TABLE V

DISSOCIATION CONSTANTS OF 3-SUBSTITUTED-3-METHYLACRYLIC ACIDS

Substituent	10^5K	Method of evaluation	Ref.	Acid
CO_2Et	553	Conductimetric	25	3-Carboxyethyl-3-methylacrylic
Et	7.1^a		11	3-Methyl-2-pentenoic
Me	7.6^a	Conductimetric	11	3-Methyl-2-butenoic
Cl	36		12	3-Chloro-2-butenoic
H	95	Conductimetric	12	Isocrotonic

All data in water at 25°. The configuration in these acids is such that the methyl group is *cis* to the carboxyl group. The dissociation constants are non-thermodynamic unless otherwise stated. ^{a} Thermodynamic constant.

From these correlations, it can be seen that the Hammett equation is directly applicable to the *trans*-olefinic systems. Other reaction series are now under consideration.

Acknowledgment.—The helpful advice and discussion of Professor H. Nechamkin, Pratt Institute, is gratefully acknowledged. The authors wish also to acknowledge the suggestion of one of the reviewers regarding the use of the substituent constants proposed by McDaniel and Brown,[20] thereby making unnecessary the use in some cases of σ_p-values.

TABLE VI

DISSOCIATION CONSTANTS OF 3-SUBSTITUTED-3-CARBOXYACRYLIC ACIDS (SUBSTITUTED MALEIC ACIDS)

Substituent	10^5K	Method of evaluation	Ref.	Acid
H	14.2	From pH	26	Maleic
Me	5.14	From pH	26	Citraconic
Et	2.30	Conductimetric	27	Ethylmaleic
Cl	10.0	From pH	26	Chloromaleic
Br	35.0	From pH	26	Bromomaleic
OH	2.505	Conductimetric	28	Hydroxymaleic

(27) K. Von Auwers and O. Ungenach, *Ann.*, **511**, 152 (1934).

(28) A. Wohl and P. Clausner, *Ber.*, **40**, 2308 (1907).

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES MEDICAL SCHOOL]

Base Strengths of Cyanoamines[1]

BY GEORGE W. STEVENSON AND DALLAS WILLIAMSON

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Substitution of aliphatic amines with cyano groups lowers their basicities. The N-cyano, α-cyano, β, γ, δ and ϵ-cyanoamines are weaker by approx. 13, 5.7, 3.1, 1.6, 0.8 and 0.4 pK units, respectively. The ΔpK_a of n cyanosubstituted amines = approx. n (single ΔpK). The lowered basicity appears due to the large inductive field effect of the cyano group. A spectrophotometric method was developed to determine the pK_a's of the very weak bases. Because of the wide range of pK_a's of the cyanoamines, their ease of preparation, and stability, aliphatic cyanoamines should be useful.

During the course of conversion of secondary to tertiary bases by cyanoethylation it was found that the tertiary cyanoethylamines were considerably weaker bases than the secondary amines and about 3 pK units weaker than the corresponding tertiary ethylamines. That the highly electron-withdrawing cyano group should exert a base-weakening effect was to be anticipated but its magnitude was surprising.

Despite the large number of cyanoamines which have been synthesized, only one paper dealing with the base strengths of the cyanoamines, by Marxer,[2a] has appeared.[2b] Marxer found that the formation of cyanomethyl tertiary amines from several secondary amines resulted in an average decrease in pK_a of 6.5 pK units.[2a] However, it was shown that the pK_a of α-piperidine-isobutyronitrile was less than that of piperidine by only 2.0 pK units.

It has been found in this investigation that the cyano group is more effective than all others in lowering basicity, possibly excluding some in which the electronegative group is attached directly to the nitrogen. Published pK values for some other types of amines are given below. Groups also can be compared using δ^*-values as shown below. Taft has compiled a list of δ^*-values.[3]

The pK_a's of N-chlorodimethylamine and N-chlorodiethylamine have been reported as 0.46 and 1.02 by Weil and Morris.[4] A series of β-chloroethylamines has been titrated by Cohen, *et al.*[5] The weakest of these was tri-β-chloroethylamine with a pK_a of 4.39. This is a much stronger base than the corresponding cyano compound which has a pK_a of 1.1. The effect of the fluoro group is comparable with that of the chloro. The hydroxyl has a considerably smaller effect, the pK_a of hydroxylamine being 5.97[6] and that of triethanolamine, 7.77.[7a]

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(1) This investigation was supported by Research Grant B-1106 from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, U. S. Public Health Service. Presented in part at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958.

