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60. Yutaka Kasuya, Minoru Watanabe, Yoshio Kanai, and Hiroaki Hamano: Syntheses of 1-Dimethoxyphenyl-3-alkylaminobutanols. I.*1

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The 1-derivatives of 1-(2,5-dimethoxyphenyl)-3-alkylaminobutanols (Ⅲ) were synthesized in order to investigate their pharmacological action. 2′,5′-Dimethoxycrotonophenone (Ⅰ) which was prepared from hydroquinone dimethylether and crotonyl chloride by the Friedel-Crafts reaction, was reacted with various aliphatic amines to form 2-alkylamino-2′,5′-dimethoxypropiophenone (Ⅱ). Compounds (Ⅲ) were obtained by the reaction of Ⅱ with various Grignard's reagents.

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One of the authors (Y. K.) reported previously about the relationship between chemical structure and spasmolytic activity of diphenylbutanolamines.[1,2] In order to obtain further information about the influence of introduction of additional asymmetrical carbon to the molecule of these amines on spasmolytic activity, the authors synthesized

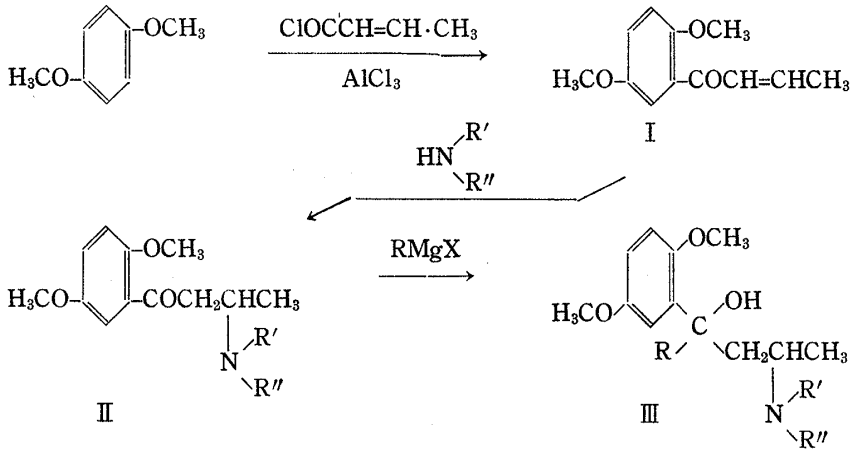

Chart 1.

a series of 1-substituted-1-(2,5-dimethoxyphenyl)-3-alkylaminobutanols.

The synthetic route is shown in Chart 1. 2′,5′-Dimethoxycrotonophenone (Ⅰ) was prepared from hydroquinone dimethylether and crotonyl chloride by the Friedel-Crafts reaction. Shapiro[3] and Pohland[4] carried out the reaction of crotonophenone with dimethylamine to obtain dimethylaminobutyrophenone. By the application of this method, 2-alkylamino-2′,5′-dimethoxypropiophenone were prepared, *i.e.*, the solution of 2′,5′-dimethoxycrotonophenone in toluene was added to the solution of piperidine, morpholine, pyrrolidine, diethylamine, or isopropylamine in toluene respectively under cooling. In the case of dimethylamino-derivative, gaseous dimethylamine which was

*1 This work was reported at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, 1965.
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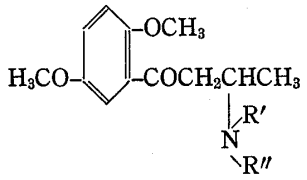
1) K. Takagi, Y. Kasuya, K. Hattori: Yakugaku Zasshi, **71**, 1328 (1951); *Ibid.*, **72**, 1592 (1952).
2) K. Takagi, Y. Kasuya, Y. Ohta: *Ibid.*, **73**, 541 (1953).
3) D. Shapiro: J. Org. Chem., **14**, 839 (1949).
4) A. Pohland, H. R. Sullivan: J. Am. Chem. Soc., **75**, 4458 (1953).

generated from its aqueous solution, was introduced to the toluene solution of 2′,5′-dimethoxycrotonophenone. These free bases are oily and considerably unstable, and can not be distilled *in vacuo*. Therefore, these were characterized as the picrates or styphnates. The yield of the aminoketones were 70~90%. The ultraviolet spectra of these compounds showed absorption maximum at 335~338 mμ. The yields, melting points, ultraviolet spectra, and the analytical data of these compounds are summarized in Table I.

