Anal. Calcd. for $C_{13}H_{15}N_2OPS$: C, 56.10; H, 5.43; N, 10.07; P, 11.13; S, 11.52. Found: C, 56.04; H, 5.56; N, 10.05; P, 11.44; S, 11.36.

Reaction of benzenesulfonyl chloride with bis(2-cyanoethyl)-phosphine. Experiment (b) above was repeated using 17.7 g. (0.1 mole) of benzenesulfonyl chloride in place of the *p*-toluenesulfonyl chloride. Following the same work up procedure there was obtained after recrystallization from isopropyl alcohol, 8.0 g. of *S*-phenyl bis(2-cyanoethyl)-phosphinothioate, m.p. 86–88°.

Anal. Calcd. for $C_{12}H_{13}N_2OPS$: C, 55.53; H, 4.96; P, 11.90; S, 12.13. Found: C, 55.44; H, 5.03; P, 12.03; S, 12.17.

Acknowledgment. The authors wish to express their appreciation to Dr. V. P. Wystrach for his interest and assistance in this work.

STAMFORD, CONN.

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

α-Amino Acid Amides. A Convenient Synthesis[1]

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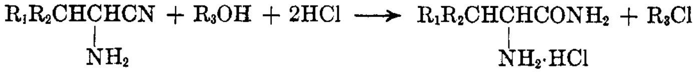
Investigation of the reaction of α-aminonitriles with alcoholic hydrogen chloride has led to a convenient high-yield synthesis of α-amino acid amide hydrochlorides.



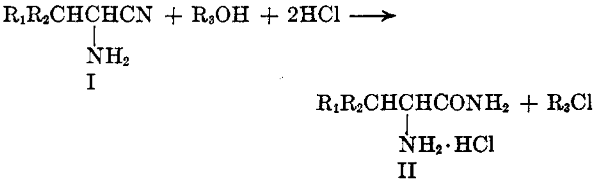
$$R_1R_2\underset{NH_2}{CH}CN + R_3OH + 2HCl \longrightarrow R_1R_2\underset{NH_2\cdot HCl}{CH}CONH_2 + R_3Cl$$

The course of the reaction is critically dependent upon the alcohol that is used for solvent. If $R_1 = H$ and $R_2 = H$ or alkyl then the alcohol R_3OH must be secondary; otherwise ester formation results. When R_1 and R_2 are both alkyl, R_3OH must be primary in order for any reaction to take place. These and related effects as well as the probable reaction mechanism are discussed.

During an investigation of the chemistry of α-aminonitriles, it became of interest to define their reaction with alcohols in the presence of anhydrous hydrogen chloride. The reaction of nitriles with alcohols and hydrogen chloride is, of course, well known; in general, imido esters are formed when equivalent amounts of alcohol are used and ortho esters result when the alcohol is present in excess.[2] Nitriles having α-substituents other than carbon have not been as extensively investigated. Steinkopf and Malinowski[3] investigated a series of α-substituted acetonitriles and observed that imido esters and/or amides were produced upon reaction with alcoholic hydrogen chloride and that amides were more readily formed when the α-substituent was a strong electron-attracting group. McElvain *et al.*,[4] observed the formation of both amides and carboxylic esters in addition to the desired ortho esters upon treatment of α-substituted nitriles with alcoholic hydrogen chloride and concluded that these by-products were due to the presence of at least two α-substituents.

Imido esters of α-aminonitriles and their sulfonyl and acyl derivatives have also been prepared.[5–8] In contrast, α-aminophenylacetonitrile is reported to give only the amide upon reaction with methanolic hydrogen chloride and the imido ester dihydrochloride of glycine to be transformed into glycinamide hydrochloride upon storage at ambient temperatures.[7] The possible general synthetic usefulness of this formation of α-amino amides, however, apparently was not recognized.