(2) (a) A. Marxer, *Helv. Chim. Acta*, **37**, 166 (1954). (b) Since the completion of this work another paper dealing with the PK_a's of N-cyano-, α-cyano- and β-cyanoamines has been published: S. Soloway and A. Lipschitz, *J. Org. Chem.*, **23**, 613 (1958). The pK_a's of 11 compounds are given, 5 of which are included also in this study. The pK_a's are in reasonable agreement except for that of diethylcyanamide which is reported by the above authors as 1.2; see footnote 7b.

(3) R. W. Taft, Jr., in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 619.

(4) I. Weil and J. C. Morris, THIS JOURNAL, **71**, 3123 (1949).

(5) B. Cohen, E. R. Van Artsdalen and J. Harris, *ibid.*, **70**, 282 (1948).

(6) T. C. Bissot, R. W. Parry and D. H. Campbell, *ibid.*, **79**, 799 (1957).

(7) (a) N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3473 (1932). (b) In addition to the value for the pK_a of this compound, −2.0 as determined by the spectrophotometric method, two additional observations indicate the pK_a of this compound must be less than zero. When diethylcyanamide (either Eastman No. 6326 or that prepared for this study) was dissolved in water at room temp., about 1.3 ml. saturated

Considering the wide range of pK_a's of the cyanoamines, their ease of preparation and their relative stability, these compounds are unique and potentially useful aliphatic amines. In order to explore preparation of these compounds, and to determine the relation between the structure of cyanoalkyl amines and their basicities, the cyanodiethylamines from diethylcyanamide to diethylaminocapronitrile and various multi-cyano substituted amines were prepared and their pK's measured. In Table I are listed the pK_a's of the various cyanoamines, their ΔpK's with the compounds in which –CN has been replaced with –H, and their ΔpK's with the unsubstituted starting amine, either ammonia, or a primary or secondary amine.

The N-cyano compound has only slight basicity with a pK_a of -2.0,[7b] whereas the longest-chained compound in the series, diethylaminocapronitrile, has a pK_a of 10.46, only 0.44 pK unit weaker a base than the corresponding alkylamine. The rate of decrease of ΔpK per additional methylene group between the amino and cyano groups appears to indicate that there is little or no difference in the pK's of the longer chained cyano- and alkylamines, although this has not yet been experimentally demonstrated.

Multi-substitution by cyanoalkyl groups on amines produces approximately equivalent decrements in the pK's in the cases of two cyanomethyl substituents or either two or three cyanoethyl substituents.

TABLE I

pK_a'S AND ΔpK_a'S OF THE CYANOAMINES[q]

RCN	pK_a	ΔpK_a (–RH) – (–RCN)	ΔpK_a (>NH) – (>NRCN)
Cyanodiethylamines			
Et_2NCN	-2.0 ± 0.3	13.0[a]	13.0[a]
Et_2NCH_2CN	4.55	5.74[b]	6.43[a]
$Et_2N(CH_2)_2CN$	7.65	3.10	3.33[a]
$Et_2N(CH_2)_3CN$	9.29	1.56	1.69[a]
$Et_2N(CH_2)_4CN$	10.08	0.82	0.90[a]
$Et_2N(CH_2)_5CN$	10.46	0.44	0.52[a]
$Et_2NC(CH_3)_2CN$	9.13		1.85[a]
Multi-cyano substituted amines			
$HN(CH_2CN)_2$[c]	$0.2 \pm .1$	10.4[d]	9.0[e]
$EtN(CH_2CN)_2$	$-0.6 \pm .1$	10.6[f]	11.3[g]
$HN(CH_2CH_2CN)_2$	5.26	5.72[a]	3.96[e]
$EtN(CH_2CH_2CN)_2$	4.55	6.20	6.12[g]
$N(CH_2CH_2CN)_3$	$1.1 \pm .1$	9.6	8.1[e]
Other cyanoamines			
H_2NCH_2CN	5.34	5.29[h]	3.88[e]
N-Piperidine-CH_2CN	4.55[i]	5.53[j]	6.67[k]
N-Piperidine-$C(CH_3)_2CN$	9.22[l]		2.00[k]
N-Amphetamine-$(CH_2)_2$-CN[m]	7.23	2.92[n]	2.65[o]
N-Methamphetamine-$(CH_2)_2CN$[p]	6.95		3.13
N-Norcodeine-$(CH_2)_2CN$	5.68		3.44