TABLE I.



No.	N(R′)(R″)	Yield (%)	UV mμ (log ε)	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	NH(iso-Pr)	84	338(3.54)	132~133	$C_{21}H_{26}O_{10}N_4$	49.40	5.13	10.97	49.49	5.18	10.88
IIb	$N(CH_3)_2$	73	338(3.54)	132~133	$C_{20}H_{24}O_{10}N_4$	50.00	5.04	11.66	50.28	5.10	11.76
IIc	$N(C_2H_5)_2$	73	336(3.63)	96~ 97	$C_{22}H_{28}O_{10}N_4$	51.96	5.55	11.02	52.15	5.80	10.87
IId		80	336(3.52)	153~154	$C_{22}H_{26}O_{10}N_4$	52.17	5.18	11.06	52.30	5.35	11.38
IIe		90	335(3.54)	149~150	$C_{23}H_{28}O_{10}N_4$	53.07	5.42	10.77	53.19	5.56	10.91
IIf		95	334(3.53)	128~129	$C_{22}H_{26}O_{11}N_4$	50.57	5.02	10.72	50.36	4.94	10.66

IIa: styphnate IIb~IIf: picrate

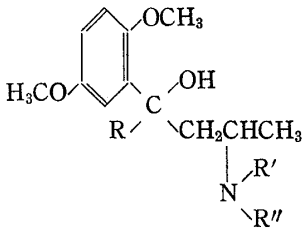
The reaction of the above aminoketones with the Grignard's reagents which were prepared from ethyl bromide, *n*-butylbromide (or chloride), bromobenzene, benzyl chloride, and cyclohexyl chloride, gave the intended compounds. In this reaction benzylmagnesiumchloride reacted easily with all of aminoketones, and gave good yields, but in the case of ethylmagnesiumbromide yields were poor. Comparing the yields of reaction in which one kind of Grignard's reagents reacted with aminoketones having various kind of amino group, the ketone having piperidino- or morpholino-group afforded the good yields, despite of poor yields by diethylamino- or pyrrolidino-ketones. The ultraviolet spectra of the 1-substituted-1-dimethoxyphenyl-3-alkylaminobutanols show the absorption maximum at 290 mμ regardless of the kind of substituents.

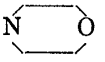
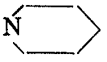
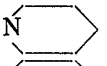
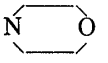
In this Grignard reaction, the alkanolamines can be extracted with diluted acids, but an oily non-basic substance is remained. For example, when diethylaminoketone (IIc) was reacted with phenylmagnesiumbromide, the yield of 1-(2,5-dimethoxyphenyl)-1-phenyl-3-diethyl-aminobutanol was 25%, but that of the by-product was 35%. Infrared spectrum of this oil showed the existence of a carbonyl group. Its 2,4-dinitrophenylhydrazone was confirmed to be 2,4-dinitrophenylhydrazone of 2′,5′-dimethoxycrotonophenone, *i.e.*, the melting point of this compound was not depressed by admixture with a sample which was prepared from 2,5-dimethoxycrotonophenone directly. Thus in this Grignard reaction it was observed that the elimination of the amino group also took place in additon to the normal reaction.

The yields, melting points, ultraviolet spectra, and the analytical data of these compounds are summarized in Table II.

Though the spamolytic activities of these compounds were not so remarkable as expected, some of them, especially compound No. IIi showed marked cocaine-like

TABLE II.



