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Keiichi Takamura, Akitoshi Shioya, Katsumaro Minamoto, Tadahiro Yamamoto, Akihito Yoshimitsu, and Yoshihiro Nitta: Studies on Analgesics of Aniline Series. II.[*1] Preparation and Properties of N-Alkyl or N,N-Dialkyl 3-(N′-Acyl- or N′-Benzyl-substituted anilino)propionamide Series and N-Alkyl or N,N-Dialkyl 3-(Substituted anilino)propylamine Series.

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In the previous paper,[*1] the authors reported on the synthesis of N-alkyl or N,N-dialkyl 3-(substituted anilino)propionamide series, and analgetic and spasmolytic activity of some of these compounds.

Recently, Takahashi, *et al.*[1)] reported on the synthesis of N-alkyl- and N-acyl-glycine derivatives, which had higher solubility in water and lower toxicity than non-alkylated or non-acylated glycine derivatives.

In the present paper, attempts were made to prepare acylated, alkylated or benzylated derivatives of N-alkyl or N,N-dialkyl 3-(substituted anilino)propionamide series in order to test analgetic activity of these compounds and to examine the structure-activity relationships.

Acylates (Ⅱ) of ethyl 3-(substituted anilino)propionates (I) were prepared by treatment of the parent compounds with acid anhydride. Conversion of Ⅱ to N-alkyl or N,N-dialkyl 3-(N-acyl-substituted anilino)propionamides (Ⅲ) were carried out by using primary or secondary amines in benzene. On the other hand, Ⅲ were also obtained from N-alkyl or N,N-dialkyl 3-(substituted anilino)propionamides (Ⅳ) with acid anhydride in pyridine at room temperature. N′-Alkylates (V) of Ⅳ were prepared by condensation of Ⅳ with formaldehyde and formic acid, according to Clarke-Eschweiler method[2)] and were also obtained by treatment of Ⅳ with alkylhalide in the presence of potassium iodide. N′-Benzylates (Ⅵ) of Ⅳ were obtained by treatment of Ⅳ with benzyl chloride in the presence of dehydrochlorinating agent, such as sodium carbonate, in boiling alcohol. The physical constants of the compounds obtained are listed in Table I.

Attempts to prepare N,N-dialkyl 3-(substituted anilino)propylamines (Ⅶ) by the reduction of N,N-dialkyl 3-(substituted anilino)propionamides (Ⅳ) with lithium aluminum hydride in tetrahydrofuran were unsuccessful. However, the preparation of Ⅶ was achieved by the following procedure. Condensation of substituted anilines with allyl alcohol in the presence of metalic sodium gave 3-(substituted anilino)propylalcohols (Ⅷ), which were converted to the chlorides (Ⅸ) by the usual method. The desired N,N-dialkyl 3-(substituted anilino)propylamines (Ⅶ) were obtained by the condensation of Ⅸ with secondary amines in the presence of catalyst, such as potassium iodide or sodium iodide.

Acylates (X) of Ⅶ were prepared by treating Ⅶ with acid anhydride. Furthermore, X were also obtained by treatment of 3-(N′-acyl substituted anilino)propyl chlorides (Ⅺ), which were prepared from Ⅸ and acid anhydride, with secondary amines in the presence of a small amount of potassium iodide or sodium iodide.

[*1] Part I: This Bulletin, **13**, 198 (1965).

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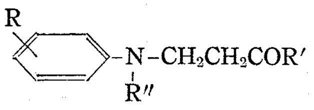
1) T. Takahasi, *et al.*: Japan. Pat., 1480 (1961).

2) *a*) W. Eschweiler: Ber., **38**, 880 (1905). *b*) H. T. Clarke, *et al.*: J. Am. Chem. Soc., **55**, 4571 (1933).

TABLE I.



