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Studies on Application of Amino Acid as Medicinal Agent. I. Syntheses of Amino-*tert*-alcohol Derivatives

Seigoro Hayashi, Mitsuru Furukawa, Yoko Fujino,[1a] Naoto Matsuishi[1b] and Tadashi Ohkawara[1c]

Faculty of Pharmaceutical Sciences, Kumamoto University,[1a] Tokyo Tanabe Seiyaku Co., Ltd.[1b] and Tanabe Seiyaku Co., Ltd.[1c]

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In order to find non-narcotic analgesics, 54 compounds of amino-*tert*-alcohol, in which a variety of substituent groups were involved at the carbon atom in 1-position and at the amino group, were synthesized by reacting various α- and β-amino acid esters with Grignard reagents. These amino acid esters were readily reacted with alkyl Grignard reagents to give the expected compounds. However, when bulky aromatic Grignard reagents were submitted to react, the reactions were found to stop at the stage of intermediate formation of the corresponding ketones.

A variety of amino-alcohols having various alkyl substituents at the carbon atom in 1-position, which contain a primary amino group, have been synthesized by Kanao,[2] and some of them were found to have a local anesthetic activity. This finding seemed to suggest that the alkyl substituents at the carbon atom in 1-position might contribute to the generation of the anesthetic activity. Though a number of studies for analgesics have hitherto been widely carried out, no excellent non-narcotic analgesics have been found yet. Thus, for the purpose of finding new effective non-narcotic analgesics, a number of substituted amino-*tert*-alcohols containing a variety of substituents at the carbon atom in 1-position and at the amino group, having the following general formula, in which R_1, R_2 and R_3 stand for hydrogen atom, alkyl or aryl group, were attempted to synthesize.

$$R_1R_2N(CH_2)_nC(R_3)_2OH \qquad (n=1, 2)$$

In order to prepare these compounds, various natural and synthetic α- and β-amino acid esters were allowed to react with a variety of Grignard reagents. Especially, the use of natural amino acids as materials implies to apply them as medical drugs. Synthetic α- and β-amino acid esters,[3a,b,c,d,e] in which various amino groups, such as primary amino, methylamino, ethylamino, dimethylamino, diethylamino, benzylamino, pyrrolidino, piperidino, morpholino and piperazino groups, were involved in the structure, were prepared by treatment of ethyl chloroacetate or carboxylic acid esters containing a double bond, such as acrylic acid, crotonic acid and cinnamic acid esters, with corresponding amines by means of several methods. Grignard reagents were prepared by treating alkyl or aryl halogenides with magnesium in absolute ether by the usual manner. To the etheral solution of these Grignard reagents thus prepared was added the free base or the hydrochloride of these amino acid esters, followed by mild reflux for 30 minutes. Then the reaction mixture was allowed to be hydrolyzed with dilute hydrochloric acid. The resulting by-products separated were removed by extraction with ether and the aqueous layer was made alkaline with ammonium hydroxide. The separated oily product was extracted with ether and purified by distillation or recrystal-

1) Location: *a*) *Oe-hon-machi, Kumamoto*; *b*) *Itabashi, Tokyo*; *c*) *Higashiyodogawa, Osaka.*

2) S. Kanao and K. Shinozuka, *Yakugaku Zasshi*, **50**, 1155 (1930).

3) *a*) C.A. Bischoff, *Chem. Ber.*, **31**, 2840 (1898); *b*) D.W. Adamson, *J. Chem. Soc.*, **1949**, 144; *c*) B. Flürscheim, *J. Prakt. Chem.*, **68**, 350 (1903); *d*) K. Morsch, *Monatsch*, **60**, 50 (1932); *e*) H. Pacheo, D. Dreux and A. Beuillian, *Bull. Soc. Chem.* (France), 1379 (1962); *C.A.*, **58**, 7933 (1963).