[a] pK_a of diethylamine = 10.98; Hall and Sprinkle, ref. 7*a*. [b] pK_a of methyldiethylamine = 10.29; J. Hansson, *Svensk. Kem. Tidskrift*, **67**, 256(1955). [c] Eastman No. P7164, recrystallized from ethanol, m.p. 75–76° (Kofl.), m.p. 75–77°, H. S. Mosher, J. Cornell, Jr., O. L. Stafford and T. Roe, Jr., THIS JOURNAL, **75**, 4951(1953). [d] pK_a of dimethylamine = 10.64; ref. 7*a*. [e] pK_a of ammonia = 9.22; D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (*London*), **A169**, 190 (1938). [f] pK_a of dimethylethylamine = 9.99; footnote *b*. [g] pK_a of ethylamine = 10.67; W. S. Fyfe, *J. Chem. Soc.*, 1347 (1955). [h] pK_a of methylamine = 10.63; D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc.* (*London*), **A177**, 511 (1941). [i] pK_a of N-piperidineacetonitrile = 4.5; A. Marxer, ref. 2d. Other pK_a's listed: N-dimethylaminoacetonitrile, 4.1; N-pyrrolidineacetonitrile, 4.8; and N-morpholineacetonitrile, *ca.* 2. [j] pK_a of N-methylpiperidine = 10.08; S. Searles, M. Tamres, F. Block and L. A. Quarterman, THIS JOURNAL, **78**, 4918 (1956). [k] pK_a of piperidine = 11.22; footnote *j*. [l] pK_a of α-piperidineisobutyronitrile = 9.2; ref. 2d. [m] Amphetamine is α-methylphenethylamine. [n] N-Ethylamphetamine was kindly supplied by Dr. Gordon A. Alles. [o] pK_a of amphetamine = 9.93; G. P. Lewis, *Brit. J. Pharmacol.*, **9**, 488 (1954). [p] Methamphetamine is N,α-methylphenethylamine. [q] See also Soloway and Lipschitz, footnote 2*b*.

The base-weakening effect of the cyano group is probably due either to inductive, field effects, or to a direct interaction of the cyano group with the amine by quasi-ring formation or intermolecular complexing. That the base-weakening is not due to direct interaction is shown by the facts that the cyanomethylamines are weak bases but could not form quasi-rings, by the equivalent decrements of pK of additional cyanoalkyl groups and by the regular decrease of the base-weakening effect with increasing chain length and apparently negligible pK differences between the long chain cyano- and alkylamines.

A generally satisfactory relationship between the base strengths of amines and the inductive, field effects of the amine substituents exists. Hall[8] has recently reported equations relating the $\Sigma\sigma^*$-values of the substituents of amines with their pK_a's. These equations can be used in conjunction with the table of σ^*-values compiled by Taft.[3] Hall's equations have been found useful in this Laboratory for predicting approximate pK values. However, only one σ^*-value for a cyanoalkyl group is available, that of the cyanomethyl group. When this value of 1.30 is used with Hall's equation, the calculated pK_a is about 1.4 pK units too high.

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10 ml. of distilled water, whereas about 1.4 ml. saturated 10 ml. of 1 *M* HCl. The pH of this latter saturated solution was within 0.02 pH unit of that of pure 1 *M* HCl, though the mole ratio of diethylcyanamide/HCl was greater than 1. Both the failure of significant increase in the solubility or pH in the 1 *M* HCl solution indicates that salt formation did not take place to any significant extent even in 1 *M* HCl. The pK_a of diethylcyanamide therefore cannot be measured using the experimental method described by Soloway and Lipschitz.

That the pK_a value -2.0 refers to protonation of the Et_2N–nitrogen is not certain, since protonation of the cyano nitrogen is also possible. Some additional observations are pertinent. When the compound was dissolved in 1.8 *M* HCl there was a rapid but gradual increase in the absorbance at 210 or 212 mμ up to approx. 20 × the initial absorbance within 1 hour. After dilution to 0.9 *M* acid there was a slower decrease in absorbance (to 35% in 20 min.). In 1.8 *M* H_2SO_4 no appreciable increase in absorbance occurred. In the higher concentrations of H_2SO_4 necessary for measurement of the pK_a, absorbance did increase with time making necessary rapid measurement of absorbance and back extrapolation of the values to obtain the initial decrease in absorbance probably due to salt formation. The most reasonable explanation of these results is that an intermediate in the hydrolysis of these compounds is formed reversibly and more readily with HCl than with H_2SO_4. The reaction may be $(CH_3CH_2)_22NC\equiv N + RH \leftrightarrows (CH_3CH_2)_2NCR{=}NH$.

The protonation of this latter type of compound is proposed as the rate-determining step in the hydrolysis of cyanamides by S. Ohishi and H. Takamura, *Bull. Chem. Soc. Japan*, **27**, 416–421 (1954).

It is most likely that $(CH_3CH_2)_2NC\equiv {}^+NH$ is only a transitory intermediate in formation of the imino chloride or imino bisulfate whereas $(CH_3CH_2)_2{}^+NHC\equiv N$ is the salt in the proton, base, salt equilibrium.

(8) H. K. Hall, Jr., THIS JOURNAL, **79**, 5441 (1957).