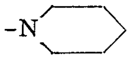
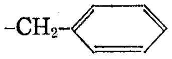
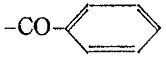
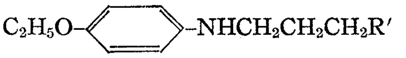
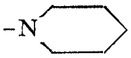
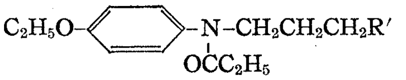
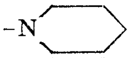
Compound	R	R″	R′	Method	m.p. (b.p./mm. Hg)	Formula	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield (%)
140	p-OC_2H_5	$-C_2H_5$	$-N{<}\substack{CH_2CH=CH_2\\CH_2CH=CH_2}$	2	free base 165~170°/0.15 Picrate 150~151°	$C_{19}H_{28}O_2N_2$ $C_{19}H_{28}O_2N_2\cdot(NO_2)_3C_6H_2OH$	72.11 55.04	8.92 5.73	8.85 12.84	72.31 55.38	8.73 5.73	9.07 12.73	86.5
137-1	〃	$-CH_2CH=CH_2$	$-N{<}\substack{CH_3\\CH_3}$	2	free base 165~170°/0.2 Picrate 112~114°	$C_{16}H_{24}O_2N_2\cdot(NO_2)_3C_6H_2OH$	52.27	5.38	13.86	52.38	5.43	13.19	36.0
137	〃	〃	$-N{<}\substack{CH_2CH=CH_2\\CH_2CH=CH_2}$	a	b.p. 160~170°/0.2 Picrate 142~143°	$C_{20}H_{28}O_2N_2$ $C_{20}H_{28}O_2N_2\cdot(NO_2)_3C_6H_2OH$	73.13 56.01	8.59 5.60	8.53 12.56	73.37 55.92	8.52 5.81	8.38 12.49	95.0
121	〃	$-CH_3$	$-N{<}\substack{CH_3\\CH_3}$	1	b.p. 170~180°/0.2	$C_{14}H_{22}O_2N_2$	67.17	8.86	11.19	66.92	8.83	10.77	36.0
139	〃	〃	$-N{<}\substack{CH_2CH=CH_2\\CH_2CH=CH_2}$	1	b.p. 175~180°/0.3 HCl m.p. 119~123°	$C_{18}H_{26}O_2N_2$ $C_{18}H_{26}O_2N_2\cdot HCl$	71.49 63.79	8.67 8.03	9.26 8.27	71.56 63.79	8.52 8.09	9.36 8.32	70.0
161	p-Br	$-COCH_3$	$-N{<}\substack{CH_3\\CH_3}$	a	95~96°	$C_{13}H_{17}O_2N_2Br$	49.85	5.47	8.95	49.91	5.61	8.89	63.5
162	〃	COC_2H_5	〃	a	69~71°	$C_{14}H_{19}O_2N_2Br$	41.30	4.71	6.88	41.50	4.85	6.85	81.2
110	p-OC_2H_5	$COCH_3$	$-NH_2$	a	114~116°	$C_{13}H_{18}O_3N_2$	62.38	7.25	11.19	62.11	7.13	11.03	78.0
112	〃	〃	$-N{<}\substack{CH_3\\CH_3}$	b	62~64°	$C_{15}H_{22}O_3N_2$	64.72	7.97	10.07	64.58	7.93	9.96	70.0
111	〃	〃	$-NHC_2H_5$	b	69.5~71.5°	〃	64.72	7.97	10.07	64.75	7.88	10.12	73.0
113	〃	〃	$-N{<}\substack{C_2H_5\\C_2H_5}$	a	49~51°	$C_{17}H_{26}O_3N_2$	66.69	8.55	9.14	66.76	8.39	8.99	71.0
114	〃	〃		a	74~76°	$C_{18}H_{26}O_3N_2$	67.90	8.23	8.80	68.19	8.16	9.22	67.0
150	〃	〃		a	68~70°	$C_{17}H_{24}O_4N_2$	63.73	7.55	8.74	63.76	7.13	8.68	86.0
122	〃	$-C_2H_5$	$-N{<}\substack{CH_3\\CH_3}$	2	155~167°/0.2	$C_{15}H_{24}O_2N_2$	59.89	8.38	9.31	59.94	8.33	9.28	50.0
163	p-Br		〃	a	70~71.5°	$C_{18}H_{21}ON_2Br$	59.84	5.86	7.75	59.67	5.53	7.47	52.0
164	〃		〃	a	129.5~130°	$C_{18}H_{19}O_2N_2Br$	57.61	5.10	7.47	57.84	5.01	7.18	60.0

