Notes

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Keiichi Takamura, Akitoshi Shioya, Katsumaro Minamoto, Noriaki Asada, Sakae Takaku, Akihito Yoshimitsu, and Yoshihiro Nitta : Studies on Analgesics of Aniline Series. I. Preparation and Properties of β-Alaninamide Series.

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Recently, Renzi, *et al.*[1] reported on the synthesis of alaninamide and glycinamide series possessing spasmolytic activity. On the other hand, Takahashi, *et al.*[2] also described on the synthesis of alaninamide and glycinamide series having analgetic activity. The present paper deals with the preparation of β-alaninamide series in order to obtain further information on the relationship between analgetic or spasmolytic activity and structure of this series, and presents several methods for the preparation of compounds of this series.

Method A——Ethyl 3-(substituted anilino)propionates (Ⅱ) were obtained in excellent yields by condensation of substituted anilines (Ⅰ) with ethyl acrylate under the presence of catalyst, such as acetic acid. When Ⅱ were treated with secondary amines in alcohol, benzene or water, N,N-dialkyl 3-(substituted anilino)propionamides (Ⅲ) were obtained. However, treatment of ethyl 3-(*p*-phenetidino)propionate with dimethylamine in water under pressure resulted in the formation of a small amount of N,N-dimethyl 3-(*p*-phenetidino)propionamide together with its hydrolysed product, 3-(*p*-phenetidino)propionic acid which was indistinguishable in melting point and infrared spectrum from the authentic one prepared by hydrolysis of N,N-dimethyl 3-(*p*-phenetidino)propionamide. On the other hand, Ⅲ were also obtained by condensation of Ⅱ with secondary amines using twice as much amount required in water at room temperature for 6 days.

Method B——Substituted anilines (Ⅰ) were condensed with N-alkyl or N,N-dialkyl acrylamides (Ⅳ) in benzene under the presence of catalyst, such as acetic acid, to give the corresponding N-alkyl or N,N-dialkyl 3-(substituted anilino)propionamides (Ⅲ).

Method C——N,N-Dialkyl 3-(substituted anilino)propionamides (Ⅲ) were also obtained in good yields by treatment of substituted anilines (Ⅰ) with N,N-dialkyl 3-dialkylaminopropionamides[3] (Ⅴ) under pressure at 100~250° for 30 hours, accompanied with the evaporation of dialkylamines.

Method D——Preparation of N,N-dialkyl 3-(substituted anilino)propionamides (Ⅲ) was attempted unsuccessfully by the condensation of substituted anilines (Ⅰ) with N,N-dialkyl 3-halogenopropionamides (Ⅵ)[4] in the presence of dehydrohalogenating agent, such as potassium carbonate and of copper catalyst and potassium iodide, in boiling alcohol.

However, N,N-dialkyl 3-(substituted anilino)propionamides (Ⅲ) were obtained by condensation of substituted anilines (Ⅰ) with N,N-dialkyl 3-halogenopropionamides (Ⅵ) in the presence of dehydrohalogenating agent, such as potassium carbonate, at 130~140°.

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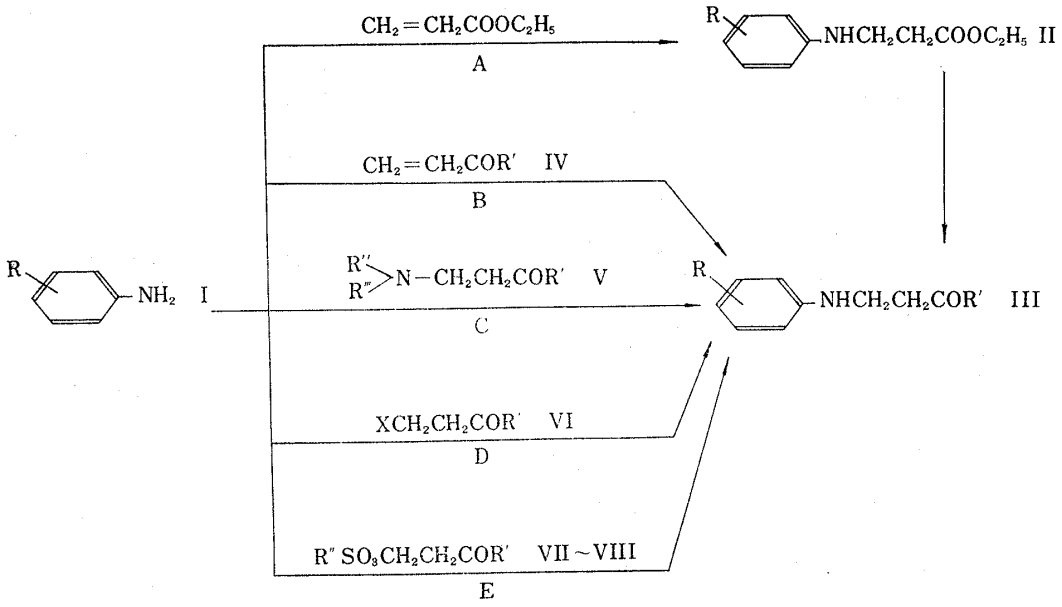
1) L. Renzi, G.B. Marini Bottolo : Gazz. chim. ital., 84, 938 (1954).
2) T. Takahashi, *et al.* : Yakugaku Zasshi, 80, 902, 905, 1579 (1960).
3) T.G. Erickson, *et al.* : J. Am. Chem. Soc., 74, 6281 (1952).
4) J.E. Gearien, K.J. Lioka : J. Am. Chem. Soc., 76, 3554 (1954).

Method E——N,N-Dialkyl 3-(substituted anilino)propionamides (Ⅲ) were prepared by treatment of substituted anilines (Ⅰ) with methanesulfonate (Ⅶ) or *p*-toluenesulfonate (Ⅷ) of N,N-dialkyl hydracylamides[5] in boiling alcohol, and were obtainable in more excellent yields by using Ⅷ rather than Ⅶ.



R=alkoxy, halogen, alkyl, H.
R″=R‴=lower alkyl.
R′=mono or dialkylamino, heterocyclic alkyl.

Chart 1.

Methods described above were illustrated in Chart 1 and the physical constants of compounds obtained were listed in Table I.

Pharmacological Test[*2]——Analgetic activity of the compounds described in this paper was determined by use of Writhing test,[6] Electrical Stimulation method[7] and Radiant heat method.[8] Analgetic activities of these compounds were compared with that of aminopyrine and phenacetin as shown in Table Ⅱ. As it can be seen in Table Ⅱ, some of them, Nos., 104, 119, 160, and 169 were found to be less potent than aminopyrine, but more potent than phenacetin.

On the other hand, the spasmolytic activity to prevent the action of acetylcholine and of barium ion on the isolated guineapig's ileum was determined. Spasmolytic activities of these compounds were compared with atropine and papaverine hydrochloride, as shown in Table Ⅲ. As it can be seen in Table Ⅲ, some of them, Nos., 107, 108, 117, 119, 131, and 132 were found to have somewhat less potent than atropine, but compound No. 131 was found to be twice as much potent than papaverine hydrochloride, while other compounds were shown to be less potent than papaverine hydrochloride.

*2 These experiments were carried out by Mr. K. Tobita and Mr. N. Takano of the Department of General Pharmacology, Biological Research Division in these Research Laboratories.

5) T. L. Gresham, *et al.*: J. Am. Chem. Soc., **73**, 3168 (1951).
6) K. H. Beecher: *a*) "Measurement of Subjective Responeses," Oxford University Press, New York, 1959. *b*) H. Fujimura, *et al.*: Folia Pharmacol. Japon., **56**, 522 (1960). *c*) R. Koster, M. Andernon, E. J. de Beer: Fed. Proc., **18**, 412 (1959).
7) H. Ozawa, *et al.*: Yakugaku Zasshi, **73**, 212 (1953).
8) H. Takagi, *et al.*: Folia Pharmacol. Japon., **57**, 585 (1961); F. E. D'Amour, P. L. Smith: J. Pharmacol., **72**, 74 (1941).

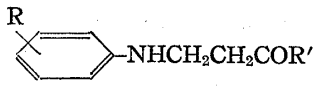
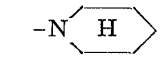
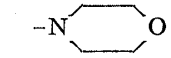
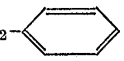
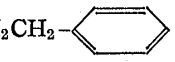
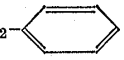
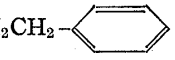
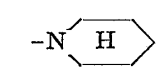
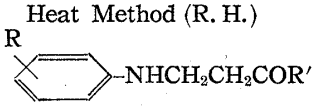


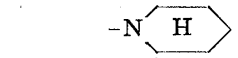
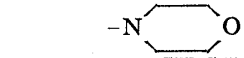
TABLE I.

Compound	R	R′	Method	m.p. (b.p./mm. Hg)
102	*p*-OC_2H_5	NH_2	A	118～119°
104	〃	$-N(CH_3)_2$	〃	74～76°
103	〃	$-NHC_2H_5$	〃	88～90°
105	〃	$-N(C_2H_5)_2$	B	80～82°
106	〃		〃	62～63°
107	〃		〃	78～80°
108	〃	$-N(CH_2CH=CH_2)_2$	〃	54～56°
138	〃	$-N(C_3H_7)_2$	〃	b.p. 177/0.2
116	H	$-N(CH_3)_2$	C	107～108°
118-1	*o*-Cl	〃	B	b.p. 143～145°/0.15
129	*m*-Cl	〃	〃	98～99.5°
118	*p*-Cl	〃	〃	110～112°
119	*p*-Br	〃	A～E	114.5～116.5°
117	*p*-OCH_3	〃	B	91～92.5°
135	*m*-OCH_3	〃	〃	95～97°
135-1	*o*-CH_3	$-NHCH_3$	〃	68～70°
142	〃		〃	111～112°
131	*p*-OC_2H_5	$-NHCH_2CH_2OH$	〃	69～71°
141	〃		〃	71～73°
142-1	H		〃	70.5～72.5°
144	2,6-$(CH_3)_2$	〃	〃	95～97°
130	〃		〃	69～71°
120	*p*-CH_3	$-N(CH_3)_2$	A	110.5～111.5°
169-1	*p*-$OCOC_2H_5$	〃	〃	154～156°
160	2,6-$(CH_3)_2$	〃	C, E	(b.p. 135～145°/1 HCl. 158～159°) styphnic acid 171～172°
169	*p*-$OCH_2CH=CH_2$	〃	C	62～63°
182	*p*-$N(CH_3)_2$	〃	C, E	128～129°
119-1	*p*-Br		C	122～124°

Formula	Analyses (%) Calcd. C	H	N	Found C	H	N	Yield (%)
$C_{11}H_{16}O_2N_2$	63.44	7.74	13.45	63.54	7.65	13.57	35.0
$C_{13}H_{20}O_2N_2$	66.07	8.53	11.86	66.46	8.74	11.57	55.0
〃	66.07	8.53	11.86	65.88	8.57	11.70	72.0
$C_{15}H_{24}O_2N_2$	68.15	9.15	10.60	68.42	9.32	10.59	49.3
$C_{16}H_{24}O_2N_2$	69.53	8.75	10.14	69.93	8.93	10.21	52.5
$C_{15}H_{22}O_3N_2$	64.72	7.97	10.07	64.73	8.01	10.12	68.0
$C_{17}H_{24}O_2N_2$	70.80	8.39	9.71	71.37	7.99	9.60	70.0
$C_{17}H_{28}O_2N_2$	69.82	9.65	9.58	69.91	9.79	9.74	47.0
$C_{11}H_{16}ON_2$	68.72	8.39	14.57	68.54	8.41	14.70	35.0
$C_{11}H_{15}ON_2Cl$	58.27	6.69	12.36	57.97	6.74	12.07	72.6
〃	58.27	6.69	12.36	58.50	6.80	11.98	18.0
〃	58.27	6.69	12.36	58.17	6.80	12.18	25.0
$C_{11}H_{15}ON_2Br$	48.72	5.58	10.33	49.00	5.77	10.60	A=73.0 B=51.0 C=64.0 D=60.0 E=62.2
$C_{12}H_{18}O_2N_2$	64.84	8.16	12.60	64.97	8.01	12.84	13.0
〃	64.84	8.16	12.60	64.89	8.17	12.62	39.2
$C_{11}H_{16}ON_2$	68.72	8.39	14.57	68.68	8.51	14.37	70.3
$C_{17}H_{20}ON_2$	76.08	7.51	10.44	76.31	7.47	10.30	82.6
$C_{13}H_{20}O_3N_2$	61.88	7.99	11.10	62.26	8.12	11.32	34.5
$C_{19}H_{24}O_2N_2$	73.04	7.74	8.97	72.84	7.70	9.01	80.0
$C_{16}H_{18}ON_2$	75.56	7.13	11.02	75.60	7.18	10.86	53.0
$C_{18}H_{22}ON_2$	76.56	7.83	9.92	76.46	7.94	9.99	75.0
$C_{19}H_{24}ON_2$	76.99	8.16	9.45	77.01	8.28	9.36	59.0
$C_{12}H_{18}ON_2$	69.87	8.80	13.58	70.26	9.04	13.46	62.0
$C_{14}H_{20}O_3N_2$	63.61	7.63	10.60	63.53	7.62	10.61	65.0
$C_{19}H_{23}O_9N_5$	49.03	4.98	15.05	49.28	5.20	15.12	C=39.7 E=61.0
$C_{14}H_{20}O_2N_2$	67.71	8.12	11.16	67.67	8.21	11.28	21.0
$C_{13}H_{21}ON_3$	66.35	9.00	17.86	66.07	8.95	17.85	C=66.5 E=44.3
$C_{14}H_{19}ON_2Br$	54.03	6.15	9.00	54.29	6.34	8.85	28.3

Table II. The Analgesic Potency of Compounds by Three Methods; Writhing Test (W. T), Electrical Stimulation Method (E. S.) and Radiant Heat Method (R. H.)



Compound No.	R	R′	W. T.	E. S.	R. H.
Aminopyrine			++	++	++
Phenacetin			−	±	+
102	*p*-C_2H_5O	NH_2	±	±	
103	〃	$-NHC_2H_5$	±	+	
104	〃	$-N(CH_3)_2$	+	+	++
105	〃	$-N(C_2H_5)_2$	−		
106	〃		−	±	++
107	〃		−	±	
108	〃	$-N(CH_2CH=CH_2)_2$	±	±	++
116	H	$-N(CH_3)_2$	−	±	
117	*p*-CH_3O	〃	−	±	
118-1	*p*-Cl	〃	−	±	
119	*p*-Br	〃	+	++	++
120	*p*-CH_3	〃	±	++	−
129	*m*-CH_3	〃	−	++	
130	2,6-$(CH_3)_2$	$-NHCH_2CH_2-C_6H_5$	−	+	
131	*p*-C_2H_5O	$-NHCH_2CH_2OH$	−	−	
132	*m*-CH_3O	$-NHCH_2CH_2-C_6H_5$	−	++	
135	〃	$-N(CH_3)_2$	−	+	
138	*p*-C_2H_5O	$-N(C_3H_7)_2$	−	±	±
141	〃	$-NHCH_2CH_2-C_6H_5$	−	−	
142	*o*-CH_3	〃	−	−	
144	2,6-$(CH_3)_2$	$-NHCH_2-C_6H_5$	−	±	
160	〃	$-N(CH_3)_2$	−	+	++
169	*p*-$OCH_2CH=CH_2$	〃	+	++	+
182	*p*-$N(CH_3)_2$	〃	++	toxic	toxic

W.T.[a]: Writhing test. E.S.[b]: Electrical stimulation method. R.H[b]: Radiant heat method.

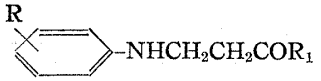
a) W.T.: The suppression rate of the Writhing syndrome (200 mg./kg. P.O.).
++≧60%, +≧40%, ±≧20%, −<20%.

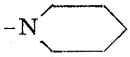
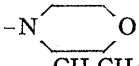
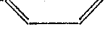
b) E.S. and R.H.: The ratio of mean reaction time of drug-treated group to the control value. (200 mg./kg. P.O.).
++≧1.3, +≧1.2, ±≧1.0, −<1.0.