Hall's equations have been used to calculate σ^*-values for the various cyanoalkyl groups and these are listed in Table II.

TABLE II

DECREASE OF INDUCTIVE EFFECT IN THE $Et_2N(CH_2)_nCN$ SERIES

n	ΔpK^a	Decrease factor^b	10.90 − pKa	Decrease factor^b	σ^{*c}	σ^* + 0.2	Decrease factor^b
0	13.0	2.26^d	12.9	2.03	3.72	3.92	2.05
1	5.74	1.85^e	6.35	1.95	1.71	1.91	1.91
2	3.10	1.99	3.25	2.02	0.80	1.0	2.00
3	1.56	1.90	1.61	1.96	.30	0.50	1.92
4	0.82	1.86	0.82	1.86	.06	.26	1.86
5	0.44		0.44		− .06	.14	
	Mean	1.97		1.96			1.95

^{a} $pK_{aRH} - pK_{aRCN}$. ^{b} Value$_n$/value$_{n+1}$. ^{c} Calculated from Hall's equation, ref. 8. ^{d} The ratio is high because the secondary amine Et_2NH is being compared with the tertiary amine Et_2NCN. ^{e} Soloway and Lipschitz report decrease factors of 1.8 for cyano methyl compounds/cyanoethyl compounds.

It is of interest to determine the decrease of inductive effect per additional methylene in the $Et_2N(CH_2)CN$ series. This has been approached in three ways: first, by dividing the ΔpK (–RH – –RCN) of a compound by the ΔpK of the compound immediately below it. The values are listed in Table II. Second, if it is assumed that there is no difference between the pK's of cyano-and alkylamines with long chains and that the pKa of the long chain diethylamines is 10.90, as is supported by the relative constancy of the pK_a's of diethylpropyl-, butyl- and amylamines, then the effect of the cyano group in any given position can be related to the zero effect of the cyano group in the cyanoamine whose pK_a is 10.90. In Table II are listed the differences obtained by subtracting the pK_a's of the diethylamines from 10.90 and the ratios of the differences. Third, if the pK_a of the diethylamine with a long-chain cyano group is 10.90, then Hall's equation can be used to calculate a σ^*-value for such a group. This value is −0.20. In order to compare all the σ^*-values with each other, as has been done above, it is necessary to use algebraic differences by adding 0.20 to each of the σ^*-values. These values and the values of the ratios are given in Table II.

The consistency of these ratios is good and indicates that the effect of the cyano group decreases by approx. $^1/_2$ rather than $^1/_{2.8}$ per methylene as postulated by Taft.[9] This consistency supports the inductive, field mechanism for the lowering of the basicity by the cyano group.

The relatively high pK_a's of the α-aminoisobutyronitriles as shown by Marxer[2a] in the case of α-piperidineisobutyronitrile has been confirmed and has been shown to be the case also with α-diethylaminoisobutyronitrile. This striking effect should be studied further.

Spectrophotometric Measurement of pK_a's.—A method was developed to determine the pK_a's of the very weak bases. It is based upon the finding that the aliphatic amino groups have appreciable ultraviolet absorption in the 200-220 mμ region but that their salts have only slight absorption. This has been noted previously with diethylamine.[10] In measuring the absorptions of various aliphatic bases without other absorbing groups a rising curve without peaks was found. At a given wave length such as 210 mμ the relation between absorbance and concentration was found to be linear. It was found that the relative proportions of salt and base at various pH's could be determined and a titration curve constructed. The ϵ of various bases and their salts are indicated in Table III.

TABLE III

ULTRAVIOLET ABSORPTION OF BASES AND SALTS AT 210 mμ

Compound	ϵ_{base}	ϵ_{salt}
$(NCCH_2CH_2)_3N$	2000	7
$(NCCH_2CH_2)_2NEt$	795	2
$NCCH_2CH_2NEt_2$	720	2
Piperidine-CH_2CN	434	8
$NCNEt_2$	400	212
$(NCCH_2)_2NEt$	390	11
$(NCCH_2)_2NH$	143	10
$(CH_3)_2NH$	134	0
$EtNH_2$	132	0
CH_3NH_2	101	0

Using this method the pK_a's of several bases with pK_a's ranging from 4 to 8 were determined and did not differ more than 0.05 pK unit from the values determined potentiometrically. Since this spectrophotometric method is more difficult to carry out, it is not preferred for stronger bases, except in special instances. With the very weak bases the Hammett acidity function, H_0, of the various mixtures of sulfuric acid and water[11] was used in place of pH's as measured by the pH meter. The relative proportions of base and salt were determined from the ϵ of the solution at 210 mμ and the H_0.[12] The ϵ-values of the neutral base forms were not found to vary appreciably with acid concentration in most cases so no elaborate calculations were necessary.

