what soluble in carbon disulfide and acetonitrile, very slightly soluble in ethanol, insoluble in water, solubility parameter[12] $\delta \approx 7.2$ (est.).

For *c*-$C_8F_{16}O$: d^{25} 1.7602, b.p. 104°, m.p. not obs. (glass below −113°) dielectric constant 1.85 ± 0.05 (1000 cyc.), loss factor less than 0.0001 (100 cyc.), dielectric strength 37 kv. (ASTM-D877), surface tension (dynes/cm., 25°), 15.2; viscosity (centipoises), 2.41 (0°), 1.45 (25°), 0.80 (60°); solubility, miscible with benzotrifluoride, somewhat soluble in heptane and carbon tetrachloride, very slightly soluble in benzene, acetone and ethanol, insoluble in water, soluble parameter[12] $\delta \approx 5.7$ (est.).

Infrared Spectra of α,α,α'-Trichloro Perfluoro Ethers.—These compounds exhibit complex spectra, difficult to interpret. In each case, however, two fairly strong infrared bands were found in the region 10.70–11.10 and 11.20–11.55 μ, using liquid sample thicknesses of 0.007 mm. These bands possibly may be attributable to the trichloro ether grouping.

Other Lewis Acids.—No reaction was observed between the ether *c*-$C_8F_{16}O$ and the less powerful Lewis acids BCl_3 (350°, 24 hours) or $NaCl{\cdot}AlCl_3$ (230°, 15 hours). The ether was recovered quantitatively, with unchanged refractive index and infrared spectrum. Aluminum bromide, however, reacted at 170° with this ether but produced only aluminum fluoride, carbonized tars and bromine; no impurities were detectable in the recovered ether phase.

Acknowledgment.—The author would like to thank Dr. H. E. Freier for the analytical data, Dr. W. E. Keiser and Dr. J. McBrady for the infrared spectra, Mr. G. Filipovich for the electrical measurements, Mr. V. Welschinger for the viscosity data, and Mr. J. D. Keating for assistance with the autoclave reactions.

ST. PAUL 6, MINN.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, LEDERLE LABORATORIES, AMERICAN CYANAMID CO.]

α-Bromoacid Amides and Ureas as Anticonvulsants

BY S. R. SAFIR, H. DALALIAN, W. FANSHAWE, K. CYR, R. LOPRESTI, R. WILLIAMS, S. UPHAM, L. GOLDMAN AND S. KUSHNER

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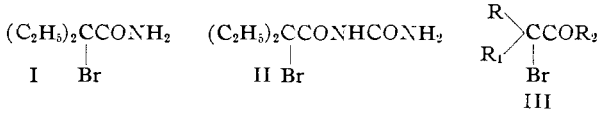
A large number of α-bromoacid amides and ureas related to neuronal and carbromal has been synthesized for anticonvulsant activity. Maximum activity was encountered with compounds in which some branching in the acid chain was coupled with the simpler amide and urea functions.

Although α-bromoamides and ureas have for many years been used in medicine as sedatives and hypnotics, no systematic survey of this class of drugs for anticonvulsant potentiality appears to have been made.[1] The finding that neuronal (I) and carbromal (II) exhibited a high degree of protection against metrazole-induced seizures in rats gave impetus to the hope that a drug useful in petit mal epilepsy might be found in the class of α-bromoamides and ureas. A synthetic program with this goal in mind is the subject of this paper.

In the selection of compounds to be synthesized, it was decided to retain the α-bromo atom while varying, on the one hand, the alkyl groups on the α-carbon atom and, on the other, the amide or urea function. These features are represented by formula III in which the nitrogen is incorporated into R_2.



The most active group among the compounds listed in Table I is that derived from 2-bromo-2-ethylbutyric acid. The N-methyl (XLI) and N-methylol (XLII) amides of this acid are about as active as neuronal and carbromal. The N_3-methyl analog LVII of carbromal, although active, is somewhat less potent than carbromal. Alterations in the alkyl amide group involving increase in the chain length, unsaturation or branching, all resulted in loss or elimination of anticonvulsant activity. The glycine amide derivatives LII, LIII, LIV, and LV, the amides LI and LVI derived from heterocyclic amines and the isothiuronium derivative LIX also proved to be inactive. Compound LVIII, 1,3-bis-(2-bromo-2-ethylbutyryl)-urea, also was inactive. Thus it appears that anticonvulsant potency is retained within narrow limits of substitution among the derivatives of 2-bromo-2-ethylbutyric acid.

