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147. Zen-ichi Horii, Takeshi Inoi, San-Wong Kim, Yasumitsu Tamura,*¹ Aritomo Suzuki, and Hiroshi Matsumoto*² :
Syntheses and Pharmacological Properties of
2- and 3-Aralkyltetrahydro-1,3-oxazines.

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In previous papers, a number of aralkylamines were synthesized¹⁾ and it was demonstrated²⁾ that the structure in which the aromatic nucleus and the nitrogen atom are separated by two or three carbon atoms is related to bronchodilator activity of the aralkylamines and, further, the tertiary amine is most effective. The present investigation was undertaken, partly, to ascertain these structural requirements for bronchodilator activity and, partly, to examine validity of tetrahydro-1,3-oxazine derivatives³⁾ as sympathomimetic drugs. This report describes the syntheses and pharmacological properties of 2-(I~VI), 3-aralkyltetrahydro-1,3-oxazines (XIX~XXX) and their preparative intermediates, 3-aralkylamino-1-propanols (VII~XVIII). The structures of the tetrahydro-1,3-oxazines prepared are also discussed.

Synthesis

The reactions employed for I~XXX are summarized by the equations shown in Chart 1 and their physical properties and chemical analyses are recorded in Tables I, II, and III.

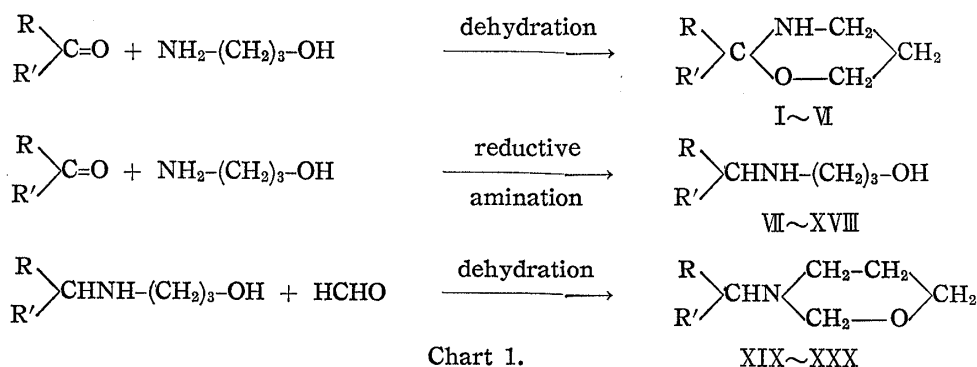


Chart 1.

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1) Z. Horii, J. Tsuji, T. Ioni : *Yakugaku Zasshi*, **77**, 248, 256 (1957); Z. Horii, T. Inoi : *Ibid.*, **77**, 1095 (1957); N. Yoshida, M. Omoto, T. Inoi : *Ibid.*, **78**, 183 (1958); T. Inoi : *Ibid.*, **78**, 187, 1174 (1958).

2) H. Fujimura, K. Ohata : *Nippon Yakurigaku Zasshi*, **55**, 466, 653 (1959).

3) Z. Eckstein, T. Urbański : "Advances in Heterocyclic Chemistry," Ed. by A. R. Kaeritzky, Vol. II, 311 (1963), Acad. Press, New York.

TABLE I. 2-Aralkyltetrahydro-1,3-oxazines



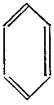


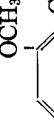

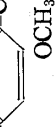
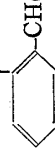
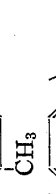
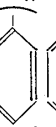
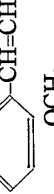
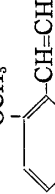
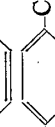
Compd. No.	R	b.p./mm. Hg	Yield (%)	Hydrochloride; m.p. (°C) ^{a)}	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
I		113~116/3	47	154.5~155.5	C ₁₂ H ₁₃ ONCl	63.21	7.62	6.14	62.91	7.88	5.96
II		146~148/2	52	158~159	C ₁₃ H ₂₀ O ₂ NCl	60.57	7.82	5.43	60.48	7.68	5.52
III		147~149/3	65	153~154	C ₁₃ H ₂₀ O ₂ NCl	60.57	7.82	5.43	60.35	7.92	5.22
IV		162~163/3	52	152~153	C ₁₄ H ₂₃ O ₂ NCl	61.49	8.16	5.15	61.90	8.19	5.49
V		110~120/0.2	16 ^{b)}	174~177 (decomp.)	C ₁₁ H ₁₄ O ₂ NCl	58.02	6.20	6.15	57.77	6.23	6.25
VI		117~120/3	53	picrate ^{c)} ; 132~134 (decomp.)	C ₁₈ H ₂₀ O ₈ N ₄	51.42	4.80	13.33	51.30	4.88	13.06

a) Recrystd. from ethanol-ether.

b) Decomposed partly on distillation; yield was calcd. on the hydrochloride.

c) Recrystd. from ethanol.