Experimental[13]

A Beckman model G pH meter with glass and calomel electrodes was used. Spectrophotometric measurements were made with a Beckman DU spectrophotometer. A Tempunit and a water cooling coil were used to maintain a constant temp. bath at 25 ± 0.1°. Solutions of these several pH's, prepared according to U.S. Bureau of Standards specifications, were used to calibrate the pH meter at 25° in the appropriate regions: 1.10 (0.1 N HCl), 3.57 (potassium hydrogen tartrate), 4.01 (potassium hydrogen phthalate), 6.86 (phosphate), 9.18 (borax), 10.02 (carbonate).

Potentiometric Measurement of pK's and Equivalent Weights.—Compounds were titrated potentiometrically in 0.01 M solutions in water at room temp. of 24–29°. Strong bases were titrated with hydrochloric acid and weak bases were titrated as their salts with sodium hydroxide.[14] Equivalent weights were calculated using as the titration endpoint the pH at which the ΔpH was maximum. If these values were satisfactory and the calculation of pK_a's for points on the curve between 15 and 85% titration were rela-

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(9) Ref. 3, p. 592.

(10) H. Ley and B. Arends, *Z. physik. Chem.*, **B17**, 197 (1932).

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 268.

(12) The equation $pK_a = H_0 + \log(\epsilon_{base} - \epsilon_{soln.})/(\epsilon_{soln.} - \epsilon_{salt})$ was used.

(13) Microanalyses by Microchemical Specialties Co., Berkeley, Calif. All m.ps. on Kofler micro hot stage, corrected.

(14) Where pKa's were 2 or less, equivalent weights were determined by formation of a salt in ether and titration of a water solution thereof. The pKa's were determined using the spectrophotometric technique.

tively constant, then the pK_a of the compound was measured at 25° by addition of 0.5 mole of standard HCl or NaOH to 1 mole of the base or the salt, respectively, and the measurement of the pH. These usually differed less than 0.05 pK unit from the values from the curves. Concentrations of total base were 0.01 M. The pK_a's were determined using the equations

$$pK_a = p\text{H} + \log(\text{salt} + \text{OH}^-)/(\text{base} - \text{OH}^-) + \log \gamma_{\text{salt}} \quad \text{for strong bases}$$

$$pK_a = p\text{H} + \log(\text{salt} - \text{H}^+)/(\text{base} + \text{H}^+) + \log \gamma_{\text{salt}} \quad \text{for weak bases}$$

The log γ_{salt} was approximated from Kielland's values.[15] Due to experimental difficulties, values for the diethylalkylamines had to be obtained using special techniques.[16]

Diethylcyanamide.—A solution of 0.15 mole of cyanogen bromide and 0.20 mole of triethylamine in chloroform was left at room temp. for 2 days. After removal of volatile material *in vacuo* at room temp., water was added to the residual solid and oil. The oil layer was separated and distilled. A 53% yield of liquid boiling at 95–103° (approx. 80 mm.) was obtained.

Glycinonitrile·$^1/_2$ H_2SO_4 was prepared from ammonium chloride through the intermediate methyleneaminoacetonitrile.[17]

Anal. Calcd. for $C_2H_5N_2O_2S_{1/2}$: equiv. wt., 105.1. Found: equiv. wt., 105.1.

N,N-Diethylglycinonitrile·HCl.—The base was dissolved in ether and anhydr. HCl was added. The ether residue was crystallized from ethanol–acetone. The crystals were dried for 30 min. at 61° (0.01 mm.), m.p. 188–190°[18]; solubility in cold ethanol approx. 9 g./100 g. of solvent.

Anal. Calcd. for $C_6H_{13}N_2Cl$: equiv. wt., 148.6; N, 18.85. Found: equiv. wt., 156.4; N, 19.05.

N-Piperidineacetonitrile.—Prepared using the method of Luten, an 87% yield of compound was obtained, b.p. 113–115° (47 mm.).[19] The liquid before it crystallized had $d^{25}{}_{14}$ 0.949, m.p. *ca.* 27°.

Hydrochloride was prepared by addition of anhydr. HCl to an ether solution of the base. The residue was crystallized from ether-acetone. After 3 crystallizations the material dried 2 hr. at 61° (0.01 mm.) had a m.p. of 186–187°.[20]

Anal. Calcd. for $C_7H_{13}N_2Cl$: equiv. wt., 160.6; N, 17.44. Found: equiv. wt., 163.3; N, 17.25.