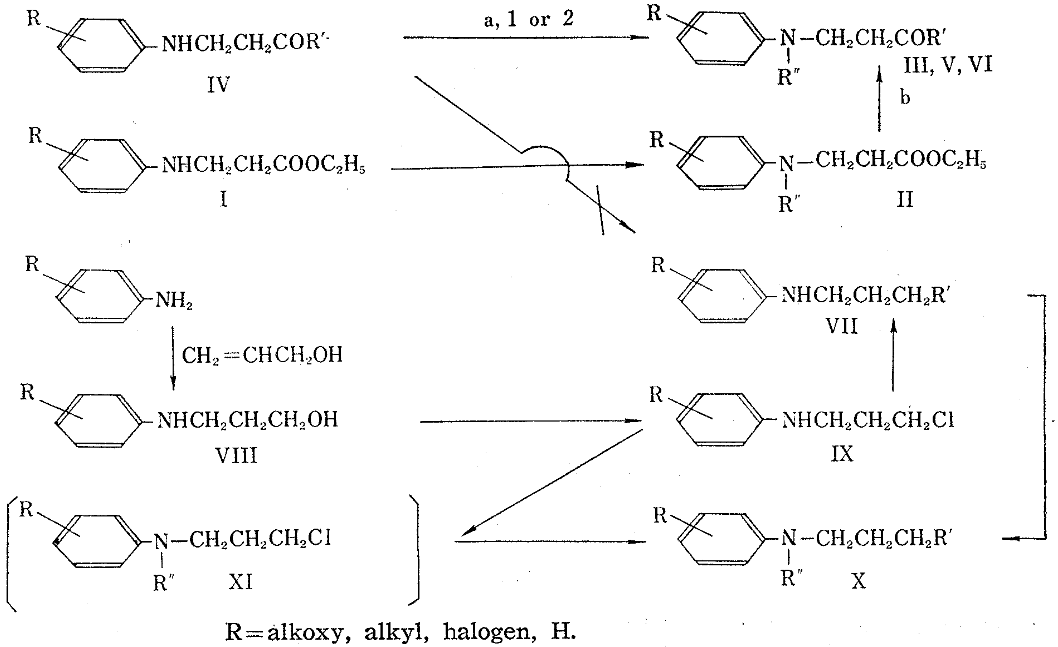
Table II.

Compound	R′	m.p. (b.p./mm. Hg)	Method	Formula	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield (%)
											
104-1	$-N<^{CH_3}_{CH_3}$	HCl. 112~113.5°		$C_{13}H_{22}ON_2\cdot 2HCl\cdot H_2O$	49.84	8.36	8.94	50.35	8.74	8.73	58.3
126	$-N<^{CH_2-CH=CH_2}_{CH_2-CH=CH_2}$	140~145°/0.3		$C_{17}H_{26}ON_2$	74.41	9.55	10.21	74.16	9.12	10.19	38.3
136	$-N<^{C_2H_5}_{C_2H_5}$	143~145°/0.4		$C_{15}H_{26}ON_2$	71.95	10.47	11.19	71.66	10.21	10.89	41.0
124		145~150°/0.2 172~173		$C_{16}H_{26}ON_2\cdot 2HCl\cdot H_2O$	54.39	7.99	7.93	54.65	8.03	7.91	81.5
125		165~180°/0.5 201~202.5°		$C_{15}H_{24}O_2N_2\cdot 2HCl\cdot H_2O$	50.70	7.94	7.88	51.06	7.92	8.13	53.5
											