Some branching of the acid chain appears to be necessary for anticonvulsant activity as may be inferred from the high potency shown by compounds XXII, XXV, XXXIII, XXXIV, XXXVIII, LX and LXI and from the virtual absence of anticonvulsant activity among the linear derivatives. Isopropyl groups in particular seem to have a salutary effect.

Comparison of the amide derivatives with the urea derivatives does not permit an unequivocal preference to be made for either group as a structural requirement for anticonvulsant activity.

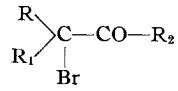
The amides were prepared by classical procedures, namely, reaction between the requisite acid chlorides or bromides and ammonia or amines. Examples of compounds requiring less conventional treatment are furnished in the Experimental section. 2-Amino-2-ethylbutyramide was prepared readily by hydrolysis of the nitrile. The urea derivatives were prepared in fair yields by reaction of the acid chlorides with urea or methylurea.

Several of the most active compounds are presently undergoing a limited clinical trial.

The pharmacological data were secured by Drs. R. W. Cunningham and W. Gray, assisted by F. Smith and C. Rauh, and will be published in full elsewhere.

(1) The Merck Index, 5th ed., Merck & Co., Inc., Rahway, N. J., 1940, p. 196, lists epilepsy as one of the uses for neuronal. Stroux, in an early clinical report [*Deut. med. Wochschr.*, **30**, 1497 (1904)] comments on the "extraordinarily favorable effect of neuronal on epilepsy but his work was performed on only a few unclassified epileptic patients without benefit of modern, long-range, controlled methods.

