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114. Keijiro Takagi, Yutaka Kasuya, Kyo Fujie, Minoru Watanabe, and Setsuko Kayaoka: Syntheses of N-Acyl Derivatives of α-Methyl-3,4-methylenedioxyphenethylamine and their Analgesic Activity.

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There are many potent narcotic analgesics, but they have harmful side effects as well. Now, the strong analgesics without the side effects, particularly without addiction liability, are still looked for. Amphetamine has been known to have some analgesic action in addition to the known central stimulatory properties. Fellows,[1] synthesizing many aralkylamines, including amphetamine analogues, searched for the compounds with analgesic activity, but failed to get any drug for practical use. In the same paper, the definite analgesic activity of α-methyl-3,4-methylenedioxyphenethylamine was revealed, but it was abandoned because of the severe central stimulatory action.

This paper concerns the syntheses of acid derivatives of α-methyl-3,4-methylenedioxyphenethylamine to obtain the analgesics without stimulatory action.

I. Syntheses

Acid amides of α-methyl-3,4-methylenedioxyphenethylamine were obtained by acylation of the amine with corresponding acyl halides (Schotten-Baumann reaction).

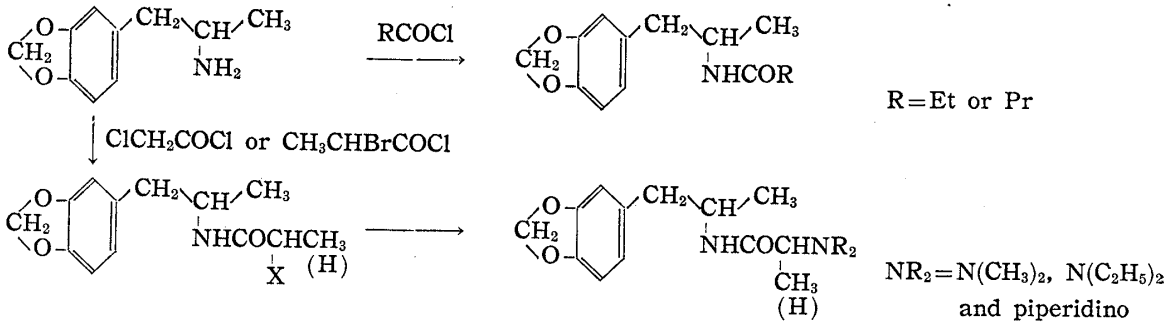
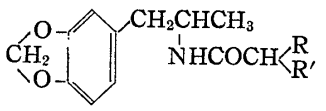


Table I.



No.	R	R′	m.p. (°C)	b.p. (°C/mm. Hg)	m.p. of picrate (°C)	m.p. of HCl salt (°C)	Yield (%)	Reaction time (hr.)
IV	N⟨ ⟩	H	63.9	183～189/0.1	146	—	44	6
V (SA-8)	H	CH_3	77	—	—	—	61	
X	Br	〃	120	—	—	—	90	
VI	$N(CH_3)_2$	〃	oil	167/0.05	184	170～195	50	10
VII	$N(C_2H_5)_2$	〃	〃	176/0.06	153～163	189	35	10
VIII	N⟨ ⟩	〃	〃	179/0.03	204	179	36	10
IX	H	C_2H_5	75	—	—	—	80	

Besides the compounds listed above, three known compounds were prepared and used for pharmacologic tests.

No.	R	R′	No.	R	R′	No.	R	R′
I	H	H	II	$N(CH_3)_2$	H	III	$N(C_2H_5)_2$	H

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1) E. J. Fellows, G. E. Ullyot: "Medicinal Chemistry," Vol. I. p. 390 (1951), Ed. By C. M. Suter, John Wiley & Sons Inc. N. Y.

Table II.

No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IV	$C_{17}H_{24}O_3N_2$	51.78	5.05	13.13	51.67	4.81	13.28
〃	$C_{17}H_{24}O_3N_2 \cdot C_6H_3O_7N_3$	67.11	7.95	9.20	66.38	7.80	9.04
V	$C_{13}H_{17}O_3N$	66.35	7.28	5.99	66.71	7.59	5.75
VI	$C_{15}H_{22}O_3N_2 \cdot C_6H_3O_7N_3$	49.69	4.97	13.80	49.99	5.23	13.96
VII	$C_{17}H_{26}O_3N_2 \cdot C_6H_3O_7N_3$	51.58	5.46	13.08	51.81	5.14	12.97
VIII	$C_{18}H_{26}O_3N_2 \cdot C_6H_3O_7N_3$	52.64	5.34	12.97	53.05	5.35	12.72
IX	$C_{14}H_{19}O_3N$	67.44	7.68	5.62	67.35	7.41	5.98

N-Aminoacyl derivatives of the amine were obtained by amination of the haloacyl amides in a sealed tube with tertiary amines. The haloacyl amides were prepared by the acylation of the amine with the haloacyl halides.