Ethyliminodiacetonitrile.—Adding 0.15 mole of ethylamine (70% in water) to 0.45 mole of glycolonitrile (50% in water) gave an exothermic reaction. After standing at room temp. overnight, the mixture was extracted with three 25-ml. portions of ether. The combined ether was washed with several portions of dilute sulfuric acid. All washes were kept at pH 2 or above. The oil from evaporation of the ether was dried with anhydr. sodium sulfate. A 19% yield of the base was obtained, b.p. 89–90° (0.3 mm.).[21]

Hydrochloride.—Anhydrous HCl was added to an ether solution of the base. Crystalline salt formed which was filtered and washed with ether. After drying, a 93% yield of salt was obtained, m.p. 109–111°.[21]

Anal. Calcd. for $C_6H_{10}N_3Cl$: equiv. wt., 159.6. Found: equiv. wt., 161.1.

α-(N,N-Diethylamino)-isobutyronitrile.—Equimolar quantities of diethylamine and acetone cyanohydrin were combined and left at room temp. for 4 hr. The reaction mixture was refluxed for 55 minutes, then heated without a condenser for 15 minutes to drive off diethylamine. A 25% yield of liquid boiling at 67° (16 mm.)[22] was obtained. The equiv. wt. of this was 156. This determination was repeated after a molecular distillation was carried out at 27° (0.01 mm.).

Anal. Calcd. for $C_8H_{16}N_2$: equiv. wt., 140.2. Found: equiv. wt., 143.

α-(N-Piperidine)-isobutyronitrile.—Equimolar quantities of piperidine and acetone cyanohydrin were refluxed for 10 hr. A 70% yield of compound with a b.p. of 92–96° (15 mm.)[23] was obtained. This was converted to solid hydrochloride in ether, reconverted to the base, and redistilled for purification; m.p. of the base, 41–45° (Kofl.).[23]

Anal. Calcd. for $C_9H_{16}N_2$: equiv. wt., 152.2. Found: equiv. wt., 153.6.

Cyanoethylation with Acrylonitrile.—Aminopropionitriles were prepared from the bases and acrylonitrile[24] with the exception of nitrilotripropionitrile which could not be prepared on a small scale in this way, although a 6% yield has been obtained on the liter scale.[25] Attempts included the use of 10-mole ratios of acrylonitrile/either ammonia or iminodipropionitrile refluxed for 24 hr.

Reactions were carried out using excess acrylonitrile as solvent either at room temp. or in refluxing acrylonitrile. The products usually were purified by removal of excess acrylonitrile *in vacuo*, formation of hydrochloride salts, and recrystallization thereof.

Iminodipropionitrile·HCl: mole ratio, 2; room temp. for 24 hrs.; yield 88%, m.p. 140–146° (Kofl.); and cold solubility in 95% ethanol, 1.6 g./100 g.

Anal. Calcd. for $C_6H_{10}N_3Cl$: equiv. wt., 159.6, C, 45.14; H, 6.32. Found: equiv. wt., 160; C, 45.37; H, 5.97.

Ethyliminodipropionitrile·HCl: mole ratio, 4; reflux for 24 hr.; yield 40%, m.p. 155–158° (Kofl.); and cold solubility in acetone, 0.4 g./100 g.

Anal. Calcd. for $C_8H_{14}N_3Cl$: equiv. wt., 187.7; N, 22.39. Found: equiv. wt., 188; N, 21.58.

Diethylaminopropionitrile.HCl: (1) mole ratio, 2; room temp. for 67 hr.; 10% yield; (2) mole ratio, 3; reflux for 2 hr.; 60% yield, m.p. 125–128° (Kofl.)[26]; and cold solubility in 95% ethanol, 1.7 g./100 g., and in acetone, 0.2.

Anal. Calcd. for $C_7H_{15}N_2Cl$: equiv. wt., 162.7; C, 51.68; H, 9.30. Found: equiv. wt., 163; C, 51.57; H, 8.72.

N-Methamphetaminepropionitrile·HCl: mole ratio, 14; room temp. for 72 hr.; 49% yield, m.p. 170–173° (Kofl.); and cold solubility in acetone, 1.7 g./100 g.

Anal. Calcd. for $C_{13}H_{19}N_2Cl$: equiv. wt., 238.8; N, 11.74. Found: equiv. wt., 239; N, 12.02.

N-Amphetaminepropionitrile·HCl: (1) mole ratio, 14; room temp. for 72 hr.; 48% yield. (2) Mole ratio, 14; reflux for 26 hr.; 55% yield. m.p. 175–178° (Kofl.); and cold solubility in acetone, 0.2 g./100 g.

Anal. Calcd. for $C_{12}H_{17}N_2Cl$: equiv. wt., 224.7; N, 12.47. Found: equiv. wt., 225; N, 12.18.