TABLE I



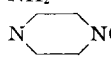
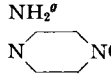
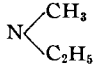
Cmpd.	R	R_1	R_2	M.p. or b.p.(mm.), °C.	Yield, %	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Nitrogen Calcd.	Nitrogen Found	Anti-metrazole activity[b]	Recrystl.–solvent
IV	CH_3	H	NH_2[c]	119–121	73										1+/100	Ether
V	CH_3	H	$NHC(CH_3)_3$	119–121	73	$C_7H_{14}BrNO$	40.4	40.7	6.7	6.8	38.4	38.8	6.7	6.5	0/250	Pet. eth.
VI	C_2H_5	H	$NHCH_3$	52.5–53	74	$C_5H_{10}BrNO$	33.4	33.7	5.6	5.6	44.4	44.7	7.8	7.7	0/100	Ether–pet. eth.
VII	C_2H_5	H	NHC_2H_5[d]	65.5–66.5	94										1+/500	Ether–pet. eth.
VIII	C_2H_5	H		94–106(0.4)	70										0/75	
IX	C_2H_5	H		102–110(0.5)	70	$C_8H_{14}BrNO_2$	40.7	40.9	6.0	6.2	33.8	34.0	5.9	5.6	0/75	
X	C_2H_5	H		Yellow sirup	76	$C_{11}H_{19}BrN_2O_3$	43.0	42.9	6.2	6.5	26.0	26.1	9.1	9.1	0/50	
XI	$CH_3(CH_2)_2$	H	NH_2[f]	80–81	97										2+/40	Ether–pet. eth.
XII	$CH_3(CH_2)_2$	H		Colorless oil	57	$C_{12}H_{21}BrN_2O_3$	44.9	45.2	6.6	6.4	24.9	24.6	8.7	8.9	0/100	
XIII	$CH_3(CH_2)_3$	H	NH_2[g]	57–58	86										0/60	Ether–pet. eth.
XIV	$CH_3(CH_2)_3$	H		Yellow oil	90	$C_{13}H_{23}BrN_2O_3$	46.5	46.9	6.9	7.1	23.8	24.0	8.4	8.2	0/75	
XV	CH_3	CH_3	NH_2[h]	144–147	35										0/135	EtOH
XVI	CH_3	CH_3	$NHCH_3$	53–55	54	$C_5H_{10}BrNO$	33.3	33.7	6.0	6.2	43.9	44.5	7.8	8.2	1+/100	Pet. eth.
XVII	CH_3	CH_3	NHC_2H_5[i]	55–57	46										0/200	Pet. eth.
XVIII	CH_3	CH_3	$NH(CH_2)_2CH_3$	39–47[j](0.05)	89	$C_7H_{14}BrNO$	40.4	40.8	6.7	6.9	38.4	37.9	6.7	6.5	0/200	
XIX	CH_3	CH_3	$NHCH(CH_3)_2$	75–77	95	$C_7H_{14}BrNO$	40.4	40.7	6.7	7.0	38.4	38.3	6.7	6.7	0/400	*i*-PrOH
XX	CH_3	CH_3		37–46[j](0.05)	20	$C_7H_{14}BrNO$	40.4	40.8	6.7	7.1	38.4	38.4	6.7	6.3	0/50	
XXI	CH_3	CH_3	$NHC(CH_3)_3$	85–88	35	$C_8H_{16}BrNO$	43.3	43.6	7.2	7.2	36.0	35.6	6.3	6.5	0/500	*i*-PrOH
XXII	CH_3	CH_3	$NHCONH_2$[k]	138–140	51	$C_5H_9BrN_2O_2$	28.9	29.2	4.3	4.2	38.2	38.2	13.4	13.5	3+/125	EtOH
XXIII	CH_3	CH_3	$NHCONHCH_3$	118–120	42	$C_6H_{11}BrN_2O_2$	32.3	32.9	4.9	5.1	35.8	35.8	12.6	13.4	0/150	*n*-PrOH
XXIV	C_2H_5	CH_3	$NHCH_3$	66–73(0.2)	72	$C_6H_{12}BrNO$	37.1	37.5	6.2	6.5	41.2	41.3	7.2	7.0	2+/40	
XXV	C_2H_5	CH_3	NHC_2H_5	57–59.5(0.1)	63	$C_7H_{14}BrNO$	40.4	40.4	6.7	6.7	38.4	38.1	6.7	6.7	3+/50	
XXVI	C_2H_5	CH_3	$NH(CH_2)_2CH_3$	39–46[j](0.05)	25	$C_8H_{16}BrNO$	43.3	44.8	7.2	7.1	36.0	37.1	6.3	6.0	0/75	
XXVII	C_2H_5	CH_3	$NHCH(CH_3)_2$	44–47	20	$C_8H_{16}BrNO$	43.3	43.3	7.2	7.2	36.0	36.1	6.3	6.3	0/200	Dil. EtOH
XXVIII	C_2H_5	CH_3	$N(CH_3)_2$	38–43[j](0.05)	31	$C_7H_{14}BrNO$	40.4	40.5	6.7	7.1	38.4	37.5	6.7	6.5	0/60	
XXIX	C_2H_5	CH_3	$NHCONH_2$[l]	96.5–97.5	31	$C_6H_{11}BrN_2O_2$	32.3	32.8	5.0	5.2	35.8	35.4	12.6	12.7	0/100	
XXX	C_2H_5	CH_3	$NHCONHCH_3$	50–51.5	31	$C_7H_{13}BrN_2O_2$	35.5	35.6	5.5	5.6	33.7	33.9	11.8	11.8	1+/200	Hexane
XXXI	$CH_3(CH_2)_2$	CH_3	NH_2[m]	68–76(0.3)	56	$C_6H_{12}BrNO$	37.1	36.8	6.2	6.2	41.2	41.3	7.2	7.4	1+/60	
XXXII	$CH_3(CH_2)_2$	CH_3	$NHCH_3$	44–51[j](0.05)	45	$C_7H_{14}BrNO$	40.4	40.4	6.7	6.8	38.4	38.5	6.7	6.7	1+/60	
XXXIII	$(CH_3)_2CH$	CH_3	NH_2	64–70	55	$C_6H_{12}BrNO$	37.1	37.6	6.2	6.3	41.2	41.7	7.2	7.6	3+/40	Pet. eth.
XXXIV	$(CH_3)_2CH$	CH_3	$NHCH_3$	43.5–45 54–60(0.3)	80	$C_7H_{14}BrNO$	40.4	40.2	6.7	7.0	38.4	38.7	6.7	6.7	4+/40	

TABLE I (*Continued*)