127	$-N<^{CH_3}_{CH_3}$	158~159°/0.3 HCl. 132~134°	a b	$C_{16}H_{26}O_2N_2\cdot HCl$	61.03	8.64	9.90	61.27	8.71	8.64	a:45.3 b:85.8
133		161~163°/0.1~0.2	a	$C_{19}H_{30}O_2N_2$	71.66	9.50	8.80	71.38	9.43	8.57	48.2
134		163~165°/0.2	a	$C_{18}H_{28}O_3N_2$	67.47	8.81	8.74	67.41	8.77	8.46	46.0

The physical constants of the compounds obtained are listed in Table II and these syntheses are illustrated in Chart 1.

Pharmacological Test

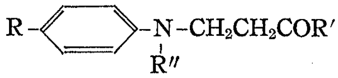
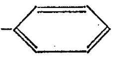
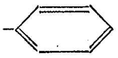
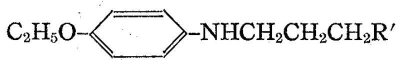
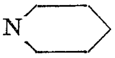
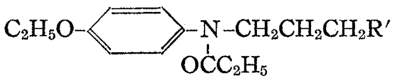
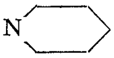
Analgetic activities of the compounds described above, were determined by the aid of Writhing test, Electrical stimulation method and Radiant heat method. Analgetic



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

Chart 1.

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

Compound No.	R	R″	R′	W. T.	E. S.	R. H.
						
Aminopyrine				++	++	++
Phenacetin				−	±	+
110	p-OC_2H_5	$-C_2H_5$	$-N{<}\begin{smallmatrix}CH_2CH=CH_2\\CH_2CH=CH_2\end{smallmatrix}$	−	+	±
112	〃	$-COCH_3$	$-N{<}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	±		
113	〃	〃	$-NHC_2H_5$	±		
114	〃	〃	-N 	−	±	
121	〃	$-CH_3$	$-N{<}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	+	±	
122	〃	$-C_2H_5$	〃	−		
137	〃	$-CH_2CH=CH_2$	$-N{<}\begin{smallmatrix}CH_2CH=CH_2\\CH_2CH=CH_2\end{smallmatrix}$	−	±	±
140	〃	$-C_2H_5$	〃	−	±	
161	p-Br	$-COCH_3$	$-N{<}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	++	−	++
162	〃	$-COC_2H_5$	〃	±	toxicity	toxicity
163	〃	$-CH_2-$ 	〃	−	+	−
164	〃	$-CO-$ 	〃	−	±	−
						
Aminopyrine				++	++	++
Phenacetin				−	±	+
124			-N 	±	−	
125			-N 	−	+	
126			$-N{<}\begin{smallmatrix}CH_2CH=CH_2\\CH_2CH=CH_2\end{smallmatrix}$	−	±	
136			$-N{<}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	±	±	
						
Aminopyrine				++	++	++
Phenacetin				−	±	+
127			$-N{<}\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$	+	++	
133			-N 	±	++	
134			-N 	−	++	

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.).
$++\geqq 60\%$, $+\geqq 40\%$, $\pm\geqq 20\%$, $-<20\%$.

b) E.S. and R.H.: The ratio of mean reaction time of drug to the control value. (200 mg./kg. P.O.).
$++\geqq 1.3$, $+\geqq 1.2$, $\pm>1.0$, $-<1.0$.

activities of the compounds were compared with that of aminopyrine and phenacetin and are shown in Table Ⅲ.

As it can be seen in Table Ⅲ, compounds of the N,N-dialkyl 3-(N′-acyl- or N′-alkyl-substituted anilino)propionamide series were found to be less potent than the corresponding compounds of the N,N-dialkyl 3-(substituted anilino)propionamide series in these test.