N-Norcodeinepropionitrile: mole ratio, 50; heated 5 min. to dissolve, then left at room temp. for 68 hr.; 62% yield, m.p. 179–184°; and solubility in cold 95% ethanol, 1.5 g./100 g.

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(15) J. Kielland, THIS JOURNAL, **59**, 1677 (1937).

(16) Since the diethylalkylamines have high pK_a's they must be titrated as the bases. But they have limited water solubility and are volatile so that while being dissolved in water variable proportions of the compounds are lost. The equiv. wts. were determined therefore by dissolving the compounds in heptane and titrating with standard acid. The pK_a's were determined by adding an excess of the base to carbon dioxide-free water in a separatory funnel, mixing thoroughly, and taking some of the aqueous solution from the bottom. This solution, or solution further diluted with water, was titrated in the usual way, but the total quantity of base present was determined by the titration rather than initial weight. This allowed a point by point calculation of the pK_a. If the concn. was too high, then additional solution was diluted and re-titrated.

(17) R. Adams and W. D. Langley, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 355–357; W. K. Anslow and H. King, *ibid.*, pp. 298–301.

(18) M.p. 191–192°; G. B. Bachman and D. E. Welton, *J. Org. Chem.*, **12**, 223 (1947).

(19) B.p. 83° (9 mm.); D. B. Luten, Jr., *ibid.*, **3**, 591 (1939); 96° (12 mm.); A. Marxer, ref. 2a.

(20) M.p. 179-181°; H. D. Moed, M. Asscher, P. J. A. van Draanen and H. Niewind, *Rec. trav. chim.*, **71**, 939 (1952).

(21) B.p. 141° (13 mm.), m.p. of the hydrochloride, 110-112° C. E. Knoevenagel and E. Mercklin, *Ber.*, **37**, 4093 (1904).

(22) B.p. 66–68° (14 mm.); R. A. Jacobson, THIS JOURNAL, **67**, 1997 (1945); b.p. 72–74° (14 mm.); D. B. Luten, Jr., ref. 19, p. 590.

(23) B.p. 96° (12 mm.), m.p. 41–44°; A. Marxer, ref. 2a; b.p. 93–94° (14 mm.); R. A. Jacobson, ref. 22.

(24) Acrylonitrile was kindly supplied by Monsanto Chemical Co.

(25) O. F. Wiedeman and W. H. Montgomery, THIS JOURNAL, **67**, 1994 (1945).

(26) M.p. 120°; A. N. Kost, *Uchenye Zapiski Moskov. Gosudarst. Univ. Im. M. V. Lomonosova*, **131**, 39 (1950); quoted from *C. A.*, **47**, 9906e (1953).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: N, 8.28. Found: N, 7.84.

Nitrilotripropionitrile.—Trichloroethylamine hydrochloride was prepared according to the method of Ward[27] using 23 g. (0.15 mole) of triethanolamine. Volatile materials were distilled from the reaction flask with formation of a crystal mass of trichloroethylamine hydrochloride. After solution in 90 ml. of water, the material was made basic with solid sodium bicarbonate. After addition of 2 g. of potassium iodide, 33 g. of solid potassium cyanide and 250 ml. of 95% alcohol, the solution was refluxed and stirred overnight. Alcohol was distilled off on the steam-bath and sufficient water added to dissolve solid. The solution was extracted with chloroform and the evaporation residue gave 13.2 g. of solid (50% over-all yield) on trituration with ether. The m.p. of this material was 52–58°. It was crystallized from water and a second crop was obtained by chloroform extraction of the filtrate and crystallization from a smaller volume of water. Combined weight of crystals of m.p. 59–61° was 10 g. (38%). The material was dissolved in 320 ml. of water, treated with carbon, filtered and, on cooling, 5 g. of colorless crystals was obtained with m.p. 59–61°. The filtrate was extracted with chloroform and a second crop was obtained from 76 ml. of water, 2.9 g. of colorless crystals with m.p. 59–61°. The material sublimes quantitatively at 80° (10 μ) over several hours; m.p. of the sublimate, 60–61° (Koff.)[28]; **hydrochloride**, m.p. 115–122° (Kofl.).

Anal. Calcd. for $C_9H_{12}N_4$: N, 31.80. Found: N, 31.84.

4-Diethylaminobutyronitrile was prepared through the intermediate 1-diethylamino-3-chloropropane[29] from chlorobromopropane; the nitrile boiled at 50–51° (1.6 mm.).[30]

Anal. Calcd. for $C_8H_{16}N_2$: equiv. wt., 140.2; C, 68.51; H, 11.50; N, 19.98. Found: equiv. wt., 140.2; C, 68.53; H, 11.46; N, 19.85.