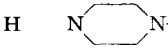
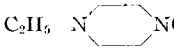
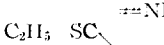
Cmpd.	R	R1	R2	M.p. or b.p.(mm.), °C.	Yield, %	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Nitrogen Calcd.	Nitrogen Found	Anti metrazole activity[b]	Recryst.-solvent
XXXV	$(CH_3)_2CH$	CH_3	NHC_2H_5	35–44[j](0.05)	17	$C_8H_{16}BrNO$	43.3	43.0	7.2	7.2	36.0	35.5	6.3	6.2	0/40	
XXXVI	$(CH_3)_2CH$	H	NH_2[n]	131–132	68										0/40	Ether
XXXVII	$(CH_3)_2CH$	H		Colorless oil	39	$C_{12}H_{21}BrN_2O_3$	44.9	44.7	6.6	6.3	24.9	24.6	8.7	8.9	0/100	
XXXVIII	$(CH_3)_3C$	H	NH_2[o]	135–138	63										3+/50	Benzene
XXXIX	$(CH_3)_3C$	H	$NHCH_3$[p]	112–114	60	$C_7H_{14}BrNO$	40.4	40.7	6.7	7.0	38.4	38.1	6.7	6.7	2+/40	Pet. eth.
XL	$(CH_3)_3C$	H	$NHCONH_2$[q]	185–188	46										1+/15	Benzene
I	C_2H_5	C_2H_5	NH_2[r]	64–66	79										4+/40	
XLI	C_2H_5	C_2H_5	$NHCH_3$	40–41 40–45[j](0.05)	71	$C_7H_{14}BrNO$	40.4	40.7	6.7	7.1	38.4	38.4	6.7	6.5	4+/40	
XLII	C_2H_5	C_2H_5	$NHCH_2OH$[s]	93–95	90										4+/40	Acetone
II	C_2H_5	C_2H_5	$NHCONH_2$[t]												4+/40	
XLIII	C_2H_5	C_2H_5	NHC_2H_5	69–71(0.5)	62	$C_8H_{16}BrNO$	43.3	43.8	7.2	7.7	36.0	35.6	6.3	6.1	1+/25	
XLIV	C_2H_5	C_2H_5	$N(CH_3)_2$	83–85(0.7)	46	$C_8H_{16}BrNO$	43.3	43.4	7.2	7.3			6.3	6.0	0/60	
XLV	C_2H_5	C_2H_5	$NH(CH_2)_2CH_3$	84–85(0.8)	62	$C_9H_{18}BrNO$	45.8	46.0	7.7	8.0	33.8	33.6	5.9	5.7	1+/225	
XLVI	C_2H_5	C_2H_5	$NHCH(CH_3)_2$	55–56(0.5)	86	$C_9H_{18}BrNO$	45.8	45.1	7.7	7.7			5.9	5.7	2+/100	
XLVII	C_2H_5	C_2H_5	$NHCH_2CH{=}CH_2$	78–79(0.3)	45	$C_9H_{16}BrNO$	46.2	46.0	6.8	7.0	34.2	33.9	6.0	5.8	0/100	
XLVIII	C_2H_5	C_2H_5		32–33 70–72(0.3)	69	$C_{10}H_{20}BrNO$	48.1	48.3	8.1	8.1	31.9	32.1	5.6	5.7	0/125	
XLIX	C_2H_5	C_2H_5	$NH(CH_2)_2CH(CH_3)_2$	107–109(0.7)	67	$C_{11}H_{22}BrNO$	50.0	50.8	8.3	8.6					0/500	
L	C_2H_5	C_2H_5	$NHCH_2C_6H_5$	56–57	75	$C_{13}H_{18}BrNO$	54.9	55.1	6.3	6.6	28.2	28.6	4.9	4.9	1+/500	Ether
LI	C_2H_5	C_2H_5		130–133(3)	29	$C_{11}H_{16}BrNO_2$	48.2	48.6	5.8	6.0	29.2	28.6	5.1	5.2	0/50	
LII	C_2H_5	C_2H_5	$NHCH_2COOH$	92–94	72	$C_8H_{14}BrNO_3$	38.1	38.0	5.6	5.8	31.8	31.4	5.6	5.5	0/500	Water
LIII	C_2H_5	C_2H_5	$NHCH_2COOEt$[u]	34–36	79										0/500	Pet. eth.
LIV	C_2H_5	C_2H_5	$NHCH_2CONH_2$[v]	108–110	16										0/80	EtOH–pet. eth.
LV	C_2H_5	C_2H_5	$NHC(Et)_2CONH_2$	181–183	36	$C_{12}H_{23}BrN_2O_2$	46.9	47.2	7.5	7.8	26.0	26.1	9.1	9.2	0/500	$CHCl_3$
LVI	C_2H_5	C_2H_5		62–62.5	65	$C_{13}H_{23}BrN_2O_3$	46.5	46.8	6.9	6.7	23.8	24.0	8.4	8.4	0/75	Benzene–pet. eth.
LVII	C_2H_5	C_2H_5	$NHCONHCH_3$	93.5–96.5	26	$C_8H_{15}BrN_2O_2$	38.3	38.7	6.0	6.3	31.9	32.0	11.2	11.0	3+/100	Acetone–pet. eth.
LVIII	C_2H_5	C_2H_5	$NHCONHCOC(Et)_2$[w] (Br)	77–79	39										0/70	MeOH
LIX	C_2H_5	C_2H_5		117–119	73	$C_7H_{14}BrClN_2OS$	29.0	29.2	4.9	5.2	27.7	27.5	9.7	9.9[x]	1+/500	HOAc–ether
LX	$(CH_3)_2CH$	C_2H_5	NH_2[y]	45–46	85										4+/25	Ether–pet. eth.
LXI	$(CH_3)_2CH$	C_2H_5	$NHCH_3$	37.5–40 54–70(0.1)	61	$C_8H_{16}BrNO$	43.3	42.9	7.3	7.1	35.9	36.2	6.3	6.3	3+/40	
LXII	$(CH_3)_2CH$	C_2H_5	NHC_2H_5	25–32 110–114(11)	80	$C_9H_{18}BrNO$	45.8	46.1	7.7	8.0	33.8	33.8	5.9	5.6	1+/40	