No.	R		Yield (%)	UV λ_{max}^{EtOH} (log ε)	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	C_2H_5	$N(C_2H_5)_2$	29	290 (3.36)	171~172 [h]	$C_{18}H_{32}O_3NCl$	62.48	9.34	4.05	62.32	9.24	4.32
IIIb	〃		40	288 (3.36)	115~116 [p]	$C_{25}H_{34}O_{10}N_4$	54.54	6.23	10.18	54.52	6.18	10.37
IIIc	C_4H_9	$N(C_2H_5)_2$	48	289 (3.38)	71~72 [f]	$C_{20}H_{35}O_3N$	71.17	10.45	4.15	71.38	10.12	4.18
IIId	〃		38	292 (3.64)	215~219 [h]	$C_{21}H_{36}O_3NCl$	65.41	9.41	3.63	65.18	9.15	3.92
IIIe	C_6H_5	NH(iso-Pr)	50	292 (3.59)	214~215 [h]	$C_{21}H_{30}O_3NCl$	66.39	7.96	3.69	66.40	8.05	3.56
IIIf	〃	$N(CH_3)_2$	31	293 (3.58)	103~104 [f]	$C_{20}H_{27}O_3N$	72.92	8.26	4.25	73.04	8.20	4.24
IIIg	〃	$N(C_2H_5)_2$	28	292 (3.49)	135~136 [f]	$C_{22}H_{31}O_3N$	73.91	8.74	3.92	73.89	8.47	4.17
IIIh	〃		23	292 (3.58)	213~214 [h]	$C_{22}H_{30}O_3NCl$	67.23	7.76	3.59	67.18	7.66	3.33
IIIi	〃		60	293 (3.59)	221~222 [h]	$C_{23}H_{33}O_3NCl$	68.04	7.94	3.45	67.92	7.74	3.44
IIIj	〃		56	293 (3.57)	215~216 [h]	$C_{22}H_{30}O_4NCl$	64.74	7.41	3.43	64.47	7.65	3.35
IIIk	$C_6H_5CH_2$	NH(iso-Pr)	80	291 (3.57)	110~111 [f]	$C_{22}H_{31}O_3N$	74.13	8.59	3.92	73.91	8.74	3.66
IIIl	〃	$N(CH_3)_2$	90	291 (3.59)	90~91 [f]	$C_{21}H_{29}O_3N$	73.43	8.51	4.08	73.58	8.32	4.24
IIIm	〃	$N(C_2H_5)_2$	90	291 (3.58)	112~113 [f]	$C_{23}H_{33}O_3N$	74.36	8.95	3.77	74.39	8.81	3.82
IIIn	〃		95	291 (3.58)	101~102 [f]	$C_{23}H_{34}O_3N$	74.76	8.46	3.79	74.57	8.31	3.56
IIIo	〃		91	292 (3.58)	108~109 [f]	$C_{24}H_{34}O_3N$	75.16	8.67	3.65	75.06	8.49	3.55
IIIp	C_6H_{11}	$N(CH_3)_2$	58	290 (3.36)	210~211 [h]	$C_{20}H_{34}O_3NCl$	64.58	9.21	3.76	64.69	9.28	3.89
IIIq	〃	$N(C_2H_5)_2$	49	290 (3.54)	249~250 [h]	$C_{22}H_{38}O_3NCl$	66.06	9.58	3.50	66.26	9.55	3.60
IIIr	〃		64	290 (3.47)	131~132 [f]	$C_{23}H_{37}O_3N$	73.56	9.93	3.73	73.64	9.76	3.94
IIIs	〃		33	290 (3.77)	249~250 [h]	$C_{22}H_{36}O_4NCl$	63.82	8.77	3.38	63.75	8.51	3.55

h: hydrochloride f: free base p: picrate

catecholamine-potentiating effect, the mechanisms of which seem to be unique and different from those of cocaine.[5,6]

Experimental*4

2′,5′-Dimethoxycrotonophenone (I)——To a solution of 207 g. (1.5 mole) of hydroquinone dimethylether and 156 g. (1.5 mole) of crotonyl chloride in CS_2 anhyd. $AlCl_3$ was added portionwise at 10°.