In the present investigation, treatment of a benzene solution of α-aminoisovaleronitrile (I; $R_1 = R_2 = CH_3$) with one or two equivalents of ethanol and hydrogen chloride resulted only in the precipitation of the corresponding hydrochloride. However, when the reaction was conducted in saturated ethanolic hydrogen chloride, valinamide hydrochloride (II; $R_1 = R_2 = CH_3$) precipitated in 75% yield upon refluxing the reaction mixture, and ethyl chloride was evolved.



$$\underset{\text{I}}{R_1R_2\underset{NH_2}{CH}CN} + R_3OH + 2HCl \longrightarrow \underset{\text{II}}{R_1R_2\underset{NH_2\cdot HCl}{CH}CONH_2} + R_3Cl$$

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[1] Presented in part at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 4, 1961.

[2] R. Roger and D. G. Neilson, *Chem. Revs.*, **61**, 179 (1961).

[3] W. Steinkopf and W. Malinowski, *Ber.*, **44**, 2898 (1911).

[4] (a) S. M. McElvain and B. Fajardo-Pinźon, *J. Am. Chem. Soc.*, **67**, 690 (1945); (b) S. M. McElvain and C. L. Stevens, *J. Am. Chem. Soc.*, **69**, 2663 (1947).

[5] R. A. Turner and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 3081 (1950).

[6] M. Mengelberg, *Chem. Ber.*, **89**, 1185 (1956).

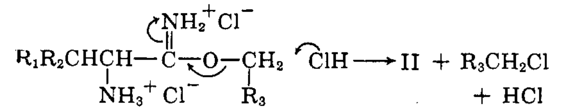
[7] A. N. Baksheev and N. I. Gavrilov, *J. Gen. Chem. U.S.S.R.*, **22**, 2077 (1952).

[8] A. Balog, E. Vargha, and I. Bolazs, *Chem. Abstr.*, **53**, 14961ª (1959).

When α-aminopropionitrile (I; $R_1 = R_2 = H$) and α-aminoisocapronitrile (I; $R_1 = H$, $R_2 = (CH_3)_2CH$) were treated similarly with ethanolic hydrogen chloride, ammonium chloride precipitated in high yield and the corresponding α-amino ester hydrochlorides were isolated. These data indicate that subtle structural differences are responsible for the unexpected and completely different paths that the reaction may assume. In any case, for the amide to be the predominant reaction product, no more than one equivalent of alcohol must react with the aminonitrile. Thus, under the existing reaction conditions, the imido ester dihydrochloride must be sufficiently hindered to prevent further reaction with the solvent. Consequently, alkyl chloride is eliminated and the desired amide hydrochloride precipitates.

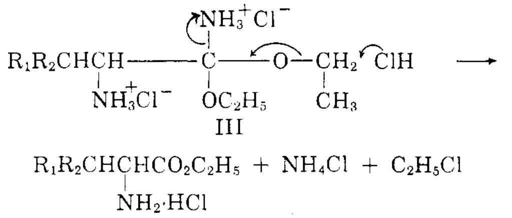
Since the imido ester derived from I ($R_1 = R_2 = CH_3$) apparently is sufficiently hindered to prevent further ethanolysis, it seemed reasonable to assume that if a secondary alcohol were used as a reaction solvent for α-aminonitriles with no β-branching, these materials should be convertible to amides also. Such was found to be the case. Treatment of I ($R_1 = R_2 = H$ and $R_1 = H$, $R_2 = (CH_3)_2CH$) with 2-propanol saturated with hydrogen chloride resulted in alaninamide and leucinamide hydrochlorides in 74% and 77% yields respectively. Furthermore, no valinamide hydrochloride was formed when 2-propanol was employed as solvent. With this understanding of the reaction, it remained routine to prepare the various α-amino acid amide hydrochlorides tabulated in Table I.