TABLE I (*Continued*)

Cmpd.	R	R_1	R_2	M.p. or b.p.(mm.), °C.	Yield, %	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Nitrogen Calcd.	Nitrogen Found	Anti-metrazole activity[b]	Recryst.–solvent
LXIII	$CH_3(CH_2)_3$	C_2H_5	NH_2[z]	70–80[j](1)	72	$C_8H_{16}BrNO$	43.3	43.2	7.3	7.4	35.9	35.7	6.3	6.4	0/40	
LXIV	$CH_3(CH_2)_3$	C_2H_5	$NHCH_3$	70–74(0.3)	68	$C_9H_{18}BrNO$	45.8	46.1	7.7	8.0	33.8	34.1	5.9	5.8	0/40	
LXV	$CH_3(CH_2)_2CH(CH_3)$	C_2H_5	NH_2[aa]	90–105[j](0.7)	72	$C_9H_{18}BrNO$	45.8	46.1	7.7	7.9	33.8	34.3	5.9	6.4	0/40	
LXVI	$CH_3(CH_2)_2CH(CH_3)$	C_2H_5	$NHCH_3$	75–80(0.2)	27	$C_{10}H_{20}BrNO$	48.1	48.4	8.1	8.1	31.9	31.5	5.6	5.8	1+/50	

[a] Analytical data were furnished by Mr. L. Braucone and associates. [b] Ratings are expressed in terms of ability to suppress metrazole-induced convulsions in rats at the asymptomatic dose in mg./kg.; 4+ indicates complete protection. [c] A. Bischoff, *Ber.*, **30**, 2312 (1897), reported m.p. 123°. [d] J. v. Braun, F. Dengel and A. Jacob, *ibid.*, **70B**, 994 (1937). [e] A. Bischoff, *ibid.*, **31**, 2846 (1898), reported m.p. 125–130° and b.p. 144–146° (25 mm.). [f] A. Pomerantz and R. Connor, THIS JOURNAL, **61**, 3386 (1939), reported m.p. 78.5–79° cor. [g] Pomerantz and Connor, ref. *f*, reported m.p. 58.5–59° cor. [h] Bischoff, ref. *c*, reported m.p. 148°. [i] J. v. Braun, F. Jostes and A. Heymons, *Ber.*, **60B**, 92 (1927), reported m.p. 57°. [j] Evaporative distillation. [k] A. v. d. Eeckhout, *Arch. exp. Pathol. Pharmakol.*, **57**, 338 (1907). [l] Fourneau and Florence, ref. 5, reported m.p. 132.5°. [m] German Patent 165,281. [n] A. Bischoff, *Ber.*, **31**, 3236 (1898), reported m.p. 133°. [o] A. H. Homeyer, F. C. Whitmore and V. H. Wallingford, THIS JOURNAL, **55**, 4209 (1933), reported m.p. 138°. [p] A. D. Bass, *J. Pharmacal. Exptl. Therap.*, **64**, 50 (1938). [q] Homeyer, Whitmore and Wallingford, ref. *o*, reported m.p. 188.5°. [r] G. Fuchs, *Z. angew. Chem.*, **17**, 1505 (1904), reported m.p. 66–67°. [s] German Patent 273,320. [t] Commercially available. [u] Rosenmund, ref. 23, reported m.p. 35–36°. [v] Rosenmund, ref. 23, reported m.p. 109–110°. [w] German Patents 283,105 and 287,001. [z] Calcd.: Cl, 12.2; S, 11.1; Found: Cl, 12.1; S, 11.2. [y] G. Kuhlmann, *Pharm. Ztg.*, **76**, 113 (1931), reported m.p. 50–51°. [z] C. L. Stevens and T. H. Coffield, THIS JOURNAL, **73**, 103 (1951), reported b.p. 128–131° (5 mm.). [aa] E. H. Volwiler and D. L. Tabern, ref. 19.