Effect of various substituents on the benzene ring of III on analgetic activity was examined. Compounds having bromine or allyloxy group in position 4 were found to be more potent than those having other kinds of substituent such as methoxyl, ethoxyl, methyl or chloro. Effect of various alkyl substituents on the nitrogen atom of amide on analgetic activity was examined. Dimethylamide derivatives were found to be most potent among in mono- or di-alkylamide derivatives.

In the spasmolytic test, effect of alkyl substituents on the nitrogen atom of amide was also found to increase in the following order; diallylamide>β-phenylethylamide> diethylamide>morpholino, ethylamide.

Table III. The Spasmolytic Activity of Compounds *in vitro*



Compound No.	R	R_1	Anti-Ach [10^{-8} g./ml. Ach] Final concentration (g./ml.)	Anti-Ach degree	Anti-Ba^{++} [2×10^{-4} g./ml. Ba^{++}] Final concentration (g./ml.)	Anti-Ba^{++} degree
Atropine			10^{-7}	++		
Papaverine·HCl					2×10^{-5}	++
103	*p*-C_2H_5O	$-NHC_2H_5$			2×10^{-5}	+
104	〃	$-N(CH_3)_2$	10^{-4}	+	2×10^{-5}	+
105	〃	$-N(C_2H_5)_2$	10^{-4}	+	2×10^{-5}	++
106	〃		10^{-4}	+	2×10^{-5}	+
107	〃		10^{-4}	+	2×10^{-5}	+
108	〃	$-N(CH_2CH{=}CH_2)_2$	10^{-4}	++	2×10^{-5}	++
117	*p*-CH_3O	$-N(CH_3)_2$	10^{-4}	+		
119	*p*-Br	〃			2×10^{-5}	
131	*p*-C_2H_5O	$-NHCH_2CH_2OH$	10^{-5}	+	10^{-5}	++
132	*m*-CH_3O	$-NHCH_2CH_2$- 			2×10^{-5}	++

Experimental

Pharmacological Test——A) Analgetic activity: Materials and methods; Three methods indicated below were employed to investigate the analgetic activity of compounds: 1) Writhing test, 2) Radiant heat method, and 3) Electrical stimulation method. The procedures were as follows.

1) Writhing test: The Writhing syndrome or stretching movements were produced in mice by the intraperitoneal injection of acetic acid (0.6%, 0.1 ml./10 g. of body weight). The analgetic potency of compounds was estimated from the suppression rate of these syndrome, when compounds were administered 30 min. prior to acetic acid injection.

2) Radiant heat method: This is the modification of D'Amour & Smith's, that is the radiant heat from electric bulb was delivered to mice, hair shaved and blockened back, until sudden movement of animal occurred. The reaction time was measured before and after the administration of drug at the definite time. The ratio of the mean reaction time of the treated to the control group was calculated, and the analgetic activity was estimated in comparing this ratio with that of aminopyrine.

3) Electrical stimulation method: Rectangular current of 50 volts-10 m. second duration was delivered to mice tail at the inside once a second. The numbers of shocks until mice squeak were counted. The way to estimate the analgetic activity was similar to that in radiant heat method as described.

B) Spasmolytic activity: The isolated guinea-pig's ileum was immersed in the Tyrode solution in the Magnus' tube, in which air was supplied adequately. Test compounds were added to make the final concentration 10^{-5} to 10^{-6} g./ml. in the tube. Papaverine hydrochloride was served as control. Barium chloride solution was then delivered to make final concentration 2×10^{-4} g./ml. From the suppression degree produced by the test compounds of contracture due to barium chloride their spasmolytic activities were determined.

Ethyl or Methyl 3-(Substituted anilino)propionates (II)——A solution of 1.8 moles of substituted anilines (I) in 0.7 mole of acetic acid was added to 1.8 moles of ethyl or methyl acrylate. The mixture was heated at 80～90° for 12 hr. After cooling, the reaction mixture was extracted with ether, and the ethereal extract was washed with 3% $NaHCO_3$ and H_2O, and then dried over anhyd. Na_2SO_4. Evaporation of the ether gave an oil which was fractionated to give ethyl or methyl 3-(substituted anilino)-propionates (II) in the yields of 60～70%.