Physicochemical constants and analytical data are given in Tables I and II.

Experimental

N-Propionyl-α-methyl-3,4-methylenedioxyphenethylamine(V)——To an ethereal solution of α-methyl-3,4-methylenedioxyphenethylamine (1.5 g.) over the layer of aqueous solution of K_2CO_3 (1.2 g.), an ethereal solution of PrOCl (0.8 g.) was added dropwise with cooling and gentle shaking. The mixture was allowed to stand for 10 min. and shaken vigorously. The ethereal layer was washed with water, with 2% HCl, and again with water, and Et_2O was distilled off after drying. Crude crystalsobtained was recrystallized from Me_2CO-Et_2O and gave 1.2 g. of white fibrous crystals.

This example is applicable for the syntheses of IX and X. X crystallized out of the reaction mixture.

N-Piperidinoacetyl-α-methyl-3,4-methylenedioxyphenethylamine (IV)——A mixture of 3.8 g. of N-chloroacetyl-α-methyl-3,4-methylenedioxyphenethylamine dissolved in 30 cc. of dried benzene and 2.6 g. of piperidine was heated in a sealed tube in boiling water for 6 hr. Crystals in the mixture were filtered off, and the solvent was distilled off under reduced pressure. The residue was extracted with 5% HCl and water, and the extract was made alkaline with K_2CO_3. Liberated amine was extracted with Et_2O, and the Et_2O was distilled off after drying and the residue was distilled under reduced pressure (Table I). The distillate was converted to hydrochloride in dried Et_2O with dried HCl. The hydrochloride was again converted to base, and it was crystallized and recrystallized from petr. ether (b.p. 70°). The example is essentially applicable for the syntheses of VI, VII and VIII, except the reaction time (Table I).

II. Pharmacological Properties

Methods

Analgesic Activity

a) Pressure Method on Mice Tail——A modification of the method of Green as described by Takagi and Kameyama[2] was used for the experiments in mice. The tail of a male mouse weighing 17~25 g. was pressed by a glass edge of about 2 mm. thick until the animal turned to the edge or bit it. The pressure was recorded on smoked paper through a mercury manometer. The pressure by which animal responded was regarded as pain threshold, which was expressed in terms of mm. Hg. Each animal was pressed two times before administration of drugs and more than five times at intervals of 15 min. after the administration of the drug. ED_{50} values were estimated with up-and-down method. An animal was considered to be analgesic when the maximum value of the five thresholds after administration of drugs was over 130 mm. Hg.

b) Hot Plate Method——A modification of the method of Woolfe and Macdonald as described by Takagi and Kameyama[3] was also used for the experiments in mice. Normal reaction time was 3~5 sec. In this case the animals were stimulated four times after the administration of drugs. To estimate ED_{50} value with the up-and-down method, we considered the animal to be analgesic when mean value of the four reaction times of the animal was over 10 sec.

2) K. Takagi, T. Kameyama, K. Yano: Yakugaku Zasshi, **78**, 553 (1958).
3) K. Takagi, T. Kameyama: *Ibid.*, **77**, 872 (1957).

Prolongation of Anesthesia Induced by Hexobarbital——Sodium hexobarbital in physiological saline was given intraperitoneally to mice, and the time interval between loss and spontaneous return of the righting reflex was recorded in minutes and was regarded as the duration of anesthesia. Animals unable to right within 2 min. were regarded as being anesthetized. The dose of sodium hexobarbital required to induce anesthesia in 50% of the animals, ED_{50}, was computed by the method of Litchfield and Wilcoxon,[4] and was found to be 48 (39.4~58.6, $p=0.95$) mg./kg. In the same way, ED_{16} was 34 mg./kg. Compounds were administered orally in suspension and sodium hexobarbital, 34 or 48 mg./kg., was injected 2 hr. later intraperitoneally and the number of anesthetized animals and the durations of anesthesia were recorded.

Materials——Water-soluble compounds were dissolved in water (NaCl was added if necessary) and given subcutaneously. Since I and SA-8 were poorly soluble in water (2.4 and 1.0 mg./ml. respectively), they were disolved in 20% propyleneglycol and given subcutaneously, or suspended in the mixture of CMC (0.8 g.), NaCl (0.9 g.), Tween 80 (0.1 g.) and 100 ml. of water and given orally or intraperitoneally.

Results

Analgesic Activity——ED_{50} values with up-and-down method are summarized in Table III. Propyleneglycol at the dosage required for dissolving the amides did not influence the pain threshold, though it sedated somewhat the amimal.