Assistance in large scale preparative work was furnished by W. L. McEwen and associates.

Experimental[2]

α-Bromoacid Halides.—2-Bromopropionyl bromide was obtained from Eastman Kodak Co.

The following α-bromoacid chlorides were prepared, in the yields indicated, by reaction of the requisite, commercially purchased bromoacids with thionyl chloride: **2-bromobutyryl chloride**,[3] b.p. 148–150° (82%); **2-bromo-2-ethylbutyryl chloride**,[4] b.p. 68–75° (15 mm.) (67%); **2-bromovaleryl chloride**,[5] b.p. 72–77° (20 mm.) (76%); **2-bromo-3-methylbutyryl chloride**,[6] b.p. 59° (15 mm.) (86%); **2-bromohexanoyl chloride**,[7] b.p. 91–94° (35 mm.) (89%); and **2-bromo-2-methylpropionyl chloride**,[8] b.p. 28–36° (28 mm.) (74%).

A group of three α-bromoacid chlorides was prepared by the method of Schwenk and Papa[9] in which bromination is carried out on the acid chlorides with excess thionyl chloride present as solvent. The chlorides then were fractionated through a Vigreux column. The three products are: **2-bromo-2,3-dimethylbutyryl chloride**, b.p. 70–78° (17 mm.), in 50% yield from 2,3-dimethylbutyric acid[10]; **2-bromo-2-methylvaleryl chloride**, b.p. 69–75° (15 mm.), in 62% yield from 2-methylvaleric acid[11]; and **2-bromo-3,3-dimethylbutyryl chloride**,[12] b.p. 67–74° (14 mm.), in 85% yield from 3,3-dimethylbutyric acid.[13]

Three α-bromoacids were prepared by the method of Clarke and Taylor.[14] These are: 2-bromo-2-methylbutyric acid,[15] b.p. 112–116° (12 mm.), in 79% yield from 2-methylbutyric acid; 2-bromo-2-ethyl-3-methylbutyric acid,[16] b.p. 102–108° (2.5 mm.), in 59% yield from 2-ethyl-3-methylbutyric acid[17]; and 2-bromo-2-ethylhexanoic acid,[16] b.p. 147–152° (17 mm.), in 78% yield from 2-ethylhexanoic acid.[18] The bromoacids were, in turn, converted into the chlorides with thionyl chloride in the yields indicated: **2-bromo-2-methylbutyryl chloride**,[5] b.p. 54–59° (14 mm.) (75%); **2-bromo-2-ethyl-3-methylbutyryl chloride**, b.p. 76–82° (12 mm.) (85%); and **2-bromo-2-ethylhexanoyl chloride**, b.p. 106.5–108° (20 mm.) (26%).

2-Bromo-2-ethyl-3-methylhexanoyl chloride,[19] b.p. 108–111° (14 mm.), was obtained in 64% yield from thionyl chloride and 2-bromo-2-ethyl-3-methylhexanoic acid.[20]

Amines.—**Ethyl 1-piperazinecarboxylate** was prepared by the method of Moore, *et al.*[21] All other amines were obtained commercially.

2-Amino-2-ethylbutyramide Hydrochloride.—To a solution of fuming hydrochloric acid prepared by saturating 670 cc. of the 12 *N* reagent at 0° with hydrogen chloride gas there was added 58.5 g. (0.52 mole) of 2-amino-2-ethylbutyronitrile.[22] The resulting solution was allowed to stand at room temperature for 24 hours and then was evaporated to dryness under reduced pressure below 45°.