Pinner[9] apparently was the first to discover that, in general, pyrolysis of imido ester hydrochlorides produces both amides and alkyl chlorides in good yield. However, the reaction has received little attention as a preparative method, presumably due to the ease with which amides can be prepared by other means. McElvain and Tate[10] studied the kinetics of this pyrolysis and proposed a bimolecular reaction mechanism, although first order kinetics (with respect to the disappearance of chloride ion) were observed. This mechanism was substantiated by Stevens *et al.*[11] and later by Cramer and Baldauf[12] who demonstrated that if the imido ester was prepared from an optically active alcohol the configuration of the chloride formed in the reaction is inverted with respect to the alcohol. The present conversion of α-aminonitriles to α-amino amide hydrochlorides probably proceeds similarly.[13]



$$R_1R_2\underset{NH_3^+Cl^-}{CH}-\overset{NH_2^+Cl^-}{C}-O-\underset{R_3}{CH_2}\ ClH \longrightarrow II + R_3CH_2Cl + HCl$$

The formation of esters from the reaction of I with ethanol when there is no β-branching is of interest. Further ethanolysis of the imidate would give an intermediate (III) which, *via* reaction with chloride as described for the amide formation, would produce ammonium chloride and the observed ester. McElvain[2b] explains ester formation from imido ester hydrochlorides by a similar reaction with alkoxide. In the present case, this sequence seems unlikely since esters are observed only when the steric requirements enable further alcoholysis. Traces of ammonium chloride (±2%) are observed in the preparation of valinamide hydrochloride (II; $R_1 = R_2 = CH_3$) when butanol is used as the reaction solvent and only about 6% is formed with the use of ethanol.



$$R_1R_2\underset{NH_3^+Cl^-}{CH}-\overset{NH_3^+Cl^-}{\underset{OC_2H_5}{C}}-O-\underset{CH_3}{CH_2}\ ClH \longrightarrow$$

III

$$R_1R_2CH\underset{NH_2\cdot HCl}{CH}CO_2C_2H_5 + NH_4Cl + C_2H_5Cl$$

When the steric requirements of the reaction are considered, it would appear that the yield of the various amides can be improved further by minor variations of the structure of the alcohol that is used for the reaction solvent. Table II illustrates the effect of various alcohols on the yield and purity of several amide hydrochlorides. Allyl alcohol was exceptional in its reactivity and cleanness of reaction, especially for the preparation of isoleucinamide. With this solvent, a 71% yield was obtained in less than 18 hours, compared with the approximately 70 hours required to obtain a 50% yield in the presence of ethanol. From

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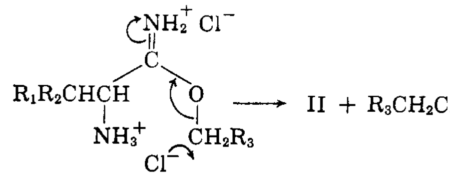
[9] A. Pinner, *Ber.*, **16**, 1643 (1883).

[10] S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2233 (1951).

[11] C. L. Stevens, D. Morrow, and J. Lawson, *J. Am. Chem. Soc.*, **77**, 2341 (1955).

[12] F. Cramer, and H. Baldauf, *Chem. Ber.*, **92**, 370 (1959).

[13] Presumably, a cyclic mechanism analogous to the one proposed by McElvain and Tate[10] is possible.



$$R_1R_2\underset{NH_3^+}{CH}-\overset{NH_2^+Cl^-}{C}-O-CH_2R_3\ Cl^- \longrightarrow II + R_3CH_2Cl$$

To define further this possibility isobutyronitrile was treated with isopropyl alcohol and hydrogen chloride under conditions that produce alaninamide hydrochloride (II; $R_1 = R_2 = H$) from I. The isopropyl imidate hydrochloride was found to be stable under these conditions, thus lending support to a cyclic mechanism and further substantiating the premise that amino amides are formed because further alcoholysis cannot take place. However, it seems equally likely that the relative instability of the imidate dihydrochloride derived from I is simply due to the inductive effect of the α-ammonium salt, as noted earlier for other electron-attracting groups.[3]