TABLE II. 3-Aralkylamino-1-propanols

Compd. No.	R	R'	b.p./mm. Hg	Method of prepn. ^{a)}	Yield (%)	Orotate m.p. (°C) ^{b)}	Formula	Analysis N (%)	
								Calcd.	Found
VII		H	138/3 ^{c)}	A, B	75, 78	165~166	C ₁₅ H ₁₉ O ₆ N ₃	13.08	12.80
VIII		H	132~133/3	A	36	185~187	C ₁₆ H ₂₁ O ₆ N ₃	12.53	12.26
K		H	158~162/6	A, B, C	36, 70, 63	185~186	C ₁₇ H ₂₃ O ₅ N ₃	12.03	11.87
X		H	142~145/2	A, B	47, 55	179~180	C ₁₈ H ₂₃ O ₆ N ₃	11.08	10.91
XI		H	173~175/3	A, B	52, 58	177.5~178	C ₁₈ H ₂₅ O ₆ N ₃	11.08	10.77
XII		H	182~184/6	A, B	67, 65	168~170	C ₁₉ H ₂₇ O ₆ N ₃	10.68	10.61
XIII		H	143~145/0.1	A	27	193.5~195.5	C ₂₂ H ₂₅ O ₆ N ₃	10.21	10.07
XIV		H	146~148/2	A	71	122.5~124.5	C ₁₇ H ₂₁ O ₅ N ₃	12.10	11.98
XV		H	170~171/0.5	A	66	oxalate ^{d)} ; 154~155	C ₁₅ H ₂₁ O ₆ N	4.50	4.46
XVI		H	176~179/1	A	57	hydrochloride ^{e)} ; 136~137	C ₁₃ H ₂₀ O ₂ NCl	5.44	5.41
XVII		H	117~120/3	A, C	68, 62	151~152	C ₁₇ H ₂₃ O ₆ N ₃	12.03	11.90
XVIII		CH ₃	132~134/3	A, B	64, 72	oxalate ^{d)} ; 156~156.5	C ₁₃ H ₂₀ O ₃ N	5.88	5.68

a) See Experimental.

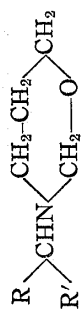
b) Hygroscopic, recrystd. from ethanol.

c) Reported b.p. 7 110~115° [G. Y. Leshner, A. R. Surrey: J. Am. Chem. Soc., 77, 638 (1955)].

d) Recrystd. from ethanol.

e) Hygroscopic, recrystd. from ethanol.

TABLE III. 3-Aralkyltetrahydro-1,3-oxazines



Compd. No.	R	R'	b.p./mm. Hg	Yield (%)	Hydrochloride m.p. (°C) ^{a)}	Formula	Analysis (%)					
							Calcd.			Found		
							C	H	N	C	H	N
XIX		H	108/3	82	156~157 ^{b)}	C ₁₁ H ₁₆ ONCl	—	—	6.56	—	—	6.55
XX		H	125~126/3	98	164~165	C ₁₂ H ₁₈ ONCl	63.15	7.97	6.18	62.95	7.86	5.90
XXI		H	147~148/8	62	159~160	C ₁₃ H ₂₀ ONCl	64.58	8.34	5.79	64.09	8.30	5.62
XXII		H	154~156/5	79	—	C ₁₄ H ₂₁ O ₂ N ^{c)}	71.45	9.00	—	71.51	8.97	—
XXIII		H	157~158/3	98	—	C ₁₄ H ₂₁ O ₂ N ^{c)}	71.45	9.00	—	71.35	8.88	—
XXIV		H	144~145/3	71	—	C ₁₅ H ₂₃ O ₂ N ^{c)}	72.25	9.30	—	72.13	9.25	—
XXV		H	145~146/0.4	95	142.5	C ₁₈ H ₂₂ ONCl	71.12	7.29	4.61	70.08	7.24	4.83
XXVI		H	145~146/3	84	162.5~163	C ₁₃ H ₁₈ ONCl	65.08	7.56	5.84	65.21	7.52	5.65
XXVII		H	162~165/1	83	—	C ₁₄ H ₁₉ O ₂ N ^{c)}	72.07	8.21	—	71.80	8.51	—
XXVIII		H	170~172/1	81	174~175	C ₁₄ H ₂₀ O ₂ NCl	62.45	7.49	5.41	62.35	7.58	5.09
XXIX		H	127~129/3	47	164~165	C ₁₃ H ₂₀ ONCl	64.58	8.34	5.79	64.43	8.34	5.62
XXX		CH ₃	155~157/4	87	149.5~150	C ₁₃ H ₂₀ ONCl	64.58	8.34	5.79	64.54	8.27	5.86