(2) All melting points and boiling points are uncorrected.

(3) M. A. Collet, *Bull. soc. chim. France*, [3] **15**, 1100 (1896).

(4) German Patent 158,220.

(5) E. Fourneau and G. Florence, *Bull. soc. chim. France*, [4] **43**, 211 (1928).

(6) E. Fischer and J. Schenkel, *Ann.*, **354**, 12 (1907).

(7) C. S. Marvel and W. A. Noyes, THIS JOURNAL, **42**, 2259 (1920).

(8) D. S. Tarbell and P. Noble, Jr., *ibid.*, **72**, 2657 (1950).

(9) E. Schwenk and D. Papa, *ibid.*, **70**, 3626 (1948).

(10) P. van Romburgh, *Rec. trav. chim.*, **5**, 228 (1886).

(11) E. Strassny, *Monatsh. Chem.*, **12**, 589 (1891).

(12) F. C. Whitmore and V. H. Wallingford, THIS JOURNAL, **55**, 4209 (1953).

(13) S. Wideqvist, *Arkiv. Kemi Mineral. Geol.*, **B23**, No. 4 (1946); *C. A.*, **41**, 1615 (1947).

(14) H. T. Clarke and E. R. Taylor, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 115.

(15) F. E. Ray, THIS JOURNAL, **50**, 558 (1928).

(16) R. C. Amin, W. H. Hartung and C. W. Chapman, *J. Am. Pharm. Assoc., Sci. Ed.*, **37**, 243 (1948).

(17) A. W. Crossley and H. R. Le Sueur, *J. Chem. Soc.*, **77**, 83 (1900).

(18) H. S. Raper, *ibid.*, **91**, 1831 (1907).

(19) E. H. Volwiler and D. L. Tabern, THIS JOURNAL, **58**, 1352 (1936).

(20) W. J. Doran and H. A. Shonle, *J. Org. Chem.*, **3**, 193 (1938).

(21) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).

(22) H. Biltz and K. Slotta, *J. prakt. Chem.*, **113**, 233 (1926).

The crude solid residue was recrystallized from methanol–ether and gave 49 g. (56%) of product, m.p. 234–237°.

Anal. Calcd. for $C_6H_{15}ClN_2O$: C, 43.5; H, 9.0; Cl, 21.3; N, 16.8. Found: C, 43.4; H, 9.0; Cl, 21.0; N, 16.4.

α-Bromoamides.—The amides listed in Table I were made by reaction of acid chlorides with ammonia or amines either in aqueous or in anhydrous media. If a concentrated aqueous solution of the base was available commercially, the aqueous procedure was used. Ether or chloroform generally was used for the anhydrous bases. After filtration of the hydrochlorides of the bases the products were obtained by evaporation of the solvent and purified in the manner indicated in Table I.

2-Ethyl-2-(2-bromo-2-ethylbutyramido)-butyramide (LV).—To an ice-cold, stirred solution of 35 g. (0.21 mole) of 2-amino-2-ethylbutyramide hydrochloride in 300 cc. of water and 50 cc. of acetone there was added, simultaneously, during 1 hour, a solution of 47.1 g. (0.22 mole) of 2-bromo-2-ethylbutyryl chloride in 100 cc. of acetone and 490 cc. (0.49 mole) of 1 *N* sodium hydroxide solution. The product separated as a white solid which was filtered and air-dried.

N-(2-Bromo-2-ethylbutyryl)-glycine (LII).—To a solution of 2.8 g. (0.01 mole) of N-(2-bromo-2-ethylbutyryl)-glycine ethyl ester[23] in 25 cc. of methanol, there was added, dropwise, at 5°, with stirring, 2 cc. (0.01 mole) of 5 *N* sodium hydroxide solution. After having been stored at room temperature overnight the solution was concentrated under reduced pressure to remove most of the methanol and the resulting solution was acidified with dilute hydrochloric acid to *p*H 1. The product separated from the cooled solution as a white precipitate which was filtered, washed with water, and dried.

1-(2-Bromo-2-ethylbutyryl)-3-methylurea (LVII).—A mixture of 25 g. (0.34 mole) of N-methylurea and 36.1 g. (0.12 mole) of 2-bromo-2-ethylbutyryl chloride was heated on a steam-bath for six hours with occasional swirling. A clear reddish-brown solution formed to which was added 100 g. of ice and 50 cc. of water. A gum formed which solidified upon trituration. The solid was filtered and washed first with cold water and then with petroleum ether (b.p. 20–40°). The crude solid was extracted with petroleum ether in a Soxhlet apparatus for 4 hours. Concentration of the solution to a small volume gave the product as a white solid.