TABLE I

α-AMINO ACID AMIDE HYDROCHLORIDES

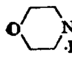
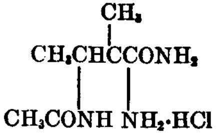
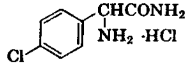
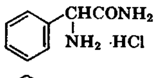
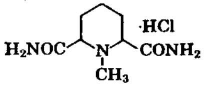
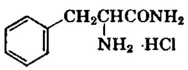
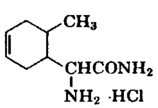
Amide Salt	M.P.	Reported M.P.	% Yield[b]	% Purity[c]	Reaction Solvent	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$HCl\cdot NH_2CH_2CONH_2$	200–203	186–189[d] 207–208[e] 203–205[f]	80	90	2-propanol	$C_2H_7ClN_2O$	—	—	—	—	—	—
$CH_3\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	169–172	170[g]	78	97	2-butanol	$C_3H_9ClN_2O$	—	—	—	—	—	—
$HCl\cdot CH_3NHCH_2CONH_2$	160–162	161[h]	91	98	2-propanol	$C_3H_9ClN_2O$	—	—	—	—	—	—
$HOCH_2\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	196–199	192–193[i]	78	98	2-propanol	$C_3H_9ClN_2O_2$	—	—	—	—	—	—
$CH_3\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	218–222	222–223[j]	72	98	2-propanol	$C_4H_{11}ClN_2O$	—	—	—	—	—	—
$(CH_3)_2\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}CONH_2$	266–268	264–266[k]	51	90	ethanol	$C_4H_{11}ClN_2O$	—	—	—	—	—	—
$(CH_3)_2CH\underset{\substack{\vert\\ NH_2\cdot HBr}}{C}HCONH_2$	237–239	233–235[f]	77	96	ethanol	$C_5H_{13}BrN_2O$	—	—	—	—	—	—
$CH_3(CH_2)_2\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	248–250	240[f]	75	95	2-propanol	$C_5H_{13}ClN_2O$	—	—	—	—	—	—
$(CH_3)_2CH\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	246–248	245[l]	89	98	butanol	$C_5H_{13}ClN_2O$	—	—	—	—	—	—
$CH_3SCH_2CH_2\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	189–190	192[m]	76	95	2-butanol	$C_5H_{13}ClN_2OS$	—	—	—	—	—	—
$CH_3CH_2OCH_2\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	165–166	—	51	82	2-propanol	$C_5H_{13}ClN_2O_2$	35.61	7.77	16.62	35.82	7.80	16.39
 NCH_2CONH_2 $\cdot HCl$	193–195	—	90	99	2-propanol	$C_6H_{13}ClN_2O_2$	39.89	7.25	15.51	39.91	7.44	15.29
$(CH_3)_2CH\underset{\substack{\vert\\ CH_3NH\cdot HBr}}{C}HCONH_2$	259–261	—	37	—	ethanol	$C_6H_{15}BrN_2O$	34.13	7.16	13.27	33.90	7.10	12.97
$(CH_3)_2CHCH_2\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	224–229	—	77	97	2-propanol	$C_6H_{15}ClN_2O$	43.24	9.07	16.81	43.51	8.98	16.80
$CH_3CH_2\underset{\substack{\vert\\ CH_3}}{C}H\underset{\substack{\vert\\ NH_2\cdot HCl}}{C}HCONH_2$	232–234	—	71	98	allyl alcohol	$C_6H_{15}ClN_2O$	43.24	9.07	16.81	43.13	8.94	16.53

TABLE I (*Continued*)

