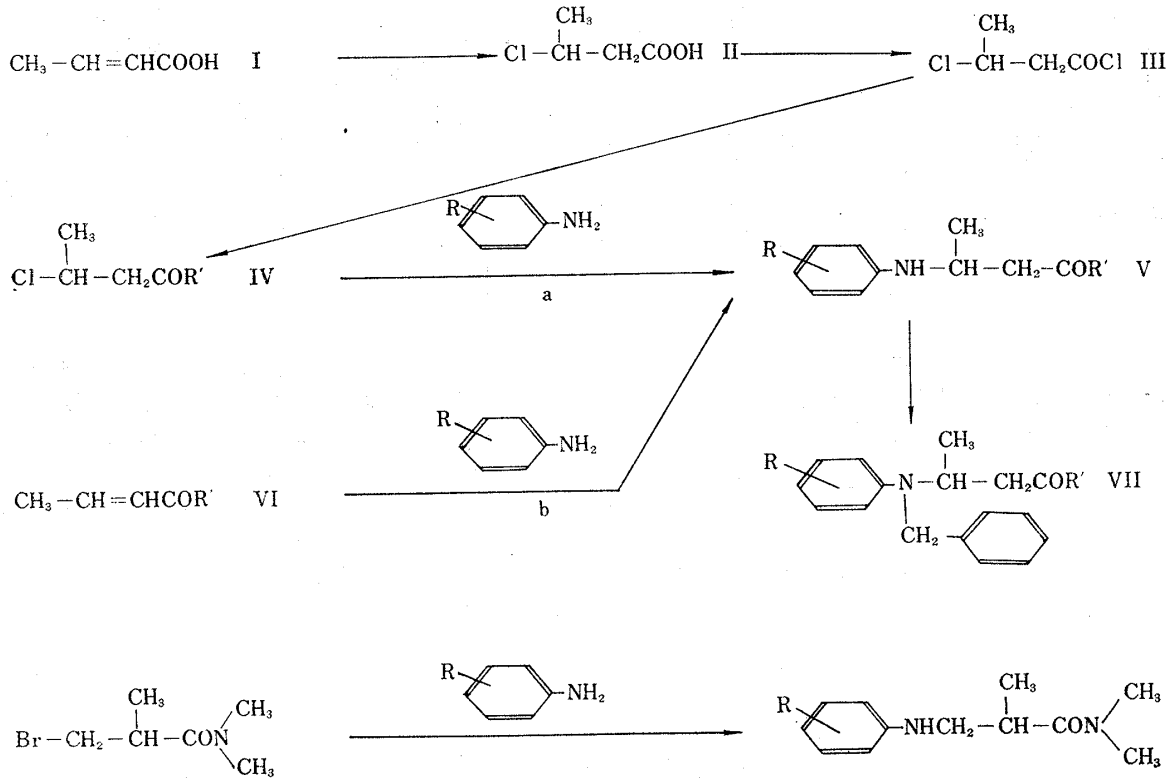
[Chem. Pharm. Bull. 13(2) 211~217 (1965)] UDC 615.782 : 547.551

Keiichi Takamura, Akitoshi Shioya, Tadahiro Yamamoto, Shin-ichi Takama, and Yoshihiro Nitta : Studies on Analgesics of Aniline Series. III.*1 Preparation and Properties of N,N-Dialkyl 3-(Substituted anilino)butyramide Series.

(*Research Laboratories, Chugai Pharmaceutical Co., Ltd.**2)

In the series of studies on β-alanine derivatives and related compounds possessing analgetic activity, the present authors first reported that N,N-dimethyl-3-(*p*-bromoanilino)propionamides showed distinguished pharmacological potency.[1] The present paper deals with preparations of N,N-dialkyl-3-(substituted anilino)butyramides and the relationship between structure of this series and analgetic activity.

3-Chlorobutyric acid (II) was prepared by adding crotonic acid (I) to ethereal hydrogen chloride solution at low temperature to give 3-chlorobutyric acid (II) which was in turn converted to 3-chlorobutyryl chloride[1] (III) by using thionyl chloride. Treatment of



R=alkoxyl, alkyl, halogen, H. R′=dialkylamino, heterocyclic alkyl.

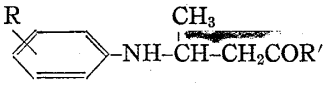
Chart 1.