*4 All melting points are uncorrected.

5) Y. Kasuya, M. Watanabe: Arzneim.-Forsch., **15**, 1279 (1965).

6) M. Watanabe: *Ibid.*, **15**, 1284 (1965).

After the addition was complete, the reaction mixture was stirred at 0° for 3 hr., then it was poured into ice-water. The organic layer was extracted with benzene, washed with 2*N* NaOH, and water, then dried over sodium sulfate. After the solvent was removed, the residue was distilled *in vacuo*. 2′,5′-Dimethoxycrotonophenone, b.p. 158~160°(1 mm.), was obtained as a pale yellow viscous oil. Yield 184 g. (58%). UV λ_{max}^{EtOH} mμ (log ε): 346 (4.15). IR cm^{-1}: $\nu_{C=O}$ 1673 (liquid film). 2,4-Dinitrophenylhydrazone, red needles, m.p. 185~186°. *Anal.* Calcd. for $C_{18}H_{18}O_6N_4$: C, 55.95; H, 4.70; N, 14.50. Found: C, 55.84; H, 4.67; N, 14.57.

2-Piperidino-2′,5′-dimethoxypropiophenone (IIe)——To a solution of 6.4 g. (0.075 moles) of piperidine in 10 ml. of toluene, a solution of 10.3 g. (0.05 moles) of 2′,5′-dimethoxycrotonophenone in 10 ml. of toluene was added dropwise below 10°, then allowed to stand at room temperature overnight. After the reaction mixture was washed with water, a base was extracted with 2*N* HCl containing crushed ice, then the extract was made to alkaline with aq. ammonia. A deposited oil was extracted with ether, washed with water, and dried over anhyd. potassium carbonate. The ether was distilled off to obtain 13.1 g. (90%) of a brown oil. This base was refined as the picrate, m.p. 149~150°. UV spectrum of the free base, λ_{max}^{EtOH} mμ (log ε): 335 (3.54). IR cm^{-1}: $\nu_{C=O}$ 1687 (liqiud film).

Compounds (IIa, IIc, IId, and IIf) were prepared by the similar method.

2-Dimethylamino-2′,5′-dimethoxypropiophenone (IIb)——Gaseous dimethylamine generated from 40% aq. dimethylamine, was introduced below 10° to 10.3 g. of I in 20 ml. of toluene. The reaction mixture was stirred for 3 hr., and then allowed to stand overnight.

The product was separated as above to obtain a base (9.4 g.).

1-(2,5-Dimethoxyphenyl)-1-benzyl-3-piperidino-*n*-butanol (IIIo)——To Grignard's reagent prepared from 1.2 g. of Mg turnings, and 6.3 g. freshly distilled benzyl chloride in 15 ml. of absolute ether, 6.0 g. of IIe in 12 ml. of absolute ether was added dropwise at −10°.

The reaction mixture was stirred at room temperature for 2 hr.. kept for 1 hr. under reflux, and then was decomposed with ice. The insoluble matter was filtered off, and the organic layer was collected.

The base was extracted with 10% acetic acid, neutralized with aq. ammonia, extracted with ether, washed with water, then dried over anhyd. sodium sulfate. The ether was distilled off to obtain 1-(2,5-dimethoxyphenyl)-1-benzyl-3-piperidino-*n*-butanol, m.p. 99~100°. Recrystallization from petr. ether afforded colorless needles, m.p. 108~109°. UV λ_{max}^{EtOH} mμ (log ε): 290 (3.58). IR cm^{-1}: ν_{OH} 3400~3300 (KBr). Yield 7.4 g. (91%).

Compounds (IIIa~IIIn, and IIIp~IIIs) were prepared by the similar method.

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