Table I.

$$R_2N\text{-}CH_2\text{-}\underset{\displaystyle R'}{\overset{\displaystyle R'}{C}}\text{-}OH$$

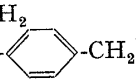
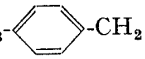
Compd. No.	R_2N	R′	bp or mp (°C/mm) (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
I	H_2N	$CH_3(CH_2)_4$	124/25	51	$C_{12}H_{27}ON$	71.55	13.51	6.95	71.13	13.13	6.25
II	H_2N	CH_2=$CHCH_2$	182—183(oxalate)	36	$C_{10}H_{17}O_5N$	51.50	7.41	6.06	52.09	7.86	6.16
III	H_2N	Ph	93—94	77	$C_{14}H_{15}ON$	78.84	7.09	6.57	79.32	7.45	6.62
IV	H_2N	$PhCH_2$	107	60	$C_{16}H_{19}ON$	79.63	7.93	5.81	80.32	7.96	5.63
V	$(CH_3)_2N$	C_2H_5	160—161/25	—	$C_8H_{19}ON$	66.15	13.18	9.64	66.39	13.27	9.21
VI	$(CH_3)_2N$	CH_2=$CHCH_2$	79—80/4	—	$C_{10}H_{19}ON$	70.95	11.31	8.27	70.96	10.94	8.51
VII	$(C_2H_5)_2N$	C_2H_5	79—80/30	—	$C_{10}H_{23}ON$	69.34	13.32	8.08	69.54	13.52	7.85
VIII	$(C_2H_5)_2N$	$CH_3(CH_2)_4$	149—151/25	—	$C_{16}H_{35}ON$	74.64	13.70	5.44	74.66	13.72	5.28
IX	$(C_2H_5)_2N$	Ph	49—50	72	$C_{18}H_{23}ON$	80.58	8.68	5.20	81.25	9.15	4.78
X		C_2H_5	122—123/28	54	$C_{11}H_{23}ON$	71.29	12.50	7.56	71.33	12.41	7.42
XI		C_3H_7	121—122/34	21	$C_{13}H_{27}ON$	73.18	12.76	6.56	73.43	12.87	6.07
XII		CH_2=$CHCH_2$	112—113/7	47	$C_{13}H_{23}ON$	74.58	11.07	6.69	74.90	11.14	6.55
XIII		$PhCH_2$	216—217 (hydrochloride)	31	$C_{21}H_{28}ONCl$	72.91	8.16	4.05	73.13	8.24	3.60
XIV		CH_3-  -CH_2	192.5—193 (hydrochloride)	42	$C_{23}H_{32}ONCl$	73.87	8.62	3.75	73.95	8.77	3.87
XV		C_2H_5	86—87/7	56	$C_{10}H_{21}ON$	70.09	12.36	8.18	69.59	12.17	8.69
XVI		C_4H_9	130—132/7	65	$C_{14}H_{29}ON$	73.95	12.86	6.16	73.52	12.73	6.14
XVII		C_5H_{11}	153—155/7	55	$C_{16}H_{33}ON$	75.22	13.02	5.48	75.24	13.09	5.44
XVIII		CH_2=$CHCH_2$	128—129/19	71	$C_{12}H_{21}ON$	73.79	10.84	7.17	73.41	10.80	6.61
XIX		$PhCH_2$	185—186 (hydrochloride)	51	$C_{20}H_{26}ONCl$	72.37	7.89	4.22	72.10	7.93	4.12
XX		C_2H_5	105—108/10 (136—137 oxalate)	27	$C_{12}H_{23}O_6N$	51.97	8.36	5.05	52.44	8.59	4.99
XXI		C_3H_7	115—117/6 (177—178 oxalate)	23	$C_{14}H_{27}O_6N$	55.06	8.91	4.59	55.31	9.01	4.63
XXII		C_5H_{11}	121—123/6 (154—155 oxalate)	14	$C_{18}H_{35}O_6N$	59.80	9.76	3.88	60.07	9.71	3.51
XXIII		CH_2=$CHCH_2$	141—142 (oxalate)	26	$C_{14}H_{23}O_6N$	55.80	7.69	4.65	56.15	7.76	4.75
XXIV		Ph	170—170.5 (oxalate)	39	$C_{20}H_{23}O_6N$	64.33	6.21	3.76	64.56	6.38	3.46
XXV		$PhCH_2$	201.5—203.5 (hydrochloride)	55	$C_{20}H_{26}O_2NCl$	69.04	7.53	4.03	69.23	7.63	4.38

$$PhCH_2\text{-}\underset{\displaystyle H_2N}{\overset{\displaystyle R}{CH}}\text{-}\underset{\displaystyle R}{\overset{\displaystyle R}{C}}\text{-}OH$$

Compd. No.	R	bp or mp (°C/mm) (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXVI	C_2H_5	115—117/4(184—185 oxalate)	27	$C_{15}H_{23}O_5N$	60.50	7.80	4.71	60.85	7.73	5.13
XXVII	C_3H_7	202.5—203(oxalate)	10	$C_{19}H_{27}O_5N$	62.74	8.36	4.31	62.79	8.55	4.24