1-(2-Bromo-2-methylpropionyl)-3-methylurea (XXIII).—A mixture of 20 g. (0.12 mole) of 2-bromo-2-methylpropionyl chloride and 17.8 g. (0.24 mole) of methylurea was heated on a steam-bath for 0.5 hour. An oily solid formed and the mass was treated with water and filtered. The white solid was dried on a porous plate.

1-(2-Bromo-2-methylbutyryl)-3-methylurea (XXX).—A mixture of 37.1 g. (0.5 mole) of dried methylurea and 39.9 g. (0.2 mole) of 2-bromo-2-methylbutyryl chloride was stirred and heated for 2 hours in an oil-bath at 60–87°. To the mixture, consisting of an amber liquid containing some colorless crystals, was added 100 cc. of water. On stirring and cooling, colorless crystals separated. These were filtered, ground in a mortar with ice-water, and filtered again.

(23) K. W. Rosenmund, *Ber.*, **42**, 4470 (1909).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.,[a] AND THE UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL[b]]

The Behavior of the Isomers of α,ε-Diaminopimelic Acid on Paper Chromatograms

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The amino acid α,ε-diaminopimelic acid can be resolved into the DD- and LL-isomers by means of paper chromatography without resorting to the use of optically active solvents. A solvent system is described in which the isomeric forms of α,ε-diaminopimelic acid can be examined in a complex protein hydrolysate.

Work[1] isolated α,ε-diaminopimelic acid (DAP) from *Corynebacterium diphtheriae* and suggested that it was the *meso*-isomer. Comparative paper chromatographic studies of this material with synthetic DAP[1,2] in a series of ten solvent systems indicated that the synthetic and natural DAP preparations behaved the same, although some streaking of the synthetic material was noted in phenol (NH_3 atmos.) using Whatman No. 4 paper.[3]

In the course of routine chromatographic studies with six solvent systems differing from those of Work[1] or Wright and Cresson,[2] we observed the presence of only one ninhydrin-positive material in synthetic DAP[4] (*cf.* Table I). However, in a methanol (80)–water (20)–pyridine (4) system,[5] we observed that this material could be separated into two distinct components. Two-dimensional paper chromatography in the above system (*cf.* Fig. 1) demonstrated that the separation was not due to the formation of ionic species or solvent artifacts and that both components were biologically active for the DAP auxotroph of *E. coli* 173-25.[6]

TABLE I

THE CHROMATOGRAPHIC BEHAVIOR OF SYNTHETIC DIAMINOPIMELIC ACID IN A VARIETY OF SOLVENT SYSTEMS

Whatman No. 1 paper, descending system, temp. 25°, 20 mcg., α,ε-diaminopimelic acid. Ninhydrin used for developing chromatogram.

Solvent system	*Rf*
n-BuOH (81)–H_2O (19)–$PTSO_3H$ (0.25)[a]	0.16
H_2O (19)–*n*-BuOH (81)	0
H_2O (90)–*n*-BuOH (4)–$PTSO_3H$ (0.25)	0.8
n-BuOH (4)–H_2O (96)	0.8
Methanol (80)–H_2O (20)–pyridine (4)	0.17, 0.26[b]
n-BuOH (50)–H_2O (25)–acetic acid (25)	0.21

[a] *p*-Toluenesulfonic acid. [b] Two components.

These data suggested that isomeric forms of DAP were being separated by means of paper chromatography. Confirmation of this fact was obtained by chromatography of the resolved isomers of DAP (LL, DD and *meso*)[7]; the LL- and DD-isomers were re-

(1) E. Work, *Biochem. J.*, **49**, 17 (1951).

(2) L. D. Wright and E. L. Cresson, *Proc. Soc. Exptl. Biol. Med.*, **82**, 354 (1953).

(3) Work, unpublished.

(4) Prepared by the method of J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2786 (1950).

(5) R. R. Redfield, *Biochim. Biophys. Acta*, **10**, 344 (1953).

(6) B. D. Davis, *Nature*, **169**, 534 (1952).

(7) E. Work, S. M. Birnbaum, M. Winitz and J. P. Greenstein, THIS JOURNAL, unpublished; kindly made available by Dr. J. P. Greenstein.