III with secondary amines in benzene afforded N,N-dialkyl 3-chlorobutyramides (IV) which were condensed with substituted anilines in the presence of dehydrochlorinating agent, such as potassium carbonate, to give N,N-dialkyl 3-(substituted anilino)butyramides (V). On the other hand, N,N-dialkyl 3-(substituted anilino)butyramides (V) were

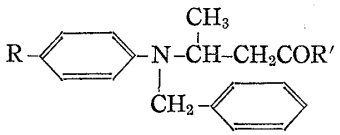
*1 Part II : This Bulletin, **13**, 205 (1965).

*2 Takadaminami-cho, Toshima-ku, Tokyo (高村圭一, 塩屋明利, 山本忠宏, 高間伸一, 新田義博).

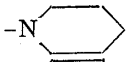
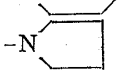
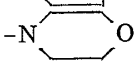
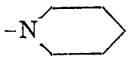
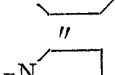
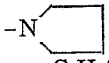
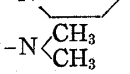
1) A. Bruylants, *et al.* : Chem. Abstr., **47**, 11125 (1953).

TABLE I. 

Compound	R	R′	Method	m.p. (b.p./mm. Hg)	Formula	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield (%)
188	*p*-C_2H_5O	$-N(CH_3)_2$	a	b.p. 188～191°/1 m.p. 51°	$C_{14}H_{22}O_2N_2$	67.17	8.86	11.19	67.41	8.95	11.13	63.0
189	〃	$-N(C_2H_5)_2$	a b	b.p. 180～190°/1 m.p. 58.5～59.5°	$C_{16}H_{26}O_2N_2$	69.03	9.41	10.06	68.86	9.34	10.04	a: 33.1 b: 35.6
193	*p*-CH_3	$-N(CH_3)_2$	a	b.p. 170～178°/1 m.p. 64.5°	$C_{13}H_{20}ON_2$	70.87	9.15	12.72	70.98	9.19	12.70	21.6
196	*p*-Br	$-N(C_2H_5)_2$	a	60～61°	$C_{14}H_{21}ON_2Br$	53.68	6.76	8.94	53.83	6.87	8.85	7.8
197	H	$-N(CH_3)_2$	a	103°	$C_{12}H_{16}ON_2$	68.87	8.80	13.58	69.97	8.77	13.56	1.7
198	*p*-CH_3O	〃	a	66°	$C_{13}H_{20}O_2N_2$	66.07	8.53	11.86	66.16	8.31	11.69	1.3
1100	*p*-C_2H_5O	$-N(C_3H_7(n))_2$	a	72.5～73.5°	$C_{18}H_{30}O_2N_2$	70.55	9.87	9.14	70.65	9.77	8.99	0.5

TABLE II. 

Compound	R	R′	Method	m.p. (b.p./mm. Hg)	Formula	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield (%)
199	CH_3O	$-N(C_2H_5)_2$		b.p. 180°/0.4 62～63°	$C_{22}H_{30}O_2N_2$	74.54	8.53	7.90	74.86	8.63	7.80	38.5
1105	CH_3	$-N(CH_3)_2$		114°	$C_{20}H_{26}ON_2$	77.38	8.44	9.03	77.49	8.41	8.98	10.0
1132	〃	$-N(CH_2CH{=}CH_2)_2$		b.p. 170～172°/0.5 58～59°	$C_{24}H_{30}ON_2$	79.52	8.34	7.73	79.45	8.13	7.73	66.0
1135	C_2H_5O	〃		59.5～60.5°	$C_{25}H_{32}O_2N_2$	76.50	8.22	7.14	76.67	8.23	7.08	23.0
1136	〃	$-N$ 		86°	$C_{24}H_{32}O_2N_2$	75.75	8.48	7.36	75.59	8.58	7.29	49.0