XXVIII	$CH_2=CHCH_2$	199—199.5(oxalate)	27	$C_{19}H_{23}O_5N$	63.53	7.22	4.36	63.67	7.28	4.01
XXIX	Ph	255—256(hydrochloride)	28	$C_{21}H_{22}ONCl$	74.21	6.52	4.12	74.62	6.67	3.78
XXX	$PhCH_2$	139—140(hydrochloride)	33	$C_{23}H_{26}ONCl$	75.25	7.14	3.82	74.83	7.24	3.97

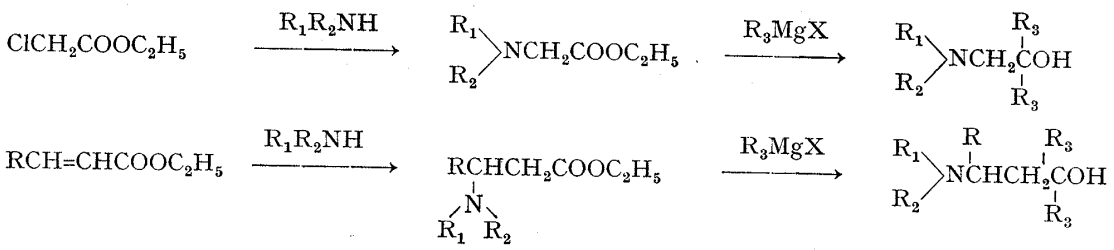
$$R_2N\text{-}CH_2\text{-}CH_2\text{-}\overset{\displaystyle R'}{\underset{\displaystyle R'}{C}}\text{-}OH$$

Compd. No.	R_2N	R′	bp or mp (°C/mm) (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXXI	$(C_2H_5)_2N$	C_2H_5	74—75/7	22	$C_{11}H_{25}ON$	70.53	13.45	7.48	70.05	12.94	7.73
XXXII	$(C_2H_5)_2N$	C_3H_7	108—109/9	25	$C_{13}H_{27}ON$	72.49	13.57	6.51	72.64	13.62	6.67
XXXIII	$(C_2H_5)_2N$	$CH_2=CHCH_2$	92—93/3	64	$C_{13}H_{25}ON$	74.88	11.92	6.63	73.66	11.93	6.78
XXXIV	$(C_2H_5)_2N$	Ph[a]	207—209(oxalate)	52	$C_{21}H_{27}O_5N$	67.54	7.29	3.76	67.95	7.43	3.90
XXXV	$(C_2H_5)_2N$	$PhCH_2$	40—41	39	$C_{21}H_{29}ON$	80.98	9.39	4.50	81.13	9.42	4.57
XXXVI	$(C_2H_5)_2N$	CH_3-  -CH_2	172—174/6	37	$C_{23}H_{33}ON$	81.36	9.80	4.12	81.34	9.94	4.49
XXXVII	$(CH_3)_2N$	C_2H_5	57—59/4	22	$C_9H_{21}ON$	67.87	12.29	8.80	67.57	13.30	8.92
XXXVIII	$(CH_3)_2N$	C_4H_9	117—118/13	18	$C_{13}H_{29}ON$	72.49	13.57	6.51	72.30	13.55	6.65
XXXIX	$(CH_3)_2N$	C_5H_{11}	125/4	44	$C_{15}H_{33}ON$	74.00	13.66	5.75	74.24	13.62	5.88
XL	$(CH_3)_2N$	$CH_2=CHCH_2$	79—80/5	65	$C_{11}H_{21}ON$	72.08	11.55	7.64	71.87	11.63	7.67
XLI	$(CH_3)_2N$	$PhCH_2$	195—198/8 63—64	38	$C_{19}H_{25}ON$	80.51	8.89	4.94	80.43	8.84	5.23
XLII	$(CH_3)_2N$	CH_3-  -CH_2	185—187/3	41	$C_{21}H_{29}ON$	80.98	9.39	4.50	80.81	9.24	4.59
XLIII		$CH_2=CHCH_2$	121—122/5	78	$C_{14}H_{25}ON$	75.28	11.28	6.27	75.17	11.47	6.35
XLIV		$PhCH_2$	170—176/7 49—50	37	$C_{22}H_{29}ON$	81.68	9.04	4.33	81.68	8.99	4.40
XLV		$CH_2=CHCH_2$	139—142/7	35	$C_{13}H_{23}O_2N$	69.29	10.29	6.22	69.20	10.30	6.18
XLVI		Ph[a]	207—208 (hydrochloride)	30	$C_{19}H_{24}O_2NCl$	68.35	7.24	4.19	68.05	7.12	4.28
XLVII		$PhCH_2$	208—209 (hydrochloride)	55	$C_{21}H_{30}O_2NCl$	69.69	7.80	3.87	70.10	7.86	4.04
XLVIII		C_4H_9	125—126/4	53	$C_{15}H_{31}ON$	74.62	12.94	5.80	74.52	13.17	5.58
XLIX		$CH_2=CHCH_2$	117—118/3	46	$C_{13}H_{23}ON$	74.58	11.07	6.69	74.21	11.08	6.52
L		$PhCH_2$	207—208 (hydrochloride)	53	$C_{21}H_{28}ONCl$	72.87	7.87	4.05	72.67	8.28	4.02
LI	$PhCH_2NH$	C_2H_5	215—216(oxalate)	12	$C_{16}H_{25}O_5N$	61.71	8.09	4.50	60.69	7.74	4.54
LII		$PhCH_2$	242—244(decomp.) (hydrochloride)	19	$C_{38}H_{48}O_2N_2Cl_2$	71.79	7.61	4.41	71.80	7.64	4.41