Amide Salt	M.P.	Reported M.P.	% Yield[b]	% Purity[c]	Reaction Solvent	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
 $\underset{NH_2\cdot HCl}{(CH_3CH_2)_2CCONH_2}$	244–246	243–247[n]	58	99	ethanol	$C_6H_{15}ClN_2O$	—	—	—	—	—	—
 $\underset{CH_3NH\cdot HCl}{CH_3(CH_2)_2CHCONH_2}$	176–177	—	53	93	allyl alcohol	$C_6H_{15}ClN_2O$	43.24	9.07	16.81	43.25	9.00	16.48
 $CH_3\underset{CH_3CONH}{CH}\overset{CH_3}{\underset{NH_2\cdot HCl}{C}}CONH_2$	281–284	—	74	80	allyl alcohol	$C_7H_{16}ClN_3O_2$	39.90	8.13	19.95	39.68	7.84	20.08
	>250	—	57	87	ethanol	$C_8H_{10}Cl_2N_2O$	43.46	4.56	12.67	43.73	4.32	12.44
	270–273	>200[p]	78	96	ethanol	$C_8H_{11}ClN_2O$	51.48	5.94	15.01	51.42	5.95	14.72
	279–281	—	50[q]	—	ethanol	$C_8H_{16}ClN_3O_2$	43.34	7.28	18.95	43.59	7.02	18.69
	238–241	238–239[r]	55	94	2-propanol	$C_9H_{13}ClN_2O$	—		—	—	—	—
	266–267	—	25	87	ethanol	$C_9H_{13}ClN_2O$	53.87	6.53	13.96	54.08	6.61	13.85
	272–274	—	66	98	allyl alcohol	$C_9H_{17}ClN_2O$	52.80	8.37	13.69	52.85	8.41	13.48

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[a] Decomposition points, except possibly for alaninamide, sarcosinamide, serinamide, *O*-ethylserinamide, 4-morpholineacetamide and *N*-methylnorvalinamide. [b] Crude yield; based on the starting carbonyl component. [c] Calculated from a chloride analysis, assuming that amide salt and ammonium chloride are the only components present. [d] P. Bergell and v. Wulfing, *Hoppe-Seyler's Z. physiol. Chem.*, 64, 354 (1910). [e] Reference 7. [f] G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 74, 1580 (1952). [g] A. P. N. Franchimont and H. Friedman, *Rec. trav. chim.*, 25, 77 (1906). [h] C. S. Marvel, J. R. Elliott, F. E. Boettner, and H. Yuska, *J. Am. Chem. Soc.*, 68, 1681 (1946). [i] E. Rothstein, *J. Chem. Soc.*, 1968 (1949). [j] E. L. Smith and W. J. Polglase, *J. Biol. Chem.*, 180, 1209 (1949). [k] Reference 7. [l] E. L. Smith, D. H. Spackman, and W. J. Polglase, *J. Biol. Chem.*, 199, 801 (1952). [m] K. Merck, F. Merck, and W. Merck, Brit. Patent 668,235. [n] S. R. Safir, H. Dalalian, W. Fanshawe, K. Cyr, R. Lopresti, R. Williams, S. Uphan, L. Goldman, and S. Kushner, *J. Am. Chem. Soc.*, 77, 4840 (1955). [p] J. V. Dubsky, *Ber.*, 52, 225 (1919). [q] Based on the dinitrile. H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, *in press.* [r] J. C. Sheehan and D. H. Yang, *J. Am. Chem. Soc.*, 80, 1154 (1958).

TABLE II

EFFECT OF SOLVENT ON THE YIELD OF α-AMINO ACID AMIDE HYDROCHLORIDES

Amide Hydrochloride	Solvent Alcohol	% Yield	Purity
Valine	Methyl	54	—
	Ethyl	75	94
	n-Propyl	82	98
	Isopropyl	No reaction	—
	n-Butyl	89	98
	Allyl	86	99
Isoleucine	Methyl	Small amount of ammonium chloride	
	Ethyl	51	84
	Allyl	71	98
Alanine	Ethyl	Ammonium chloride only	
	Isobutyl	"	"
	Isopropyl	74	96
	2-Butyl	78	97
Methionine	Ethyl	Ammonium chloride only	
	Isopropyl	71	93
	2-Butyl	76	95

these results, it is apparent that many of the yields of amides listed in Table I are not optimal.