5-Diethylaminovaleronitrile.—To 20 g. (0.124 mole) of 5-bromovaleronitrile[31] was added 90 g. (1.24 moles) of diethylamine. This was left at room temp. for 4 days after which the crystalline diethylamine hydrobromide was filtered off and the filtrate was distilled to remove diethylamine. This method has the advantage that the completion of the reaction is indicated by failure of new salt crystals to form. The distillation residue contained some crystals which were removed by washing the oil with sodium carbonate solution and then with water. The base, dried with anhydr. magnesium sulfate, distilled at 101–106° (approx. 22 mm.) to give a 57% yield of oil. A second distillation gave an 85% recovery of oil, b.p. 105–106° (15 mm.).[32]

Anal. Calcd. for $C_9H_{18}N_2$: equiv. wt., 154.25. Found: equiv. wt., 154.0.

6-Diethylaminocapronitrile was prepared from 6-bromocapronitrile which was prepared by the method of Cason and Rapoport,[33] from 1,5-dibromopentane. The bromonitrile was carefully fractionated in order to remove all unreacted dibromide. To 9.7 g. (0.055 mole) of 6-bromocapronitrile was added 40.2 g. (0.55 mole) of diethylamine. After 2 days at room temp. the crystals were filtered off, the filtrate distilled to remove diethylamine, and the residue dissolved in ether. The ether was extracted with dilute phosphoric acid (the *p*H after extraction was less than 7). The aqueous solution was washed with 2 half-portions of ether. The aqueous solution was brought to *p*H 11 with sodium hydroxide. The oily base was separated and the solution extracted with 2 portions of ether. The oil and the ether residue totaled 6.3 g. and was dried over anhydr. magnesium sulfate. The 3.8 g. of base distilled at 49–51° (0.05 mm.)[34] and represented a 41% yield.

Anal. Calcd. for $C_{10}H_{20}N_2$: equiv. wt., 168.3. Found: equiv. wt., 168.0.

Diethylpropylamine was prepared using the method of Elderfield.[35] A 34% yield of material with b.p. of 111–113° (760 mm.) was obtained.[35]

Anal. Calcd. for $C_7H_{17}N$: equiv. wt., 115.2. Found: equiv. wt., 121.

Diethylbutylamine and Diethylamylamine.—Diethylpropylamine has been prepared by pyrolysis of the triethylpropylammonium iodide.[36] Attempted preparation of diethylpropylamine seemed to give a mixture of amines. Use of this method gave reasonably pure diethylbutylamine and diethylamylamine. The triethylalkylammonium iodide salts were heated to about 270° in a distillation set-up under water aspirator vacuum. The receiver contained an excess of aqueous acid. The ethyl iodide layer was removed, the acid washed with additional ether, the solution boiled, alkalinized with separation of the layer of base, and the base dried and distilled.

Diethylbutylamine.—A 61% yield of the crude oil was obtained. After drying over anhydr. magnesium sulfate, the material was distilled at 65–67° (75 mm.) giving a 40% yield of that distilled.[37]

Anal. Calcd. for $C_8H_{19}N$: equiv. wt., 129.2. Found: equiv. wt., 131.6.

Diethylamylamine.—A 66% yield of crude oil was obtained. After drying over anhydr. magnesium sulfate, the compound was distilled at 85–87° (76 mm.) in 44% yield (from the iodide).[38]

Anal. Calcd. for $C_9H_{21}N$: equiv. wt., 143.3. Found: equiv. wt., 145.

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[27] K. Ward, Jr., THIS JOURNAL, **57**, 914 (1935).

[28] M.p. 59°; ref. 25, p. 1995.

[29] D. S. Breslow, H. G. Walker, R. S. Yost and C. R. Hauser, THIS JOURNAL, **67**, 1474 (1945).

[30] B.p. 92–93° (14 mm.); W. J. Humphlett, M. J. Weiss and C. R. Hauser, *ibid.*, **70**, 4020 (1948).

[31] Matheson No. 7139.

[32] B.p. 108–112° (15 mm.); P. Kurtz, *Ann.*, **577**, 23 (1951); 107° (13 mm.); H. Normant and G. Voreaux, *Compt. rend.*, **231**, 703 (1950).

[33] J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, pp. 279–281.

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[35] R. C. Elderfield, F. J. Kreysa, J. H. Dunn and D. D. Humphreys, THIS JOURNAL, **70**, 42 (1948), reported b.p. 111.9–1112.2°.

[36] K. v. Auwers and W. Mauss, *Ber.*, **61**, 2411 (1928).

[37] C. H. Horning and F. W. Bergstrom, THIS JOURNAL, **67**, 2110 (1945).

[38] C. Prevost and H. C. de Mauny, *Compt. rend.*, **216**, 771 (1943).