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On the Cleavage of Tertiary Amines with Ethyl Chloroformate

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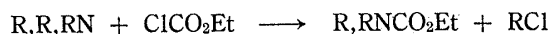
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Forty-seven *tert.* amines were examined in order to observe the relative lability of the various N-substituents in respect to cleavage by ClCO_2Et in refluxing benzene. The aromatic amines did not react with ClCO_2Et , while aliphatic and alicyclic amines were cleaved to give carbamate(s); the tendency to cause R-N cleavage was: benzyl > allyl > methyl > ethyl > other alkyl groups.

It was found that the reaction of a *tert.* amine with ClCO_2Et is greatly influenced by the polarity of the solvent, reaction temperature and N-substituents.

The cleavage of several tertiary amines by chloroformates has been fragmentarily reported in the literature²⁾ as a means of preparing carbamates and for the opening of tetrahydroisoquinoline rings. This cleavage offered some interesting problems from the preparative and mechanistic point of view, especially in the preparation of carbamates and/or secondary amines from tertiary amines.

The present work was undertaken in order to observe the relative lability of the various N-substituents of tertiary amines in respect to cleavage by ethyl chloroformate and shed light on the reaction mechanism.



Forty-seven tertiary amines were examined. Each of the amines was treated with 1.5 equiv. of ethyl chloroformate in refluxing benzene for an hour, then the reaction products were detected and determined by gas chromatography and/or isolated by preparative gas chromatography or by classical work-up procedure. The structure of each isolated product was determined through the use of infrared (IR) and nuclear magnetic resonance (NMR) spectra, gas chromatography and the use of classical techniques. The results are illustrated in Table I.

The aromatic amines examined in this work did not react with ethyl chloroformate, resulting in recovery of both reactants. This may be explained in terms of the weak basicity of the aromatic amines. These results are in contrast to those of von Braun reaction³⁾ with cyanogen bromide in which one of the N-alkyl groups of the aromatic tertiary amine was replaced by a cyano group.

In the case of aliphatic amines, one of the N-substituents was replaced to give carbamate(s). Tribenzylamine, N-allyl-dibenzylamine and N-cyclohexyl-dibutylamine were exceptions: they did not react with the chloroformate. This may have been caused by the high steric hindrance of the amines. It is of interest that ring-opening did not occur in simple six- and seven-membered cyclic amines, and morpholine and piperazines, while pyrrolidine rings were opened easily. These results are also different from those of von Braun reaction.³⁾

As can be seen in Table I, it is clear that the tendency to cause R-N cleavage is in the following order: benzyl > allyl > methyl > ethyl > the other alkyl groups, and that the reactivity

1) Location: a) 13 Hongo, Toyama; b) 1076 Tawame, Sakado-machi, Saitama.

2) a) J. Gadamer and F. Knoch, *Arch. Pharm.*, **259**, 135 (1931); b) F.v. Bruchhausen and J. Knabe, *ibid.*, **287**, 601 (1954); c) E.H. Flynn, Jr., P.F. Wiley and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954); d) J.A. Campbell, *J. Org. Chem.*, **22**, 1259 (1957); e) W.B. Wright and H.J. Brabander, *ibid.*, **26**, 4057 (1961); f) J.P. Li and J.H. Biel, *ibid.*, **35**, 4100 (1970).

3) H.A. Hageman, "Organic Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1953, p. 198.

TABLE I. Cleavage of Tertiary Amines with Ethyl Chloroformate

Amine (Compd. No.)	Carbamate(s) (Compd. No.)	Yield ^{a)} %	Amine (Compd. No.)	Carbamate(s) (Compd. No.)	Yield ^{a)} %
PhNMe ₂ (1)		0	Piperazine-		
PhNEt ₂ (2)		0	1,4-di-Me (29)	{ piperazine-1-Me-4-CO ₂ Et (55) piperazine-1,4-di-CO ₂ Et (56)	72 10
MeO(p)-C ₆ H ₄ NMe ₂ (3)		0	1,4-di-CH ₂ Ph (30)	{ piperazine-1-CH ₂ Ph-4-CO ₂ Et (57) (56)	89 9
PhN(CH ₂ Ph) ₂ (4)		0	Py-tetrahydro-isoquinoline-		
PhN(Me)CH ₂ Ph (5)		0	2-Me (31)	Py-tetrahydroisoquinoline- 2-CO ₂ Et (58)	{ 90 100
α-C ₁₀ H ₇ NMe ₂ (6)		0	2-CH ₂ Ph (32)		
Py-tetrahydro-quinoline-		0	Dimethylamine-		
1-Me (7)		0	N-CH ₂ Ph (33)	Me ₂ NCO ₂ Et (59)	66
1-CH ₂ Ph (8)		0	N-(CH ₂) ₂ Ph (34)	MeN(CH ₂) ₂ PhCO ₂ Et (60)	71.8
Pyrrolidine-			N-(CH ₂) ₃ Ph (35)	MeN(CH ₂) ₃ PhCO ₂ Et (61)	75.5
1-Ph (9)		0	N-C ₆ H ₁₁ (cyclo) (36)	MeN(C ₆ H ₁₁)CO ₂ Et (62)	77
1-Me (10)	Cl(CH ₂) ₄ NMeCO ₂ Et (48)	69.5	Et ₃ N (37)	Et ₃ NCO ₂ Et (63)	47.1
1-CH ₂ Ph (11)	{ Cl(CH ₂) ₄ NCH ₂ PhCO ₂ Et (49) pyrrolidine-1-CO ₂ Et (50)	22 33	(PhCH ₂) ₂ N (38)	PhCH ₂ NMeCO ₂ Et (64)	0 ^{b)}
1-allyl (12)	{ Cl(CH ₂) ₄ N(allyl)CO ₂ Et (51) (50)	85 5	(PhCH ₂) ₂ NMe (39)		80
Piperidine-			(PhCH ₂) ₂ N-allyl (40)	(62)	0 ^{b)}
1-Me (13)		91.6	(C ₆ H ₁₁ (cyclo)) ₂ NMe (41)		29 ^{c)}
1-Et (14)		81.0	Dibutylamine-		
1-Pr(n) (15)		58.4	N-Me (42)	{ Bu ₂ NCO ₂ Et (65) BuNMeCO ₂ Et (66)	39 (44) ^{d)} 44 (52) ^{d)}
1-Bu(n) (16)		57.5	N-Et (43)	{ BuNEtCO ₂ Et (67) (65)	18 (31) ^{d)} 19 (52) ^{d)}
1-C ₆ H ₁₃ (n) (17)		60.5	N-Bu(n) (44)	(65)	28 (54) ^{d)}
1-Pr(iso) (18)		75.3 ^{e)}	N-allyl (45)	(65)	42 (82) ^{d)}
1-C ₆ H ₁₁ (cyclo) (19)		51.5 ^{f)}	N-CH ₂ Ph (46)	(65)	51 (63) ^{d)}
1-allyl (20)		96.4	N-C ₆ H ₁₁ (cyclo) (47)	(65)	1 (2.2) ^{d)}
1-CH ₂ Ph (21)		100			
1-(CH ₂) ₂ Ph (22)		27.0			
Hexahydro-azepine-					
1-Me (23)	hexahydro-azepine- 1-CO ₂ Et (53)	{ 81 85.5			
1-CH ₂ Ph (24)					
Morpholine-					
4-Me (25)		49			
4-Et (26)		9.5 (37) ^{d)}			
4-Bu(n) (27)		3.5			
4-CH ₂ Ph (28)	morpholine-4-CO ₂ Et (54)	31.5			

a) Analysis by gas chromatography on a 1 m × 3 mm SE-30 (5% on Shimalite) column.

c) Hydrochloride of amine 41 was obtained in 42% yield.

e) Hydrochloride of the amine 18 was obtained in 25% yield.

b) Quantitative recovery of both reactants.

d) The parenthesized number is the % yield after a 5 hr-reaction time.

f) Hydrochloride of the amine 19 was obtained in 43% yield.

Ph = phenyl

of an amine to ethyl chloroformate decreases with an increase in size of the groups around the nitrogen atom. Thus, ethyl chloroformate should be a useful and fairly selective reagent for the cleavage of benzyl-N, allyl-N, and methyl-N bond in tertiary amines.

In order to observe the influence of solvent and temperature on this cleavage, N-methyl-piperidine (**13**), N-ethyl-piperidine (**14**), N-benzyl-piperidine (**21**), N,N-dimethyl-phenethylamine (**34**), triethylamine (**37**), tributylamine (**44**) and N,N-diethyl-allylamine (**68**) were reacted with 1.0 equiv. of ethyl chloroformate in hexane, benzene, chloroform and nitrobenzene at 5° and ~80°, and the products were determined.

Mixing of **13**, **14**, **34**, and **37** with ethyl chloroformate in hexane and benzene at 5° gave colorless crystalline precipitates in almost quantitative yield, respectively, in a short time. The adducts were unstable to heat and moisture. The one from **14**, however, was somewhat stable at room temperature in dry air. In the IR spectrum (in CHCl_3), it showed a carbonyl band at 1820 cm^{-1} . The NMR spectrum (in CDCl_3) exhibited two quartets at 5.23τ ($J=7.0\text{ Hz}$) and 6.40τ ($J=7.0\text{ Hz}$) and two triplets at 8.45τ ($J=7.0\text{ Hz}$) and 8.50τ ($J=7.0\text{ Hz}$). The IR spectra of mixtures of **13**, **14**, **34**, **37**, **44**, and **68** with ethyl chloroformate in chloroform at room temperature also showed a carbonyl band at 1820 cm^{-1} , respectively, but no carbonyl band of ethyl chloroformate (1785 cm^{-1}) (each of the spectra was taken in 3 min). These spectral data gave support for the structure of the adducts, N-ethoxycarbonylammonium chlorides.⁴⁾

Heating of the ammonium salt from **14** in hexane, benzene (suspension), chloroform and nitrobenzene (solution) and neat gave carbon dioxide, ethyl chloride and **14** as the main products. When the mixtures of **13**, **14**, **21**, **34**, **37**, **44**, and **68** with 1.0 equiv. of ethyl chloroformate in hexane, benzene, chloroform and nitrobenzene were heated at the temperature around 80°, the corresponding carbamates, carbon dioxide and the original tertiary amines were obtained in the yields varying 0 to 100%. The reactions of these amines in chloroform and nitrobenzene at the temperature around 80° gave the similar results, while the reactions in refluxing benzene afforded significantly higher yield of carbamates. The results are summarized in Table II and III.

TABLE II. Decomposition of 1-Ethoxycarbonyl-1-ethyl-1-piperidinium Chloride

Solvent	Temp. (°C)	Products, % yield		
		Piperidine-1- CO_2Et^a	CO_2^b	Piperidine-1-Et ^a
Hexane	reflux	trace	83	88
Benzene	reflux	25	60	68
Chloroform	reflux	4	80	81
Nitrobenzene	85	0	92	80
Neat	60—80	trace	86	76

a) Analysis by gas chromatography on a $1\text{ m} \times 3\text{ mm}$ SE-30 (5% on Shimalite) column at 86°

b) Analysis by absorption on Ascarite.

These facts suggest that the ammonium salt is not a main intermediate in the formation of carbamate from a tertiary amine with chloroformate, except for N-benzyl- and N-allylamine, and that the reactivity of the reactants and the course of the reaction are greatly influenced by the polarity of the solvent, temperature and the substituents on the nitrogen atom. Thus, it may be rationalized that the reaction of a tertiary amine with chloroformate would give, at the first stage, a tetrahedral transition complex (A), which would undergo either R-N cleavage to afford carbamate, via an intimate ion pair (B) or a four-membered cyclic inter-

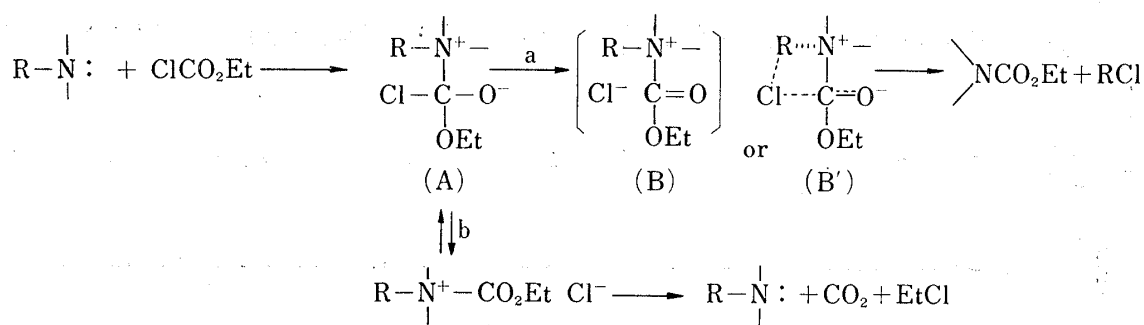
4) J.V. Paukstelis and Moon-geu Kim, *J. Org. Chem.*, **39**, 1499 (1974).

TABLE III. Effects of Solvent and Temperature on the Cleavage of Tertiary Amines with Ethyl Chloroformate

Amine (Compd. No.)	Solvent	Temp. (°C)	Time, hr	Products, % yield		Amine	Temp. (°C)	Time, hr	Products, % yield		Amine
				Car- bamate ^{a)}	CO ₂ ^{b)}				Car- bamate ^{a)}	CO ₂ ^{b)}	
Piperidine-1-Me (13)	hexane	5	2	—	88	—	chloroform	5	—	7	—
	+ reflux		1	1	95	—	+ reflux		11	61	76
	benzene	5	2	—	83	—	nitrobenzene	5	—	19	—
	+ reflux		1	4	85	—			7	73	—
	chloroform	5	2	—	67	—	hexane	85	6	94	94
	+ reflux		1	7	83	—	benzene	reflux	68	20	20
	nitrobenzene	5	2	—	76	88	chloroform	reflux	31	50	57
	+ reflux		1	0	85	90	nitrobenzene	85	11	64	—
	hexane	85	1	4	trace	—	hexane	5	—	26	—
	+ reflux		1	64	36	—	+ reflux		3	66	—
Piperidine-1-Et (14)	benzene	reflux	1	10	78	—	benzene	5	—	58	—
	chloroform	reflux	1	0	81	84	+ reflux		9	88	87
	nitrobenzene	85	1	0	22	—	chloroform	5	—	0	—
	hexane	5	2	—	78	75	+ reflux		9	90	90
	+ reflux		1	0	77	—	nitrobenzene	5	—	76	—
	benzene	5	2	23	77	71			0	100	97
	chloroform	5	2	—	3	—	hexane	85	3	11	—
	+ reflux		1	5.5	91	63	benzene	reflux	60	7	52
	nitrobenzene	5	2	—	28	—	benzene	reflux	14	85	52
	hexane	5	2	0	98	80	chloroform	reflux	3	97	50
Piperidine-1-CH ₂ Ph (21)	+ reflux		1	0	11	90	nitrobenzene	85	—	30	—
	benzene	reflux	1	0	44	40	hexane	5	5	45	95
	reflux		1	56	44	40	+ reflux		—	10	—
	benzene	60	1	43	56	50	benzene	5	20	84	80
	benzene	40	1	30	62	59	+ reflux		—	20	—
	chloroform	reflux	1	14	86	77	chloroform	5	5	95	95
	nitrobenzene	85	1	0	99	87	+ reflux		—	49	—
	hexane	5	0.5	—	trace	—	nitrobenzene	5	—	91	—
	+ reflux		0.5	52	7	—	+ reflux		trace	91	—
	benzene	5	1	100	0	0	hexane	reflux	0	0	100
N,N-Dimethyl-phenethylamine (34)	chloroform	5	1	100	0	0	benzene	reflux	33	30	67
	nitrobenzene	5	1	100	0	0	chloroform	reflux	13	87	87
	hexane	reflux	1	47	trace	—	nitrobenzene	85	trace	100	—
	benzene	reflux	1	100	0	0	hexane	5	—	33	—
	chloroform	reflux	1	99	trace	—	+ reflux		9	43	—
	nitrobenzene	85	1	100	0	0	benzene	5	—	36	—
	hexane	5	2	—	7	—	+ reflux		39	48	—
	+ reflux		1	8	92	80	chloroform	5	—	6	—
	benzene	5	2	—	8	—	+ reflux		55	37	—
	+ reflux		1	58	41	41	nitrobenzene	5	—	53	—

a) Analysis by gas chromatography on a 1 m × 3 mm SE-30 (5% on Shimalite) column. b) Analysis by absorption on Ascarite.

mediate (B') (path a), or formation of ammonium salt (path b). The reaction sequence may be represented by the following equations.



Chloride ion is a fairly good nucleophile, so the reaction path b may be always somewhat reversible. The mechanism of path a would resemble that of $\text{S}_{\text{N}}\text{i}$ reactions, such as formation of alkyl chloride from alcohol with thionyl chloride and decomposition of secondary chloroformates to give alkyl chloride and carbon dioxide.⁵⁾ Path a would predominate in benzene at higher temperature, and path b would predominate in more polar solvents and at lower temperature. In the case of N-benzyl- and N-allyl-amine, carbamate would be formed also through the path b because of the high tendency to form benzyl and allyl cations. In hexane at higher temperature, the transition complex (A) would form only with difficulty because of the very low polarity of the solvent; therefore, the yield of carbamate or carbon dioxide would be much smaller.

Experimental

Infrared spectra were recorded on a Japan Spectroscopic IR-E spectrophotometer. Nuclear magnetic resonance spectra were recorded on a JNM C-60H spectrometer and Hitachi R-24 spectrometer in CDCl_3 with

TABLE IV. New Tertiary Amines Prepared for This Study

Compd. No.	bp, (°C) (mmHg)	Formula	mp, (°C)	Picrate					
				Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
12	125—128	$\text{C}_{13}\text{H}_{16}\text{O}_7\text{N}_4$	76—78	45.88	4.74	16.47	46.13	4.61	16.56
18	160—170	$\text{C}_{14}\text{H}_{20}\text{O}_7\text{N}_4$	150—152	47.19	5.66	15.08	46.97	5.80	15.34
22	90—95(1)	$\text{C}_{19}\text{H}_{22}\text{O}_7\text{N}_4$	149—150	54.54	5.30	13.39	54.72	5.28	13.13
24	95—100(4)	$\text{C}_{19}\text{H}_{22}\text{O}_7\text{N}_4$	159—160	54.54	5.30	13.39	54.30	5.52	13.30
26	135—137	$\text{C}_{12}\text{H}_{16}\text{O}_8\text{N}_4$	188—193	41.86	4.68	16.27	42.04	4.68	16.24
27	172—175	$\text{C}_{14}\text{H}_{20}\text{O}_8\text{N}_4$	129—131	45.16	5.41	15.05	45.45	5.68	14.98
28	85—87(1)	$\text{C}_{17}\text{H}_{18}\text{O}_8\text{N}_4$	190—193	50.24	4.47	13.79	50.27	4.54	13.56
34	85—90(20)	$\text{C}_{16}\text{H}_{18}\text{O}_7\text{N}_4$	136—137	50.79	4.80	14.80	51.03	4.77	14.64
35	218—220	$\text{C}_{17}\text{H}_{20}\text{O}_7\text{N}_4$	97—98	52.04	5.14	14.28	52.26	5.14	14.03
39	114—115(2)	$\text{C}_{21}\text{H}_{20}\text{O}_7\text{N}_4$	101—103	57.27	4.58	12.72	57.52	4.56	12.74
40	145—150	$\text{C}_{23}\text{H}_{22}\text{O}_7\text{N}_4$	143—145	59.22	4.75	12.01	59.36	4.76	11.96
42	158—163	$\text{C}_{15}\text{H}_{24}\text{O}_7\text{N}_4$	87—88	48.38	6.50	15.05	48.52	6.53	15.01
43	175—178	$\text{C}_{16}\text{H}_{26}\text{O}_7\text{N}_4$	84—87	49.73	6.78	14.50	49.50	6.63	14.44
45	183—185	$\text{C}_{17}\text{H}_{26}\text{O}_7\text{N}_4$	108—111	51.25	6.58	14.06	51.46	6.55	13.84
46	128—130(10)	$\text{C}_{22}\text{H}_{28}\text{O}_7\text{N}_4$	74—76	56.24	6.29	12.49	56.23	6.27	12.39
47	130—134(20)	$\text{C}_{20}\text{H}_{32}\text{O}_7\text{N}_4$	102—104	54.53	7.32	12.72	54.63	7.28	12.59
41	75—80	hydrochloride: $\text{C}_{13}\text{H}_{26}\text{NCl}$	197—199	67.36	11.31	6.04	67.13	11.60	5.98

5) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, New York, 1959, pp. 294—296.

TABLE V. New Carbamates Obtained in This Study

Compd. No.	bp, (°C) (mmHg)	$\nu_{C=O}$ cm^{-1}	NMR (in $CDCl_3$), τ	Analysis
48	95—97 (4)	1720	8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 8.00—8.50 (4H, m, $-CH_2CH_2-$) 7.10 (3H, s, NMe) 6.40—6.90 (4H, m, $-CH_2N$, $-CH_2Cl$) 5.84 (2H, q, $J=7.0$ Hz, $-CH_2CH_3$)	Calcd. for $C_8H_{16}O_2NCl$ C, 49.61; H, 8.33; N, 7.23 Found: C, 50.24; H, 8.54; N, 7.55
49	138—145	1720	8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 8.10—8.50 (4H, m, $-CH_2CH_2-$) 6.37—6.95 (4H, m, $-CH_2N$, $-CH_2Cl$) 5.81 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$) 5.53 (2H, s, NCH_2Ph) 2.75 (5H, s, $-Ph$)	Calcd. for $C_{14}H_{20}O_2NCl$ C, 62.33; H, 7.47; N, 5.19 Found: C, 62.57; H, 7.66; N, 5.39
51	114—115 (3)	1720	8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 8.00—8.50 (4H, m, $-CH_2CH_2-$) 6.30—6.90 (4H, m, $-CH_2N$, $-CH_2Cl$) 6.12 (2H, d, $J=6.0$ Hz, $NCH_2CH=$) 5.85 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$) 3.85—5.05 (3H, m, $-CH=CH_2$)	Calcd. for $C_{10}H_{13}O_2NCl$ C, 54.67; H, 8.26; N, 6.37 Found: C, 54.48; H, 8.53; N, 6.65
55	94—95 (5)	1720	8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 7.55—7.85 (4H, m, $-CH_2NCH_2-$) Me 7.73 (3H, s, NMe) 6.40—6.70 (4H, m, $-CH_2NCH_2-$) CO ₂ Et 5.88 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$)	picrate: mp 43—45° Calcd. for $C_{14}H_{19}O_9N_5$ C, 41.90; H, 4.77; N, 17.45 Found: C, 42.06; H, 4.76; N, 17.33
57	150—160 (1)	1720	8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 7.61 (4H, t, $J=5.0$ Hz, $2 \times -CH_2NCH_2Ph$) 6.52 (4H, t, $J=5.0$ Hz, $2 \times -CH_2NCO_2Et$) 6.50 (2H, s, NCH_2Ph) 5.85 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$) 2.70 (5H, s, $-Ph$)	picrate: mp 142—144° Calcd. for $C_{20}H_{23}O_9N_5$ C, 50.32; H, 4.86; N, 14.67 Found: C, 50.44; H, 4.83; N, 14.65
60	124—127 (1)	1720	8.77 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 7.20 (2H, t, $J=7.0$ Hz, $-CH_2CH_2N$) 7.15 (3H, s, NMe) 6.50 (2H, t, $J=7.0$ Hz, $-CH_2CH_2N$) 5.87 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$) 2.75 (5H, s, $-Ph$)	Calcd. for $C_{12}H_{17}O_2N$ C, 69.54; H, 8.27; N, 6.76 Found: C, 69.78; H, 8.31; N, 7.03
61	116—120 (2)	1715	8.77 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 8.18 (2H, qn, $J=7.0$ Hz, $-CH_2CH_2CH_2-$) 7.40 (2H, t, $J=7.0$ Hz, $-CH_2CH_2N$) 6.72 (2H, t, $J=7.0$ Hz, $PhCH_2CH_2-$) 5.89 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$) 7.17 (3H, s, NMe) 2.16 (5H, s, $-Ph$)	Calcd. for $C_{13}H_{19}O_2N$ C, 70.56; H, 8.65; N, 6.33 Found: C, 70.87; H, 8.46; N, 6.14
62	110—115 (5)	1720	8.00—9.00 (11H, m) 8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 7.25 (3H, s, NMe) 5.85 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$)	Calcd. for $C_{10}H_{19}O_2N$ C, 64.83; H, 10.34; N, 7.56 Found: C, 64.75; H, 10.52; N, 7.65
67	100—105 (20)	1715	8.30—9.30 (7H, m) 8.90 (3H, t, $J=7.0$ Hz, $-NCH_2CH_3$) 8.75 (3H, t, $J=7.0$ Hz, $-OCH_2CH_3$) 6.80 (2H, t, $J=7.0$ Hz, $-NCH_2CH_2-$) 6.75 (2H, q, $J=7.0$ Hz, $-NCH_2CH_3$) 5.87 (2H, q, $J=7.0$ Hz, $-OCH_2CH_3$)	Calcd. for $C_9H_{19}O_2N$ C, 62.39; H, 11.05; N, 8.09 Found: C, 62.15; H, 11.32; N, 8.11

Ph=phenyl

tetramethylsilane as internal standard. Melting points were taken with Yanagimoto micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyama.

Materials— ClCO_2Et was a commercially obtained reagent and was purified by distillation just before use. The following amines were also obtained commercially and used after appropriate purification: **1**, **2**, **6**, **10**, **13**, **14**, **25**, **29**, **36**, **37**, and **44**.

Amine **3** was prepared by the method of Hodgson,⁶⁾ **4** and **38** by Birkofer,⁷⁾ **5** by Desai,⁸⁾ **7** by Decker,⁹⁾ **8** and **20** by Wedekind,¹⁰⁾ **9** by Craig,¹¹⁾ **11** by Schlink,¹²⁾ **15**, **16**, and **17** by Magnusson,¹³⁾ **19** by Smith,¹⁴⁾ **21** by Schotten,¹⁵⁾ **23** by Lukes,¹⁶⁾ **30** by Gabriel,¹⁷⁾ **31** and **32** by Wedekind,¹⁸⁾ **33** by Sommelet¹⁹⁾ and **68** by Cope.²⁰⁾

Amines **12**, **40**, and **45** were prepared by allylation of pyrrolidine, dibenzylamine and dibutylamine with $\text{CH}_2=\text{CHCH}_2\text{Br}$, respectively. Amine **18** was prepared by reaction of piperidine and iso- $\text{C}_3\text{H}_7\text{Br}$ in the presence of KOH. Amine **22** was prepared by reduction of 1-phenacyl-piperidine with LiAlH_4 . Amines **34**, **35**, **39**, **41**, and **42** were prepared by methylation of phenethylamine, phenylpropylamine, dicyclohexylamine and dibutylamine by the Clarke-Eschweiler method. Amines **24**, **28**, and **46** were prepared from the corresponding secondary amines and PhCH_2Cl by the usual procedure, respectively. Amines **26** and **43** were prepared from morpholine and dibutylamine by ethylation with EtI in the presence of K_2CO_3 . Amine **27** was prepared by reaction of morpholine with $n\text{-C}_4\text{H}_9\text{Br}$ in the usual manner. Amine **47** was prepared by a Leukart reaction of dibutylamine with cyclohexanone. The physical data of these new amines are tabulated in Table IV.

Reaction of Tertiary Amines with ClCO_2Et —General procedure: To a refluxing solution of an amine in benzene was rapidly added a solution of 1.5 equiv. of ClCO_2Et in benzene, and refluxing was continued for 1 hr. After cooling, the benzene solution was analyzed by gas chromatography using an internal standard method. When a reaction gave single carbamate, the reaction mixture was washed with dil. HCl and water, and dried. After evaporation of the solvent, the residue was distilled to give a pure sample of the carbamate. When a reaction gave two or three carbamates, each of the carbamates was isolated by preparative gas chromatography. The structure of each carbamate was confirmed by comparison of IR spectrum with that of the authentic sample, by NMR spectrum and the elemental analysis. The spectral data and the elemental analyses of the new carbamates are shown in Table V.

The authentic sample of carbamates **50**,²¹⁾ **52**,²¹⁾ **53**,²²⁾ **54**,²¹⁾ **56**,²³⁾ **58**,²⁴⁾ **59**,²⁴⁾ **60**,²⁵⁾ **63**,²⁵⁾ **64**,²⁶⁾ **65**,²⁷⁾ and **66**²⁶⁾ were prepared from the corresponding secondary amine and ClCO_2Et in the usual manner, and the samples of the other carbamates were prepared by isolation from the reaction mixture using preparative gas chromatography.

Formation of 1-Ethoxycarbonyl-1-ethyl-piperidinium Chloride and Its Thermal Decomposition—A solution of 1.5 g of ClCO_2Et in 3 ml of benzene was dropped into a solution of **14** in 6 ml of benzene in a round bottomed flask at 5° during 10 min, with stirring. After stirring for 5 min, the solvent and the excess ClCO_2Et were evaporated under reduced pressure at $10\text{--}20^\circ$ avoiding moisture. The resultant colorless crystalline powder was suspended in 30 ml of hexane, benzene, or dissolved in 30 ml of chloroform or nitrobenzene. The flask was connected to a three-necked adapter equipped with a reflux condenser, a cold-trap and a weighed Ascarite-tube serially, and an N_2 inlet tube. The suspension (or solution) was heated at 85--

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90° under N₂ stream for 1 hr. The amount of CO₂ was determined by weighing the Ascarite-tube. The yields of amine 14 and carbamate 52 were determined by gas chromatography using an internal standard method.

Reactions of Amines 13, 14, 21, 34, 37, 44, and 68 with ClCO₂Et in Hexane, Benzene, Chloroform and Nitrobenzene—a) In a three-necked flask equipped with a reflux condenser, cold-trap and a weighed Ascarite-tube serially, an N₂ inlet tube and a dropping funnel, was placed a solution of 1.00 g of amine in 30 ml of hexane, benzene, chloroform or nitrobenzene and the solution was cooled at 5°. To this solution, a solution of 1.00 equiv. of ClCO₂Et in 10 ml of the solvent was dropped during 3 min, with stirring and under a stream of N₂. After 2 hr, the amount of CO₂ evolved was determined. Then, the mixture was heated at the temperature around 80°, and the yields of carbamate, CO₂ and amine were determined.

b) In the similar apparatus, was placed a solution of 1.00 g of amine in 30 ml of hexane, benzene, chloroform or nitrobenzene and the solution was heated at 85–90°. To this solution, a solution of 1.00 equiv. of ClCO₂Et in 10 ml of the solvent was added dropwise during 3 min, with stirring and under a stream of N₂. After 1 hr, the amounts of CO₂, carbamate and amine were determined as described above.

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Methanesulfonic Acid Derivative of N-Alkyl Aniline: Basicity of Aniline and Reactivity^{1,2)}

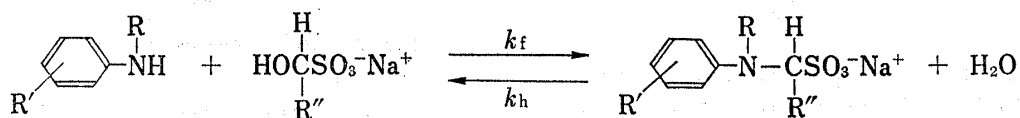
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Effects of N-alkyl substituents on the formation and hydrolysis rates of N-substituted aniline methanesulfonic acid derivatives were investigated in connection with substituted aniline derivatives. Their rates were satisfactorily correlated to the basicity of aniline derivatives which was corrected by hydration effect, that is Folkers, *et al.*'s H value.

In a series of studies on the water soluble methanesulfonic acid derivatives (MSD) of aniline homologous drugs, the basicity of the parental aniline has been found to be the dominant factor for the reversible MSD formation, which can be expressed by the following general formula:^{4–6)}



In the previous studies^{4,6)} the effect of R' substituent of aniline on the formation rate constant (k_f , second-order) and the hydrolysis rate (k_h , first order) could be satisfactorily represented by the linear free energy relationship (LFER) between $\text{p}K_a$ of substituted anilinium ion and $\log k_f$ or $\log k_h$. The plots for N-methyl aniline, however, deviated positively from the linear relationship on which further explanation was not made.

- 1) Presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, Japan, April 1975.
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