a) Recrystd. from ethanol.

b) Hygroscopic.

c) Characterized as the free base.

The 2-substituted tetrahydro-1,3-oxazines (I~VI) (Table I) were prepared by azeotropic distillation of the desired carbonyl compounds and 3-amino-1-propanol with benzene according to the method of Bergmann and Kaluszyner.⁴⁾ The products purified by distillation *in vacuo* were generally unstable and, therefore, had to be converted immediately to the stable hydrochlorides. Phenylacetone did not give a stable condensation product. Phenylacetaldehyde and diphenylacetaldehyde failed to give condensation products.

The 3-aralkylamino-1-propanols (VII~XVIII) (Table II) were synthesized by reductive amination of the desired carbonyl compounds with 3-amino-1-propanol by means of sodium borohydride reduction or hydrogenation over platinum oxide. Compounds (IX and XVII) were also prepared by reductive cleavage of I and VI by hydrogenation over platinum oxide. The γ -aminoalcohols thus obtained tended to form carbonates, which made the purification procedure somewhat difficult. The orotates were prepared for characterizations and pharmacological tests.

The 3-aralkyltetrahydro-1,3-oxazines (XIX~XXX) (Table III) were obtained by condensation of VII~XVIII with formaldehyde by a similar method to that for the 2-substituted tetrahydro-1,3-oxazines (I~VI). The products were relatively stable than the above 2-substituted tetrahydro-1,3-oxazines, however, these compounds as well as the 2-substituted tetrahydro-1,3-oxazines were hydrolyzed in the presence of acid to give the starting materials.

Structures of Tetrahydro-1,3-oxazines*³

It has been established^{4,5)} that the condensation of carbonyl compounds with 3-amino-1-propanol gives, in some cases, tetrahydro-1,3-oxazines, in some, Schiff bases and, in some, mixtures of these two possible products which, in liquid phase, are in a state of mobile equilibrium, oxazine (cyclic form) \rightleftharpoons Schiff base (open form). For confirmation of their structures, molecular refractivities and infrared spectra have been utilized.*⁴ The bases of both methods are stated as follows. A pure open form or Schiff base shows the typical C=N band at about 1650 cm^{-1} in its infrared spectrum, while a pure cyclic form or tetrahydro-1,3-oxazine lacks this band. In the case of a mixture of the two forms, the molecular refraction value gives more information regarding their quantities present in a given reaction product. The experimental molecular refraction value of the cyclic form is about 2.00 units lower than that of the open form; the difference in the theoretical value of both forms is 1.50, the cyclic form having the lower refraction, and the cyclic form experimentally causes a depression by about 0.5.^{4,6)}

Measurement of the molecular refractions and infrared spectra of the 3-substituted tetrahydro-1,3-oxazines (XIX~XXX), for which only a cyclic oxazine structure is possible, proved that the above physicochemical means were tenable as shown in Table V. As to the structure of the 2-substituted tetrahydro-1,3-oxazines (I~VI), the free bases showed the C=N absorption at near 1650 cm^{-1} , indicating the presence of Schiff bases. The molecular refraction (Table V) led to the same conclusion, that is, these compounds contain a considerable amount of the open form. However, their hydrochlorides

*³ For this experiment, particular attention was paid to the purity of the products (I~VI) and (XIX~XXX): they were distilled under reduced pressure, crystallized as salts, recovered as bases and redistilled under reduced pressure.

*⁴ Ultraviolet spectrum, in some cases, has been used for the support of the conclusions thus obtained. See ref. 3.