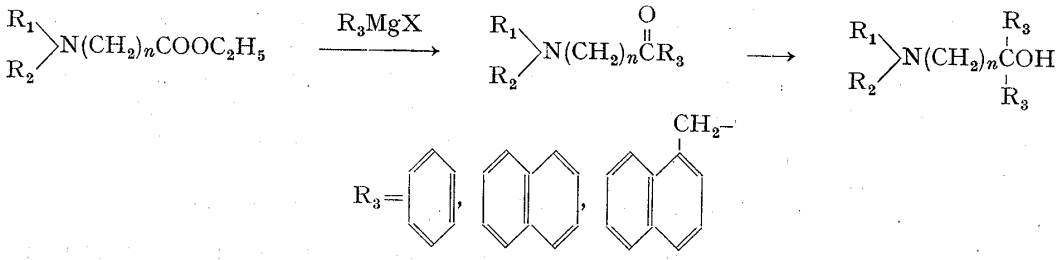
$$R_2N\text{-}\overset{\displaystyle R'}{\underset{}{C}}H\text{-}CH_2\text{-}\overset{\displaystyle R''}{\underset{\displaystyle R''}{C}}\text{-}OH$$

Compd. No.	R_2N	R′	R″	bp or mp (°C/mm) (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
LIII	$(C_2H_5)_2N$	CH_3	$CH_2=CHCH_2$	96—98/4	38	$C_{14}H_{27}ON$	74.61	12.08	6.22	74.43	12.17	6.35
LIV		Ph	$PhCH_2$	104—105	42	$C_{27}H_{31}ON$	84.09	8.11	3.62	84.25	8.27	3.48

a) These compounds were known.



lization. When Grignard reagents containing comparative bulky substituents, such as amyl, benzyl, phenyl, *p*-xylyl and naphthyl, were employed in the reaction, the corresponding amino alcohols were directly isolated from the reaction mixture in the form of crystals of the hydrochloride in the course of this procedure for their slight solubility. Generally, aliphatic alkyl Grignard reagents were reacted readily with amino acid esters to give the corresponding amino alcohols. However, when aromatic Grignard reagents were submitted to react with amino acid esters, the reaction was stopped at the stage of the intermediate formation of ketones and the further reaction was not able to proceed, probably because of the increasing steric bulkiness due to aromatic ring.



All of these amino-*tert*-alcohols synthesized were summarized in Table I. The pharmacological activities of these compounds will be reported in the other paper.

Experimental

α-Amino Acid Esters——L-Phenylalanine Ethyl Ester Hydrochloride: It was prepared by the method of Fischer–Schodler[4] using 30 g (0.184 mole) of L-phenylalanine, 300 ml of abs. EtOH and dry HCl.

L-Aspartic Acid Ethyl Ester Hydrochloride: It was prepared by the method of Fischer[5] using 30 g (0.226 mole) of L-aspartic acid, 300 ml of abs. EtOH and dry HCl.

L-Valine Ethyl Ester Hydrochloride: It was prepared by the method of Tafel[6] using 30 g (0.26 mole) of L-valine, 200 ml of abs. EtOH and dry HCl.

General Method for Preparation of α-Substituted Amino Acid Esters: To 0.57 mole of ethyl chloroacetate was added 1.14 mole of amines in small portions under cooling with ice and salt. The mixture was allowed to stand overnight at room temperature. Amine hydrochloride precipitated was removed by suction, and the filtrate was diluted with H_2O and extracted with ether. After removal of ether, the residue was distilled under reduced pressure.

β-Amino Acid Esters——Method I: By the method of Adamson[3b] adding 1 mole of amine to a solution of 0.5 mole of ethyl acrylate in 250 ml of EtOH.

Method II: By the method of Flürscheim[3c] refluxing a mixture of 0.5 mole of ethyl acrylate and 1 mole of amine.

Method III: By the method of Adamson adding a solution of 0.5 mole of ethyl acrylate in 100 ml of abs. EtOH to 1 mole of amine.

Method IV: By the method of Pacheo[3e] from 0.17 mole of ethyl cinnamate and 0.34 mole of amine.

Method V: A solution of 0.5 mole of ethyl acrylate in 100 ml of EtOH was added to 0.5 mole of amine. The solution was refluxed for 5 hr on a water bath. After removal of EtOH, the residue was extracted with ether, dried over Na_2SO_4, and distilled under reduced pressure.

These compounds obtained were summarized in Table II.

4) E. Fischer and W. Schoeller, *Ann.*, **357**, 14 (1907).
5) E. Fischer, *Chem. Ber.*, **34**, 452 (1901).
6) J. Tafel, *Chem. Ber.*, **22**, 1862 (1889).

Table II. Ethyl 2-Substituted Amino-2-alkylpropionate

$$R_2N\text{–}\underset{\displaystyle R'}{\underset{|}{CH}}\text{–}CH_2\text{–}COOC_2H_5$$

R_2N	R′	Method	Solvent	Time (hr)	Tempt. (°C)	bp or mp (°C/mm) (°C)	Yield (%)
C_2H_5NH	H	I	EtOH	24	10—20	101—103/17	75
$(CH_3)_2N$	H	I	EtOH	24	10—20	65—66/24	76
$(C_2H_5)_2N$	H	II	no	4	50—60	94.5—95.5/24	73
$(C_2H_5)_2N$	CH_3	II	no	4	50—60	94—95/17.5	11
$(C_2H_5)_2N$	CH_3	I	EtOH	7	10—20	94—95/17.5	14
	H	II	no	6	90—100	93—95/2	78
	Ph	IV	no	3	70—80	135—138/3 (171—172 hydrochloride)	14
	H	II	no	6	100—110	127—128/32	88
	Ph	IV[a]	no	3	70—80	205 (hydrochloride)	16
	H	II	no	6	100—110	111—112/10	82
$PhCH_2NH$	H	III	EtOH	5	80—85	122—125/1.5	43
	H	V	EtOH	5	70—80	34—35 (211 hydrochloride)	11[b]

a) In this case, 3-phenyl-3-piperidinopropiopiperidide (mp 119—120) and cinnamoylpiperidide (mp 122—125) were also isolated.
b) N,N-carboethoxyethylpiperazine hydrochloride: *Anal.* Calcd. for $C_{14}H_{28}O_4N_2Cl_2$: C, 46.80; H, 7.85; N, 7.79. Found: C, 47.00; H, 7.90; N, 7.78.

General Method for Synthesis of Amino-*tert*-alcohol——Magnesium turnings (0.145 atom) was covered with 20 ml of ether and a small amount of halide was added with warming to initiate the reaction. If the reaction did not initiate, a catalytic amount of iodine was added. As soon as the reaction was initiated, the remainder of halide (total 0.145 mole) was gradually added at such a rate that the mixture boils gently. After addition, the mixture was warmed to complete the reaction. To this solution was added a calculated amount of amino acid ester at such a rate that the reaction mixture boils continuously. The reaction mixture was refluxed for 30 min to complete the reaction, and then treated with 15% aqueous solution of HCl containing ice pieces. The insoluble oily substance, mainly hydrocarbon produced by coupling, was removed by extraction with ether. The aqueous layer was made alkaline with aqueous NH_4OH, and extracted with ether. The product was purified by distillation or recrystallization in the form of oxalate.

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