On the other hand, compounds of the N,N-dialkyl 3-(substituted anilino)propylamine series were found to be more toxic than the corresponding compounds of the N,N-dialkyl 3-(substituted anilino)propionamide series.

Moreover, compounds of the N,N-dialkyl 3-(N′-acyl- or N′-alkyl-substituted anilino)-propylamine series were found to have less activity than the corresponding compounds of the N,N-dialkyl 3-(substituted anilino)propylamine series in these tests.

Experimental

Pharmacological Test——Analgetic and spasmolytic activity of the compounds was determined by the previous paper.*[1]

Ethyl 3-(N′-Acetyl-*p*-phenetidino)propionate (II)——A mixture of 0.05 mole of ethyl 3-(*p*-phenetidino)-propionates and 4 moles of acetic anhydride was refluxed for 5 hr. The resulting mixture was concentrated by evaporation, and to the residue a small amount of 10% Na_2CO_3 was added. This was extracted with benzene, and the benzene layer was washed with H_2O, and dried over anhyd. Na_2SO_4.

Benzene was removed off and the residue was fractionated under reduced pressure to give ethyl 3-(N-acetyl-*p*-phenetidino)propionate, b.p$_1$ 153~154°. Yield 83%. *Anal.* Calcd. for $C_{15}H_{21}O_4N$: C, 64.49; H, 7.58; N, 5.01. Found : C, 64.18; H, 7.46; N, 5.01.

N,N-Dialkyl 3-(N′-Acetyl-substituted anilino)propionamides (III)——Method a) To solution of 0.2 mole of N-alkyl or N,N-dialkyl 3-(substituted anilino)propionamides (Ⅳ) in 1.3 moles of pyridine was added 1.6 moles of acid anhydride. The resulting mixture was allowed to stand for 22 hr. at room temperature, and was concentrated to a small volume at reduced pressure. The residue was added to ether with stirring at low temperature, and then crystals began to separate. After cooling, they were collected by filtration and then recrystallized from benzene or ethanol to afford (Ⅲ). Yield, 60~86%.

Method b) A solution of 1 mole of Ⅱ and 3 moles of 30% of secondary amines in benzene was allowed to stand for 7 days at room temperature. The reaction mixture was concentrated to dryness at reduced pressure, and recrystallization of the residue from ethanol gave Ⅲ. Yield, 70~73%.

3-(N′-Acetyl-*p*-phenetidino)propionic Acid——A mixture of 1 mole of Ⅱ and 3 moles of 40% aq. solution of dimethylamine was heated in a 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% HCl was added to the residue to afford a crystalline precipitate which was collected by filtration after cooling.

Recrystallization from ethanol gave colorless crystals. m.p. 110~112°. *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found : C, 62.37; H, 6.78; N, 5.60.

Identity with an authentic sample, 3-(N-acetyl-*p*-phenetidino)propionic acid, obtained by hydrolysis of Ⅲ with 10% NaOH was proved by comparision of IR spectra and by the fact that no depression of melting point was observed upon admixture of the two samples.

N′-Alkylates (V) of IV——1) A mixture of 0.23 mole of Ⅳ and 0.4 mole of formic acid was added to 0.32 mole of formaldehyde. The resulting mixture was heated for 8 hr. at 90~100°, concentrated to a small volume at reduced pressure, and then dissolved in 5% NaOH solution. This was extracted with ether. The ether solution was washed with H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the ether gave an oil which was fractionated to give the desired products in yields of 36~70%.

2) To a solution of 1 mole of Ⅳ and 1.2 moles of alkylhalogenide in iso-PrOH or *m*-xylene was added 3 moles of K_2CO_3 or Na_2CO_3. The mixture was refluxed for 5 hr., and then concentrated to a small volume at reduced pressure. The residue was extracted with ether. The ether solution was washed with H_2O, and dried over anhyd. Na_2SO_4.

Distillation under reduced pressure gave an oily substance in yields of 36~86.5%.