1137	CH_3O	〃		75°	$C_{23}H_{30}O_2N_2$	75.37	8.25	7.64	75.28	8.23	7.58	15.0
1138	CH_3	〃		99°	$C_{23}H_{30}ON_2$	78.81	8.63	7.99	78.45	8.38	8.10	34.0
1106	CH_3	$-N(C_3H_7(n))(C_3H_7(n))$	a	b.p. 170～172°/0.35 m.p. 49.5～50.5°	$C_{17}H_{28}ON_2$	73.86	10.21	10.14	74.10	10.08	10.00	71.0
1110	C_2H_5O	$-N(C_4H_9(n))(C_4H_9(n))$	a	42°	$C_{20}H_{34}O_2N_2$	71.81	10.25	8.38	71.44	10.53	7.88	1.0
1111	CH_3	〃	a	42°	$C_{19}H_{32}ON_2$	74.95	10.59	9.20	75.11	10.61	9.35	1.0
1113	C_2H_5O	$-N(C_4H_9(iso))(C_4H_9(iso))$	a	82.5～83°	$C_{20}H_{34}O_2N_2$	71.81	10.25	8.38	71.48	10.44	8.44	6.1
1116	CH_3O	〃	a	74.5～50°	$C_{19}H_{32}O_2N_2$	71.21	10.07	8.74	71.22	10.07	8.54	1.2
1117	CH_3	〃	a	71.5～72.5°	$C_{19}H_{32}ON_2$	74.05	10.36	9.20	73.97	10.65	8.97	21.0
1118	CH_3O		a	65.5°	$C_{16}H_{24}O_2N_2$	69.53	8.75	10.14	69.21	8.84	10.41	2.8
1119	C_2H_5O		a	69.5°	$C_{17}H_{26}O_2N_2$	70.31	9.02	9.65	70.06	9.04	9.60	5.9
1122	CH_3		a	94.5～95.5°	$C_{15}H_{22}O_2N_2$	68.71	8.45	10.68	68.87	8.88	10.46	19.8
1122-1	〃	$-N(CH_2-CH=CH_2)(CH_2-CH=CH_2)$	B	b.p. 170～172°/0.5	$C_{17}H_{24}ON_2$	74.96	8.88	10.29	74.68	8.57	10.05	56.5
1123	〃		a	78.5°	$C_{16}H_{24}ON_2$	73.80	9.29	10.76	73.62	9.42	10.53	19.0
1125	Br	〃	a	88°	$C_{15}H_{21}ON_2Br$	55.39	6.51	8.61	55.51	6.64	8.53	4.7
1126	C_2H_5O		a	76.5°	$C_{16}H_{24}O_2N_2$	69.53	8.75	10.14	69.25	8.88	10.15	4.2
1127	Me	〃	a	108°	$C_{15}H_{22}ON_2$	73.13	9.00	11.37	73.54	8.40	11.22	11.7
1129	Br	〃	a	117°	$C_{14}H_{19}ON_2Br$	54.03	6.15	8.99	54.38	6.08	8.75	5.2
1130	C_2H_5O	$-N(CH_2CH=CH_2)(CH_2CH=CH_2)$	a	b.p. 190°/1 34～35°	$C_{18}H_{26}O_2N_2$	71.49	8.67	9.26	71.24	8.54	9.24	48.0
1131	CH_3O	〃	a	b.p. 180～182°/1 42.5～43°	$C_{17}H_{24}O_2N_2$	70.80	8.39	9.71	70.96	8.59	9.97	43.0
1134	CH_3	$-N(C_2H_5)(C_2H_5)$		88.5～89.5°	$C_{22}H_{30}ON_2$	78.06	8.69	8.27	77.89	9.24	8.49	66.0
1139	C_2H_5O			68°	$C_{23}H_{30}O_2N_2$	75.37	8.25	7.64	75.32	8.06	7.71	22.6
1140	CH_3	$-N(C_3H_7(n))(C_3H_7(n))$		58.5～59.5°	$C_{24}H_{34}ON_2$	78.64	9.40	7.64	78.51	9.40	7.61	23.0
1141	C_2H_5O	$-N(C_4H_9(iso))(C_4H_9(iso))$		107°	$C_{27}H_{40}O_2N_2$	76.37	9.50	6.60	76.31	9.38	6.51	42.5
1143	CH_3O	$-N(CH_2CH=CH_2)(CH_2CH=CH_2)$		58.5～59.5°	$C_{24}H_{30}O_2N_2$	76.16	7.99	7.40	76.23	8.09	7.36	61.0
1145	Br			138°	$C_{22}H_{27}ON_2Br$	63.31	6.52	6.94	63.84	6.66	6.28	16.0
1147	〃	$-N(CH_3)(CH_3)$		63.5°	$C_{19}H_{23}ON_2Br$	60.81	6.11	7.46	60.88	6.28	7.10	52.0
1148	H	〃		97～98°	$C_{19}H_{24}ON_2$	76.99	8.16	9.45	76.97	8.09	9.24	59.3

also obtained by condensation of substituted anilines with N,N-dialkyl crotonamides[2] (Ⅵ) in the presence of catalyst, such as acetic acid at 100° for 10 hours. The physical constants of the compounds obtained are listed in Table Ⅰ.