N,N-Dialkyl or N-Alkyl 3-(Substituted anilino)propionamides (III)——A. 1) A mixture of 1 mole of II and 2～3 moles of primary or secondary amines in ethanol or benzene was heated in a sealed tube

at 150° for 25～30 hr., and the solvent was distilled off. Recrystallization of the residue from ethanol or acetone gave Ⅲ.

2) A mixture of 1 mole of ethyl 3-(substituted anilino)propionates and 2 moles of 33% aq. solution of secondary amines was allowed to stand for 6 days at room temperature. The resulting mixture was concentrated to dryness at reduced pressure. The residue was dissolved in dry $CHCl_3$, and chromatographed on an alumina column. Elution with $CHCl_3$ gave N,N-dialkyl 3-(substituted anilino)propionamides (Ⅲ).

3) A solution of 1 mole of ethyl 3-(*p*-phenetidino)propionate in 3 moles of 40% aq. solution of dimethylamine was heated in sealed tube at 150° for 25 hr. The resulting mixture was concentrated to a small volume at reduced pressure, and a small amount of 10% Na_2CO_3 solution was added to the residue. The mixture was extracted with benzene, and the benzene layer was washed with H_2O, dried over anhyd. Na_2SO_4, and then the solvent removed by distillation. Recrystallization of the residue from acetone gave a small amount of crystals, N,N-dimethyl 3-(*p*-phenetidino)propionamide (Ⅲ), m.p. 74～76°. *Anal.* Calcd. for $C_{13}H_{20}O_2N_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.46; H, 8.74; N, 11.57. When the aqueous layer was neutralized with 10% HCl solution and cooled, a colorless precipitate was obtained. The product was filtered and recrystallized from ethanol to give a colorless needles of 3-(*p*-phenetidino)propionic acid, m.p. 108～110°. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.15; H, 7.16; N, 6.42. Identity with an authentic sample, 3-(*p*-phenetidino)propionic acid, obtained by hydrolysis of N,N-dimethyl 3-(*p*-phenetidino)propionamide with 10% NaOH solution was proved by comparison of infrared spectra and by the fact that no melting point depression was observed upon admixture of the two samples.

B. To a solution of 0.23 mole of substituted anilines and 0.125 mole of N,N-dialkyl acrylamides in 35 ml. of ethanol was added a few drops of acetic acid. The mixture was allowed to stand for 4 days at room temperature, and then refluxed for 4 hr. on a water bath. The resulting mixture was concentrated to dryness at reduced pressure. Recrystallization of the residue from ethanol gave crystals of Ⅲ. Yield, 13～84.2%.

C. A mixture of 1 mole of substituted anilines and 1.2 moles of N,N-dialkyl aminopropionamides was heated at 100～250° for 30 hr. The resulting mixture was allowed to stand overnight at room temperature and was filtered to give crystals. Recrystallization from ethanol gave crystals of Ⅲ. Yield, 21～66.5%.

D. To a mixture of 0.054 mole of substituted anilines and 0.037 mole of N,N-dialkyl 3-halogenopropionamides and 0.037 mole of N,N-dialkyl 3-halogenopropionamides was added 0.037 mole of K_2CO_3. The mixture was heated at 130～140° for 3 hr., and was dissolved by addition of boiling benzene. The resulting mixture was filtered to give crystals. Recrystallization from ethanol gave crystals of Ⅲ.

E. A solution of 0.123 mole of substituted anilines and 0.061 mole of *p*-toluenesulfonates or methanesulfonates of N,N-dimethyl hydracrylamides in 100 ml. of ethanol was refluxed for 12 hr. The solvent was distilled off, and to the residue was added 200 ml. of 5% KOH solution with stirring. The precipitate obtained was collected, washed with H_2O and recrystallized from ethanol to give crystals of Ⅲ. Yield, 44.3～62.2%.

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Summary

N-Alkyl or N,N-dialkyl 3-(substituted anilino)propionamide derivatives were prepared by several procedures.

Some of these compounds were found to possess valuable analgetic and spasmolytic activities.

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