N′-Benzylates (VI) of IV——A solution of 0.022 mole of Ⅳ in 30 ml. of ethanol and 0.025 mole of benzyl chloride was refluxed in the presence of 0.03 mole of K_2CO_3 and 0.003 mole of KI, for 18 hr. The resulting mixture was cooled, filtered and evaporated to dryness. The residue was recrystallized from a mixed solvent of petr. ether-ethanol to give colorless crystals. Yield, 80%.

3-(*p*-Phenetidino)-1-propanol (VIII)——To a solution of 1 atom of metalic sodium in 3 moles of allyl alcohol was added 1 mole of substituted anilines. The resulting mixture was heated for 80 hr. at 110°, and an excess of allyl alcohol was extracted with ether after acidification with HCl. The residual solution was basified with NaOH solution, and was extracted with benzene. Benzene was distilled off to give an oily substance. It was fractionated under reduced pressure to afford 3-(*p*-phenetidino)-1-propanol, b.p$_{0.7}$ 165~170°. Yield, 50%.

Chlorides (IX) of VIII——A solution of $SOCl_2$ (36.7 g.) in dry benzene (30 ml.) was added dropwise, with stirring, at a temperature maintained below −5°, to a solution of VIII (4.7 g.) in a mixture of 80 ml. of dry benzene : dry $CHCl_3$ (1:1). The mixture was stirred for 2 hr. at room temperature and the solvent was removed off. The residue was recrystallized from ethanol to give a colorless needles of HCl salt of IX, m.p. 160~161°. Yield, 42.7 g. (65%).

N,N-Dialkyl 3-(Substituted anilino)propylamines (VII)——To a solution of 1 mole of IX and 3 moles of secondary amines in benzene was added a small amount of KI or NaI. The resulting mixture was refluxed for 10 hr., and then evaporation of benzene at reduced pressure gave (VII) in yields of 38.3~81.5%.

N,N-Dialkyl 3-(N′-Acyl-*p*-phenetidino)propylamines (X)——a) A mixture of 1 mole of VII and 3 moles of acid anhydride was refluxed for 7 hr., and the excess acid anhydride was removed at reduced pressure. To the residue was added a small volume of 5% NaOH to make alkaline, and then it was extracted with ether, washed with H_2O, and dried over anhyd. Na_2SO_4.

Distillation gave X in yields of 45.3~48.2%.

b) A mixture of 1 mole of 3-(*p*-phenetidino)propyl chloride (IX) and 2 moles of propionic anhydride was heated for 2 hr. at 100°. To the resulting mixture was added 10% HCl, and it was extracted with benzene. The benzene solution was washed with H_2O, dried over anhyd. Na_2SO_4, and the benzene was distilled off. Distillation of the residue gave 3-(N′-propionyl-*p*-phenetidino)propyl chlorides (XI). To a solution of 1 mole of 3-(N′-propionyl-*p*-phenetidino)propyl chlorides (XI) and 3 moles of 40% secondary amines in benzene was added small amount of KI or NaI.

The mixture was refluxed for 10 hr., and benzene was distilled off to give an oily substance.

The IR spectrum of this product was essentially identical with X.

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Summary

N-Alkyl or N,N-dialkyl 3-(N′-acyl-, N′-alkyl- or N′-benzylsubstituted anilino)propionamide derivatives were prepared from corresponding N-alkyl or N,N-dialkyl 3-(substituted anilino)propionamides by treating with acid anhydride, alkylhalide, or formaldehyde, formic acid and benzyl chloride, respectively.

N,N-Dialkyl 3-(substituted anilino)propylamines were also prepared by condensation of 3-(substituted anilino)propyl chlorides with secondary amines.

N,N-Dialkyl 3-(N′-acyl-substituted anilino)propylamines were obtained by treatment of 3-(substituted anilino)propylamines with acid anhydrides.

Some of these compounds were found to possess analgetic activities.

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