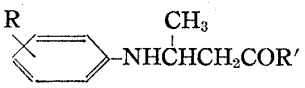
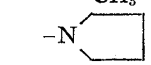
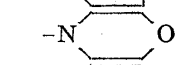
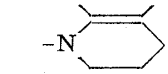
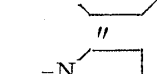
An attempt to prepare N,N-dialkyl 3-(N'-benzyl substituted anilino)butyramides (Ⅶ) from N,N-dialkyl 3-(substituted anilino)butyramides (Ⅴ) by using benzyl chloride in the presence of potassium carbonate and a small amount of potassium iodide, was made successfully. The physical constants of the compounds obtained are listed in Table Ⅱ. However, further attempts to prepare N,N-dimethyl 2-methyl-3-(substituted anilino)-propionamides by condensing N,N-dimethyl 2-methyl-3-dimethylaminopropionamides or N,N-dimethyl methacrylamides with substituted anilines were unsuccessful. The reaction of substituted anilines with methacrylamides appears to be difficult because of the inductive effect of the α-methyl group. N,N-Dimethyl 2-methyl-3-(*p*-phenetidino)propionamide, on the other hand, was successfully prepared by condensing phenetidine with N,N-dimethyl 2-methyl-3-bromopropionamide.

Pharmacological Test

Analgetic activity of the compounds described above, were determined by using of Writhing test, electrical stimulant method and radiant heat method.

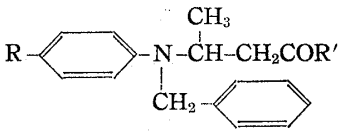
Analgetic activity of the compounds was compared with that of aminopyrine and phenacetin by using these tests, as shown in Table Ⅲ, and found to be less potent.

Table Ⅲ. 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			−	±	+
188	*p*-C_2H_5O	$-N(CH_3)_2$	±	±	++
189	〃	$-N(C_2H_5)_2$	±	+	+
193	*p*-CH_3	$-N(CH_3)_2$	+	±	−
196	*p*-Br	$-N(C_2H_5)_2$	±	±	±
197	H	$-N(CH_3)_2$	+	±	−
1119	*p*-C_2H_5O		+	±	±
1122	*p*-CH_3		++	±	±
1123	〃		−	±	−
1125	*p*-Br	〃	−	−	−
1126	*p*-C_2H_5O		±	−	±
1129	*p*-Br	〃	−	−	±
1131	*p*-CH_3O	$-N(CH_2CH{=}CH_2)_2$	−	−	±
198	〃	$-N(CH_3)_2$	±	±	±
1100	*p*-C_2H_5O	$-N(C_3H_7(n))_2$	−	±	−
1106	*p*-CH_3	〃	+	++	−

2) H. R. Snyder, R. E. Putnam : J. Am. Chem. Soc., **76**, 33 (1954).

1110	p-C_2H_5O	$-N\langle^{C_4H_9(n)}_{C_4H_9(n)}$	±	−	±
1111	p-CH_3	〃	±	+	−
1113	p-C_2H_5O	$-N\langle^{C_4H_9(iso)}_{C_4H_9(iso)}$	−	−	−
1116	p-CH_3O	〃	−	−	−
1117	p-CH_3	〃	−	−	−
1118	〃	$-N$ 	−	−	−
1148	H	$-N\langle^{CH_3}_{CH_3}$	−	−	−



Aminopyrine			++	++	++
Phenacetin			−	±	+
199	$-CH_3O$	$-N\langle^{C_2H_5}_{C_2H_5}$	−	±	±
1105	$-CH_3$	$-N\langle^{CH_3}_{CH_3}$	−	++	±
1132	〃	$-N\langle^{CH_2CH=CH_2}_{CH_2CH=CH_2}$	−	−	−
1135	$-C_2H_5O$	〃	±	−	±
1136	〃	$-N$ 	−	−	−
1137	$-CH_3O$	〃	±	−	−
1138	$-CH_3$	〃	±	−	±
1134	〃	$-N\langle^{C_2H_5}_{C_2H_5}$	−	−	±
1139	$-C_2H_5O$	$-N$ 	±	−	−
1140	$-CH_3$	$-N\langle^{C_3H_7(n)}_{C_3H_7(n)}$	−	±	±
1141	$-C_2H_5O$	$-N\langle^{C_3H_7(iso)}_{C_3H_7(iso)}$	−	−	−
1143	$-CH_3O$	$-N\langle^{CH_2CH=CH_2}_{CH_2CH=CH_2}$	+	−	±
1147	$-Br$	$-N\langle^{CH_3}_{CH_3}$	−	±	−

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.D. 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.

Experimental

Pharmacological Test——Analgetic and spasmolytic activity of the compounds was determined by the methods described in the previous paper.*1

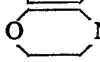
3-Chlorobutyric Acid (II)——Dried HCl gas was passed through an abs. ether solution of 1.13 moles of crotonic acid under cooling with ice-water for 5 hr., and the resulting mixture was allowed to stand for 16 hr. at room temperature. This was fractionated to give an oily substance, b.p_{16} 106°, in 90% yield.

3-Chlorobutyryl Chloride (III)——A mixture of 1.33 moles of II and 1.6 moles of $SOCl_2$ was refluxed for 5 hr. Distillation of the resulting mixture gave a light yellow oil, b.p_{55} 65~75°, in 93% yield.

N,N-Dialkyl 3-Chlorobutyramide (IV)——A solution of 1 mole of secondary amines and 1 mole of trimethylamine in benzene was added dropwise with stirring into a slution of 1 mole of III in benzene at a temperature maintained below 0°, and was then allowed to stand for 2 hr. at room temperature.

The resulting mixture was poured into H_2O, and benzene layer was washed successively with 5% NaOH, 5% HCl, and H_2O and dried over anhyd. Na_2SO_4. This was fractionated under reduced pressure to give an oily substance, N,N-dialkyl 3-chlorobutyramide in yields of 30.4~91%.

Table IV. $CH_3-\underset{Cl}{CH}-CH_2COR$

	b.p. °C/mm. Hg	Yield (%)
$(CH_3)_2N$	90～105/4	87.0
$(C_2H_5)_2N$	93～110/2	81.0
$(C_3H_7)_2N$	90～99/0.7	56.1
$(n\text{-}C_4H_9)_2N$	130～137/1.5	75.0
$(iso\text{-}C_4H_9)_2N$	112～121/2	82.3
$(CH_2=CH-CH_2)_2N$	98～108/3	91.0
	121～128/2	76.5
	110～115/2	30.4
	120～131/1.5	47.5

N,N-Diethyl Crotonamide (VI)——A mixture of 1.16 moles of crotonic acid and 1.59 moles of $SOCl_2$ was heated for 1 hr., and distillation of the resulting mixture gave crotonyl chloride, b.p. 120～125°, in 60% yield. A solution of 0.7 mole of crotonyl chloride in 250 ml. of benzene was added with stirring to a solution of 0.7 mole of diethylamine and 0.7 mole of trimethylamine in benzene a temperature maintained below 0°. The resulting mixture was allowed to stand for 5 hr. at room temperature, then was washed successively with 10% Na_2CO_3, 10% HCl, and NaCl solution, and dried over anhyd. Na_2SO_4.

This was fractionated under reduced pressure to give N,N-diethyl crotonamide, $b.p_3$ 81～84°, in 69.5% yield.

N,N-Dialkyl 3-(Substituted anilino)butyramides (V)——a) Two moles of K_2CO_3 and a small amount of KI were added to a mixture of 1.5 moles of substituted anilines and 1 mole of N,N-dialkyl 3-chlorobutyramides. The resulting mixture was heated for 20 hr. at 160° and poured into H_2O, and the oily substance was extracted with ether, and then reextracted with 10% HCl.

Addition of NaOH solution to the HCl solution separated an oily substance, which was extracted with ether, washed with H_2O, and dried over anhyd. Na_2SO_4, and evaporated at reduced pressure. The residue was purified by vacuum distillation or recrystallization to give N,N-dialkyl 3-(substituted anilino)butyramides (V).

b) A mixture of 1 mole of N,N-dialkyl crotonamides (VI) and 1 mole of substituted anilines was added to a solution of 1 mole of CH_3COOH. The mixture was heated for 10 hr. at 100°, and distilled off at reduced pressure. The residue was fractionated to give N,N-dialkyl 3-(substituted anilino)butyramides in yields of 55.6～56.5%.

The infrared spectra of these products were essentially identical with those of N,N-dialkyl 3-(substituted anilino)butyramide (V) prepared by method a) as described above.

N,N-Dialkyl 3-(N'-Benzyl-substituted anilino)butyramides (VII)——To a mixture of 1 mole of N,N-dialkyl 3-(substituted anilino)butyramides (V) and 1.05 moles of benzyl chloride dissolved in CH_3OH were added 2 moles of K_2CO_3 and a small amount of KI.

The resulting mixture was heated for 18 hr., and filtered. The filtrate was concentrated to a small volume and was acidified with 10% HCl solution and washed with ether. The aqueous layer was neutralized with 10% NaOH solution and extracted with ether. The ether solution was dried over anhyd. Na_2SO_4 and distilled off to give crystals. The products were recrystallized from C_2H_5OH to afford N,N-dialkyl 3-(N'-benzyl-substituted anilino)butyramides in yields of 10～70%.

N,N-Dimethyl 2-Methyl-3-(*p*-phenetidino)propionamides——A solution of 20 g. of methyl 2-methyl-3-bromopropionate and 30 g. of phenetidine in 20 ml. of benzene was heated for 10 hr. in a sealed tube. After cooling, it was washed with 10% NaOH and H_2O, and dried over anhyd. Na_2SO_4. Methyl 2-methyl-3-(*p*-phenetidino)propionate was obtained by distillation of resulting mixture at reduced pressure. $b.p_{0.6}$ 135～145°. Yield, 12.5 g. (47.5%). Picrate, orange yellow needles, m.p. 128～130° (from C_2H_5OH). *Anal.* Calcd. for $C_{19}H_{22}O_{10}N_4$: C, 48.93; H, 4.75; N, 12.01. Found: C, 49.24; H, 4.87; H, 11.99.

A mixture of 10 g. of ethyl 2-methyl-3-(*p*-phenetidino)propionate and 25 ml. of benzene containing 30% of dimethylamine was heated in a sealed tube for 30 hr. Filtration of the cooled solution gave 3.2 g. of reaction product.

Recrystallization from acetone-ether (1:1) gave colorless needles, m.p. 104～109°. *Anal.* Calcd. for $C_{18}H_{30}O_2N_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.23; H, 8.32; N, 11.57.

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Summary

N,N-Dialkyl 3-(substituted anilino)butyramides were prepared by condensing of N,N-dialkyl crotonamides or N,N-dialkyl 3-chlorobutyramides with substituted anilines.

N,N-Dialkyl 3-(N′-benzyl-substituted anilino)butyramides were prepared from N,N-dialkyl 3-(substituted anilino)butyramides and benzyl chloride.

Some of the compounds thus prepared have analgetic activities.

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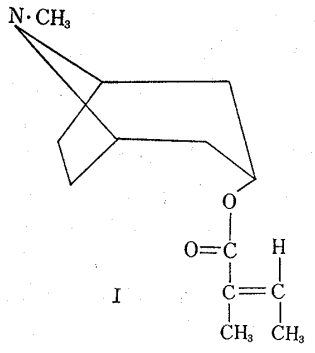
Hideo Yamaguchi and Kuniko Nishimoto: Studies on the Alkaloids of the Root of *Physalis alkekengi*. (1). Isolation of 3α-Tigloyloxytropane.

(*Osaka College of Pharmacy*[*1])

Physalis alkekengi L. *var franchettii* HORT *forma bunyardii* MAKINO which belongs to Solanaceae has been called Sanshō (or Hōzuki) in Japan and its root, named Sanshōkon, has been used as a drug which has the expectorant and antitussive actions or oxytocic action and, up to date, many studies were reported on the components of this plant. For example, physalin, a bitter principle, isolated from the fruits and the leaves,[1] and physalien (zeaxanthine dipalmitate),[2] physoxanthin and lutein[3] were also obtained from the fruits, the calyx, and the leaves. However, no systematic studies on the alkaloids have been shown except one which was reported by Haraoka, Takano and Horibe[4] in 1958. They isolated a liquid alkaloid whose picrate showed m.p. 175° in a small quantity besides physalin and suggested the existence of ethylenic double bond, carbonyl group and imino group in this alkaloid by infrared specrtra on both of free base and picrate. But no further studies were investigated by its small amount.



I

This time the authors carried out the systematic extraction and isolation of the alkaloids on the root of this plant and, as a result, besides two alkaloids, isolated an alkaloid as picrate which showed the same m.p. 176° as described by Haraoka, *et al.*[4] and its structure was confirmed to be 3α-tigloyloxytropane (I) by the following study.

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*1 Matsubara city, Osaka Pref. (山口秀夫, 西本邦子).

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