This method of synthesis of α-amino acid amide hydrochlorides appears to be novel and widely applicable, affording a class of α-amino acid derivatives that, in general, have always been difficult to obtain. The synthesis avoids the troublesome separation from inorganic salts which has plagued the isolation of amino acids and, in addition, affords amino acid derivatives in a form amenable to resolution, where desired. Nutritional studies directed at determining the extent to which these amide hydrochlorides are capable of replacing the corresponding essential α-amino acids have been conducted and will be reported in detail.[14]

EXPERIMENTAL[15]

The following preparations of valinamide and isoleucinamide hydrochlorides serve as a general procedure for the synthesis of α-amino acid amide hydrochlorides and hydrobromides. The only necessary variations involve an appropriate change in the alcohol that is used for a solvent, as noted in Tables I and II, and, for highly hindered nitriles, a longer reaction period before the final heating.

With ketones that do not form cyanohydrins readily, the α-aminonitrile is conveniently prepared by the action of ammonia on the mixture of ketone and hydrogen cyanide. Most of the amide salts tabulated in Table I can be further purified, if desired, by crystallization from acetic acid (preferred) or alcohols.

DL-*Valinamide hydrochloride.* One-half mole of crude isobutyraldehyde cyanohydrin (from 36 g. of isobutyraldehyde, 14 g. of hydrogen cyanide and 1 ml. of pyridine) was allowed to react under autogenous pressure with 100 ml. of anhydrous ammonia at about 25° for 18 hr. The excess ammonia was then allowed to evaporate and the last traces were removed by warming to 40° *in vacuo.* A solution of the crude nitrile in 300 ml. of butanol was saturated with anhydrous hydrogen chloride at 20°, 119 g. being required. The reaction mixture was allowed to stand overnight at 25° and then heated to boiling over a period of 1 hr. After refluxing the slurry of precipitated product for 15 min., it was cooled to 10° and the solids were collected. The filter cake was washed with butanol followed by ether and dried to give 68 g. (89%) of valinamide hydrochloride, m.p. 243–245° dec.

DL-*Iso- and alloisoleucinamide hydrochloride.* A solution of 0.5 mole of crude α-amino-β-methylvaleronitrile (prepared as described above for α-aminoisovaleronitrile) in 300 ml. of allyl alcohol was saturated with anhydrous hydrogen chloride at 20°, 139 g. being required. The temperature gradually rose to 33° and the mixture was then allowed to stand overnight. After cooling the mixture to 5°, the precipitated solids were collected, washed with ether, and dried. A total of 59 g. (71%) of product was obtained as colorless crystals, m.p. 214–219° dec.

Reaction of isobutyronitrile with 2-propanol and hydrogen chloride. A solution of 138 g. (2.0 moles) of isobutyronitrile in 1 l. of anhydrous 2-propanol was saturated with dry hydrogen chloride (351 g.) at 25°. The mixture was allowed to stand at room temperature overnight and was then heated under reflux for 2 hr. Volatile material was then evaporated *in vacuo* at steam bath temperature leaving 270 g. of colorless solids. An analytical sample of this material was obtained as colorless crystals, m.p. 96–98° (gas) after several crystallizations from isopropyl ether. The analytical data are consistent with those expected for the imido ester hydrochloride.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.74; H, 9.74; Cl, 21.40; N, 8.46. Found: C, 50.87; H, 9.89; Cl, 20.90; N, 8.34.

The above imido ester was readily pyrolyzed to isobutyramide in 80% yield, b.p. 136–142° (50 mm.), m.p. 109–120°. Subsequent purification raised the melting point to 129–130°.

Acknowledgment. The authors wish to thank C. R. McClure and F. G. Bollinger for their able assistance and Q. Quick and his associates for microanalyses and spectral data.

SOUTH CHARLESTON, W. VA.

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[14] D. G. Crosby, J. R. Thomson, and H. E. Johnson, *J. Nutrition.*

[15] Melting points are corrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer.