

(COOCH₃). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 249 (4.20), 284 (4.43), 382 (4.04). NMR (in TFAA) ppm: 4.21 (3H, s, OCH₃), 4.24 (3H, s, OCH₃). Mass Spectrum m/e : 315 (M⁺), 283, 272, 258.

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Synthesis of N-(Alkylaminomethyl)amides

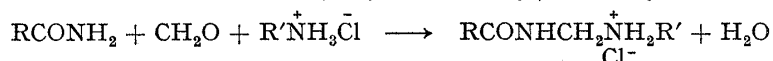
YUKIHIRO WATASE, YOSHIYASU TERAQ and MINORU SEKIYA


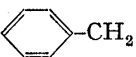
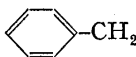

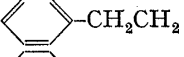
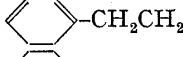






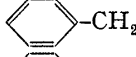
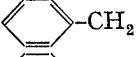
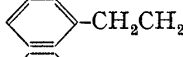
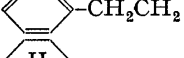


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Up to the present there has been known an abundance of the methylene compounds bound to both amine nitrogen (N^I) and amide or imide nitrogen (N^{II}), simply expressed by a general formula, >N^I-CH₂-N^{II}<. As well known they are easily prepared by heating formaldehyde, amine and amide (or imide) together in solution. Nevertheless, the usual method is unsatisfactory in obtaining the compound, of which N^I is grouped in the type of -NHR (R=alkyl), although by the use of amphoteric α -amino acid as the amine reactant the compound, RCO-NHCH₂NHCH(R')CO₂H, has been reported²⁾ to be obtained.

TABLE I. Formation of N-(Alkylaminomethyl)amide Hydrochlorides



R	R'	Yield (%)	R	R'	Yield (%)
		80	C ₂ H ₅		72
		93	C ₂ H ₅		75
		71	C ₂ H ₅		86
	<i>n</i> -C ₄ H ₉	90	C ₂ H ₅	<i>n</i> -C ₄ H ₉	83
	C ₂ H ₅	85	C ₂ H ₅	C ₂ H ₅	72
	<i>iso</i> -C ₄ H ₉	83	H		85
CH ₃		82	H		75
CH ₃		82	H		93
CH ₃		77	H	<i>n</i> -C ₄ H ₉	87
CH ₃	<i>n</i> -C ₄ H ₉	76	H	C ₂ H ₅	73
CH ₃	C ₂ H ₅	81			

1) Location: 2-2-1, Oshika, Shizuoka.

2) H. Fraenkel-Conrat and H.S. Oleott, *J. Am. Chem. Soc.*, **70**, 2673 (1948); F. Lauria, C. Bernardelli, G. Tosolini and W. Logemann, *Ann.*, **706**, 233 (1967); *idem, ibid.*, **706**, 237 (1967); C. Bernardelli, G. Bucher, F. Lauria, W. Logemann, G. Tosolini, and G. Vita, *ibid.*, **706**, 243 (1967).

TABLE II. Physical and Analytical Data of N-(Alkylaminomethyl)amide Hydrochlorides

$\text{RCONHCH}_2\overset{+}{\text{NH}_2}\text{R}'$ Cl^-										
R	R'	Appearance (recryst. from EtOH)	mp (°C)	IR $\nu_{\text{max}}^{\text{KBr}}$ (cm ⁻¹)			Formula	Analysis (%)		
				NH	NH ₂ ⁺	CONH		Calcd. (Found)	C	H
C ₆ H ₅	C ₆ H ₅ CH ₂	needles	169	3285	2650	1652	C ₁₅ H ₁₇ ON ₂ Cl	65.07	6.20	10.12
						1534		(65.25)	(6.27)	(10.10)
C ₆ H ₅	C ₆ H ₅ CH ₂ CH ₂	leaflets	174—175	3298	2650	1662	C ₁₆ H ₁₉ ON ₂ Cl	66.06	6.59	9.63
						1546		(66.29)	(6.65)	(9.64)
C ₆ H ₅	C ₆ H ₁₁	plates	156—157	3356	2650	1656	C ₁₄ H ₂₁ ON ₂ Cl	62.53	7.88	10.42
						1534		(62.25)	(8.02)	(10.49)
C ₆ H ₅	n-C ₄ H ₉	plates	170 (decomp.)	3290	2680	1658	C ₁₂ H ₁₉ ON ₂ Cl	59.35	7.90	11.53
						1546		(59.56)	(8.14)	(11.38)
C ₆ H ₅	C ₂ H ₅	leaflets	164—165	3302	2660	1662	C ₁₀ H ₁₅ ON ₂ Cl	55.95	7.04	13.08
						1549		(55.98)	(7.03)	(12.91)
C ₆ H ₅	iso-C ₄ H ₉	leaflets	165—166	3312	2680	1660	C ₁₂ H ₁₉ ON ₂ Cl	59.35	7.90	11.53
						1542		(59.22)	(8.04)	(11.57)
CH ₃	C ₆ H ₅ CH ₂	plates	143	3323	2655	1682	C ₁₀ H ₁₅ ON ₂ Cl	55.92	7.05	13.04
						1534		(55.86)	(7.18)	(13.14)
CH ₃	C ₆ H ₅ CH ₂ CH ₂	needles	145—148	3300	2680	1692	C ₁₁ H ₁₇ ON ₂ Cl	57.74	7.50	12.24
						1558		(57.85)	(7.63)	(12.17)
CH ₃	C ₆ H ₁₁	prisms	152—153	3366	2680	1682	C ₉ H ₁₉ ON ₂ Cl	52.26	9.27	13.54
						1544		(52.31)	(9.29)	(13.60)
CH ₃	n-C ₄ H ₉	needles	135—136	3299	2680	1677	C ₇ H ₁₇ ON ₂ Cl	46.50	9.49	15.50
						1543		(46.30)	(9.52)	(15.44)
CH ₃	C ₂ H ₅	needles	117—118	3395	2730	1680	C ₅ H ₁₃ ON ₂ Cl	39.32	8.59	18.34
						1540		(39.56)	(8.55)	(18.28)
C ₂ H ₅	C ₆ H ₅ CH ₂	needles	144—146	3322	2710	1690	C ₁₁ H ₁₇ ON ₂ Cl	57.74	7.50	12.24
						1535		(57.87)	(7.55)	(12.30)
C ₂ H ₅	C ₆ H ₅ CH ₂ CH ₂	needles	139—141	3312	2680	1686	C ₁₂ H ₁₉ ON ₂ Cl	59.35	7.90	11.53
						1536		(59.39)	(7.87)	(11.41)
C ₂ H ₅	C ₆ H ₁₁	needles	122—124	3360	2720	1686	C ₁₀ H ₂₁ ON ₂ Cl	54.38	9.60	12.68
						1539		(54.27)	(9.55)	(12.51)
C ₂ H ₅	n-C ₄ H ₉	needles	129—131	3309	2800	1699	C ₈ H ₁₉ ON ₂ Cl	49.35	9.76	14.39
						1536		(49.22)	(9.70)	(14.26)
C ₂ H ₅	C ₂ H ₅	needles	120—122	3308	2700	1683	C ₆ H ₁₅ ON ₂ Cl	43.21	9.08	16.80
						1532		(43.56)	(9.11)	(16.74)
H	C ₆ H ₅ CH ₂	needles	124—126	3304	2640	1688	C ₉ H ₁₃ ON ₂ Cl	53.84	6.54	13.95
						1502		(53.71)	(6.58)	(13.91)
H	C ₆ H ₅ CH ₂ CH ₂	needles	134—136	3329	2670	1674	C ₁₀ H ₁₅ ON ₂ Cl	55.92	7.05	13.04
						1500		(55.98)	(7.28)	(12.83)
H	C ₆ H ₁₁	needles	126—128	3312	2670	1679	C ₈ H ₁₇ ON ₂ Cl	49.84	8.90	14.53
						1536		(49.95)	(8.93)	(14.52)
H	n-C ₄ H ₉	needles	109—111	3311	2690	1678	C ₆ H ₁₅ ON ₂ Cl	43.21	9.08	16.80
						1534		(42.99)	(8.94)	(16.74)
H	C ₂ H ₅	needles	114—116	3291	2700	1687	C ₄ H ₁₁ ON ₂ Cl	34.64	8.01	20.20
						1504		(34.63)	(7.96)	(20.04)

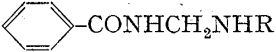
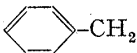
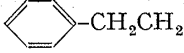


In the present work, the compounds of the type RCONHCH₂NHR' (R'=alkyl) were obtained as their hydrochlorides when primary amine hydrochloride was allowed to react with formaldehyde and amide. Normally the reaction was carried out by heating aqueous ethanolic solution of primary amine hydrochloride, formaldehyde and amide in 1:1.2:1 molar proportion. This reaction is generally applicable in good yield of the product by the use of a wide range of primary aliphatic amines and of primary amides as can be seen in Table I.

All of the products listed in Table I have not been described previously. The structures of these products were confirmed by their elemental analyses and infrared (IR) spectral measurements. As shown in Table II, their IR spectra measured in KBr disk exhibit the charac-

teristic absorption bands as follows: 3285—3399 cm^{-1} ($-\text{CONH}-$), 2650—2730 cm^{-1} ($-\text{NH}_2^+$), 1652—1699 cm^{-1} (CO) and 1500—1558 cm^{-1} (amide II).

The free N-(alkylaminomethyl)amides were obtained from their hydrochlorides with three benzamide derivatives by treating them with aqueous potassium bicarbonate (Table III), while with the other amides free N-(alkylaminomethyl)amide could not be isolated because of difficulty in crystallization. The three N-(alkylaminomethyl)benzamides obtained are stable crystals and their physical, spectral and analytical data are listed in Table III. Their nuclear magnetic resonance (NMR) spectra measured in deuteriochloroform exhibit a singlet at τ 7.55—7.71 due to one proton of amine NH, a doublet at τ 5.56—5.62 due to two protons of the bridged methylene and a broad signal at τ 2.89—3.37 due to one proton of amide NH. These data suggest coupling of the bridged methylene protons with the amide NH proton, which coupling is recognizable by the following facts. The NMR spectrum of the known N-(piperidinomethyl)benzamide shows the same pattern as above (see Table III). After treatment with deuterium oxide, the NMR spectrum of N-(benzylaminomethyl)benzamide showed that both peaks of amine NH proton and amide NH proton disappeared and a doublet at τ 5.62 was converted to a singlet at τ 5.62, while the other signals remained unchanged at almost same chemical shifts with the same patterns.

TABLE III. Spectral and Analytical Data of N-(Alkylaminomethyl) benzamides

									
Compound No.	R	Appearance (recryst. solv.)	mp ($^{\circ}\text{C}$)	IR, CHCl_3 , cm^{-1}		Formula	Analysis (%)		
				NH	CONH		Calcd. (Found)	C	H N
I		needles (iso-Pr ₂ O)	83—85	3445 3333	1664 1515	C ₁₅ H ₁₆ ON ₂	74.95 (74.93)	6.72 (6.75)	11.65 (11.74)
II		prisms (ether)	66—68	3448 3330	1658 1517	C ₁₆ H ₁₈ ON ₂	75.54 (75.50)	7.14 (7.03)	11.01 (11.20)
III		prisms (iso-Pr ₂ O)	61—63	3448 3318	1659 1515	C ₁₄ H ₂₀ ON ₂	72.36 (72.38)	8.69 (8.56)	12.05 (12.07)
NMR Spectral Data (τ -Value in CDCl ₃)									
Compound No.	$-\text{NH}-$	$-\text{CONHCH}_2\text{NH}-$	$-\text{CONH}-$	Other signals					
I	7.55 (s)	5.62 (d, $J=5.5$ Hz)	2.95—3.30 (br)	6.17 (2 H, s, $-\text{CH}_2-$) 2.10—2.82 (10 H, m, Ar)					
II	7.83 (s)	5.63 (d, $J=6.0$ Hz)	3.00—3.37 (br)	7.15 (4 H, ca. t, $-\text{CH}_2\text{CH}_2-$) 2.11—2.91 (10 H, m, Ar)					
III	7.71 (s)	5.56 (d, $J=5.3$ Hz)	2.80—3.25 (br)	7.05—7.55, 7.86—9.14 [11 H, m, $-(\text{CH}_2)_5\text{CH}-$] 1.94—2.78 (5 H, m, Ar)					
cf. 		5.71 (d, $J=6.0$ Hz)	2.86—3.49 (br)	7.15—7.56, 8.00—8.75 [10 H, m, $-(\text{CH}_2)_5-$] 1.95—2.71 (5 H, m, Ar)					

s=singlet, d=doublet, t=triplet and br=broad

a) A. Einhorn, *Ann.*, **343**, 207 (1905)

Experimental³⁾

N-(Alkylaminomethyl) amide Hydrochlorides—General Procedure: N-(Alkylaminomethyl)amide hydrochlorides listed in Table II were prepared by the following general procedure.

- 3) All melting points are uncorrected. NMR spectra were taken with a JEOL-C-60-H high resolution spectrometer using tetramethylsilane as an internal standard and IR spectra were recorded with a Hitachi EPI-G2 spectrophotometer.

To a solution of 0.03 mole of primary alkylamine hydrochloride in 30 ml of water, 3.0 g of 37% formalin and then a solution of 0.03 mole of amide in 30 ml of EtOH were added. The mixture was heated at 35–40° with occasional shaking. After 30 min the reaction solution was concentrated under reduced pressure and the resulting residue was solidified, if necessary, by washing with small amount of dry ether. By recrystallization from EtOH pure N-(alkylaminomethyl)amide hydrochloride was obtained. Yields of the products are shown in Table I and their physical, spectral and analytical data are listed in Table II.

N-(Alkylaminomethyl) benzamides—N-(Benzylaminomethyl) benzamide, N-(2-phenylethylaminomethyl) benzamide and N-(cyclohexylaminomethyl) benzamide were obtained by the following procedure.

To a solution of 4.5 g (0.045 mole) of potassium bicarbonate in 50 ml of water, finely powdered N-(alkylaminomethyl) benzamide hydrochloride was added and the mixture was stirred at room temperature. The suspending product was extracted with benzene. The benzene solution was dried over K₂CO₃. Removal of benzene and recrystallization of the solid residue gave N-(alkylaminomethyl) benzamide. Physical, spectral and analytical data of the products are shown in Table III.

Acknowledgement We thank Mr. K. Narita and other members of Analysis Center of this college for elemental analyses and Mr. S. Katayama of the same for NMR measurements.

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Synthesis of Arctigenin-4'-β-gentiobioside

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In the preceding papers²⁾ we reported the isolation and structural elucidation of arctigenin-4'-β-gentiobioside (I), which is a sole example of naturally occurring of lignan having glucosyl glucose moiety.

In this paper the synthesis of I has been achieved to confirm finally the structure.

Hepta-O-acetyl-α-gentiobiosyl bromide (III), mp 141–143° (lit.³⁾ mp 143–144.5°), was prepared according to the procedure described in literature³⁾ from octa-O-acetyl-β-gentiobiose. Sodium arctigenate (IV) was added to III in chloroform. After stirring the mixture for 12 hr at room temperature, the product was extracted with chloroform and the chloroform

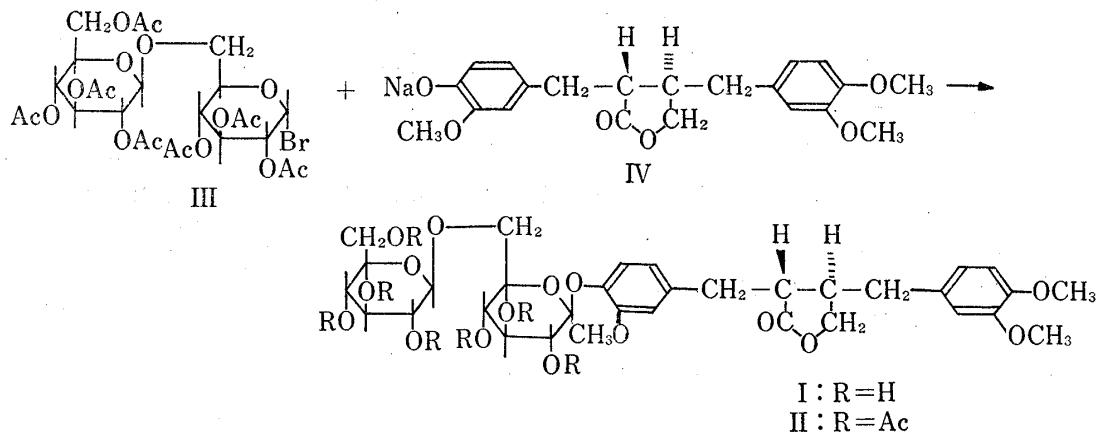


Chart 1

1) Location: Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan.

2) S. Nishibe, S. Hisada, and I. Inagaki, *Experientia*, **29**, 17 (1973); *idem*, *Chem. Pharm. Bull.* (Tokyo), **21**, 639 (1973).

3) K. Takiura, S. Honda, T. Endo, and K. Kakehi, *Chem. Pharm. Bull.* (Tokyo), **20**, 438 (1972).