Analgesic activities of SA-8 and aminopyrine were compared by pressure pain method according to four point assay, the maximum of five thresholds of each animal being used for indices. The potency ratio of SA-8 was 1.41 and fiducial limits were 0.72 and 2.77 ($p=0.95$) (Fig. 3). The time courses of the activity of SA-8 given sub-

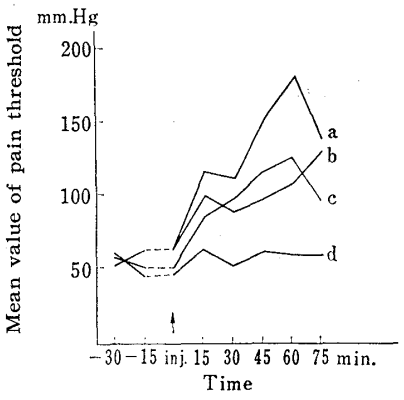

Fig. 1. Influence of Subcutaneous SA-8 and Aminopyrine on the Pain Threshold in Mice

a : SA-8 100 mg./kg.
b : SA-8 50 mg./kg.
c : Aminopyrine 70 mg./kg.
d : Requisite volume of solvent
(Ten mice were used for each dosage)

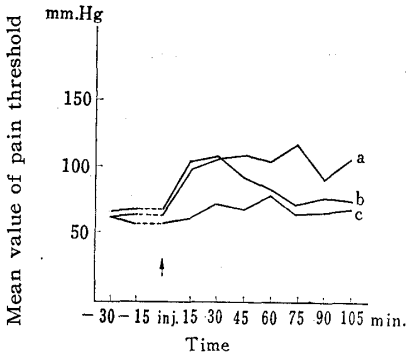

Fig. 2. Influence of Oral SA-8 and Aminopyrine on the Pain Threshold in Mice

a : SA-8 70 mg./kg.
b : Aminopyrine 140 mg./kg.
c : Requisite volume of solvent
(Ten mice were used for each dosage)

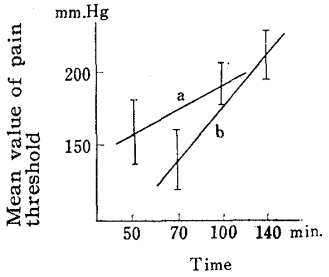

Fig. 3. Four-point Assay of Analgesic Activities of SA-8 and Aminopyrine in Mice Tail Pressure Method

a : SA-8 b : Aminopyrine
(Ten mice were used for each dosage)
Vertical lines represent standard errors.

4) J. T. Litchfield, Jr. F. Wilcoxon : J. Pharmacol. Exptl. Therap., **96**, 99 (1949).

cutaneously and orally are shown in Figs. 1 and 2. The results show that SA-8 administered by the two routes has approximately equal activities.

Prolongation of Anesthesia Induced by Hexobarbital——The results are given in Table IV. None of the animals died during the observation period. SA-8 and I, even in toxic doses, did not induce the loss of the reflex.

Table III. Analgesic Activities of the Compounds Synthesized

Compounds	Pressure method		Hot plate method	
	No. of animals used	ED_{50} (mg./kg.)	No. of animals used	ED_{50} (mg./kg.)
I	7	210	15	185
II[a)]	11	167	14	269
III[a)]	10	—	7	—
IV	5	—	6	—
V	10	72	7	133
VI[a)]	12	—	14	166
VII[a)]	10	—	11	—
VIII[a)]	4	—	10	—
Morphine hydrochloride	11	3.7	14	5.8
Aminopyrine	10	145		

The sign — means that the compound was more toxic than analgesic.
All the compounds were administered subcutaneously.
a) HCl salts

Table IV. The Effect of Compounds on the Duration of Anesthesia induced in Mice by Sodium Hexobarbital

Compound	Dose	Average Duration of Anesthesia ± S.E. (min.) Sodim hexobarbital			
	(mg./kg.)	34 mg./kg.	§	48 mg./kg.	§
I	100	—	—	167± 41.1	5[a)]
SA-8	20	30.5± 9.5	6	90.6±19.6	10
	28	39.1±19.5	5	159.6±38.1	10
	40	80.4±30.5	8	204.0±61.4	9
Chlorpromazine hydrochloride	2.8	39.0±22.8	3	20.4± 6.7	6
	4.0	13.2± 7.8	3	53.0±15.4	7
	5.6	21.8± 7.4	7	63.1±19.7	8
Saline[b)]		—		8.5± 3.2	5

Ten mice were used for each test.
§ : Number of anesthetized animals.
a) Five mice were used.
b) Computed graphically as described in the methods.

Summary

Several acids- and aminoacids-derivatives of α-methyl-3,4-methylenedioxyphenethylamine were synthesized and their analgesic activities in mice were estimated by two methods. The most potent compound was propionamide of the amine (SA-8) and this was 1.4 times more potent than aminopyrine. SA-8 was sedative in mice, and it markedly augmented the hypnotic action of hexobarbital.

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