acknowledge support of this work under National Institutes of Health Grant GM-11968.

(2) Paper XII of this series: E. Brill and H. P. Schultz, *J. Org. Chem.*, **29**, 579 (1964).

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Experimental Section

Ultraviolet absorption spectra were determined with a Bausch and Lomb 505 spectrophotometer at concentrations of 5 mg/l. of 95% ethanol. Amino acids utilized were of CP grade, purchased from Mann Research Laboratories.

2-(D-*arabino*-Tetrahydroxybutyl)quinoxaline Monohydrate.—A solution of 1505 g of sucrose, 432 g of *o*-phenylenediamine, 1600 ml of water, and 480 ml of acetic acid was stirred and refluxed for 2 hr while air was bubbled through the solution. Cooling the solution at 10° for 12 hr gave 213 g (19.9%) of light brown crystals, mp 189–190° (lit. mp 188°,[8] mp 190–191°[9]). The material was used without further purification.

2-Quinoxalinecarboxylic Acid.—Sodium hydroxide (140 g) was dissolved in a solution of 200 ml of 30% H_2O_2 and 800 ml of water at 5°. After warming the solution to room temperature, 107 g of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline monohydrate was added, and the mixture was stirred while warmed carefully to 75°, at which time the reaction became self-sustaining. The temperature was carefully maintained at 80 ± 1° by use of an ice bath until vigorous reaction ceased (about 30 min); stirring and heating at 80° of the light yellow solution was continued for 1 hr. (If the solution were dark and/or if solid were present, 25-ml portions of 30% H_2O_2 solution were added with continued stirring and heating until the solution was a clear, light yellow color.) The solution was transferred to a large beaker, stirred, and cooled to 0°, and then neutralized with 111 ml of cold (0°) H_2SO_4. The precipitate was filtered, then redissolved in a solution of 30 g of KOH in 500 ml of water. The basic solution was treated with 5 g of decolorizing carbon and of filter aid, filtered, and then added to a stirred, cold (0°) solution of 30 ml of H_2SO_4 in 1 l. of water. The precipitation was repeated to give 46 g (66%) of light yellow material, mp 200–201° dec. The product could be recrystallized from hot water or ethanol, mp 215° dec (lit.[8] mp 210°). However, the per cent yield and quality of 2-quinoxaloyl chloride obtained in the subsequent procedure was the same whether precipitated or recrystallized material was used.

N-(2-Quinoxaloyl)-L-α-alanine.—A mixture of 2.94 g of L-α-alanine, 180 ml of water, 9.9 g of $NaHCO_3$, and 6.35 g of quinox-

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