4) E. D. Bergmann, A. Kaluszyner: *Rec. trav. chim.*, **78**, 289 (1959).

5) E. M. Hancock, E. M. Hardy, D. Heyl, M. E. Wright, A. C. Cope: *J. Am. Chem. Soc.*, **66**, 1747 (1944); W. A. Watanabe, L. E. Conlon: *Ibid.*, **79**, 2825 (1957).

6) E. D. Bergmann: *Chem. Revs.*, **53**, 309 (1953).

TABLE IV. Molecular Refractions of Some 2- and 3-Aralkyltetrahydro-1,3-oxazines^{a)}

Compd. No.	d_4^{10}	n_D^{10}	MR		
			Calcd. as open form	Calcd. as cyclic form	Found
I	1.0356	1.5350	58.54	57.06	57.50
II	1.0970	1.5454	64.80	63.32	63.82
III	1.0850	1.5408	64.80	63.32	64.10
IV	1.0766	1.5364	69.42	67.94	68.21
VI	1.0620	1.5440	58.54	57.06	56.86
XX	1.0469	1.5321		57.40	56.62
XXI	1.0266	1.5260		62.02	61.39
XXII	1.0685	1.5312		68.28	68.16
XXIII	1.0655	1.5299		68.28	68.21
XXIV	1.0667	1.5301		72.90	72.22
XXIX	1.0274	1.5281		62.02	61.54

a) The refractivity increments used in calculating [MR] were C, 2.418; H, 1.100; $-CH_2-$, 4.618; $-C=C-$, 1.733; *sec.* N 2.499; *tert.* N 2.840; $-O-$ (acetal) 1.643; $-O-$ (hydroxy) 1.525 [F. Eisenlohr: Z. phys. Chem., 75, 585 (1911)], *Ibid.*, 79, 129 (1912)]; $-C=N-$ 4.100 [K. v. Auwers: *Ibid.*, 147, 436 (1930)].

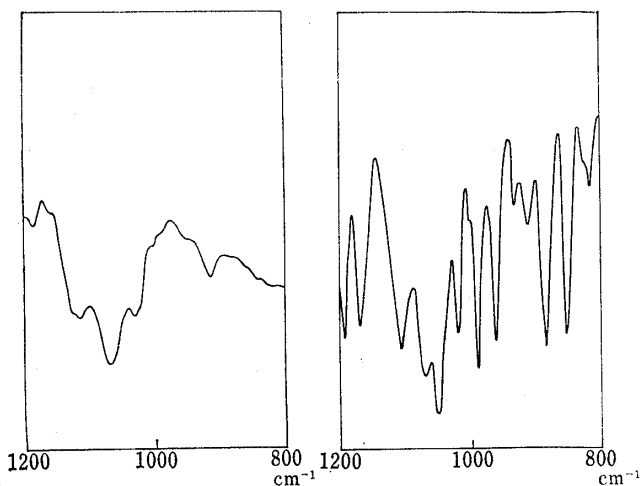


Fig. 1. Infrared Absorption Spectrum of N- β -Methylphenethyl-3-amino-1-propanol (X) (Liquid)

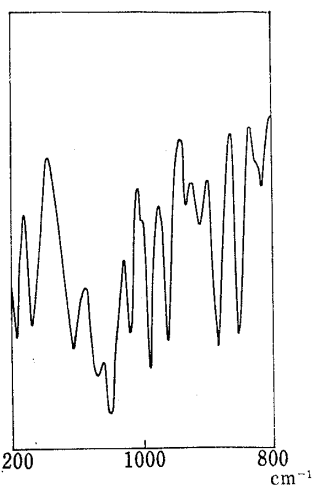


Fig. 2. Infrared Absorption Spectrum of 3- β -Methylphenethyltetrahydro-1,3-oxazine (XX) (Liquid)

lacked an absorption due to a $C=N^+$ group at near 1700 cm^{-1} region, indicating that the hydrochlorides have a cyclic oxazine structure. These results would indicate that the 2-substituted tetrahydro-1,3-oxazines are in a tautomeric mixture of the cyclic and open forms and that the formation of salts displaces the equilibrium in favor of more stable oxazine salt.

Concerning the infrared spectra of tetrahydro-1,3-oxazine derivatives,^{3,4,7)} a number of bands in the $1150\sim 1050$, $955\sim 925$, and $855\sim 800\text{ cm}^{-1}$ regions⁷⁾ have been assigned to the $C-O-C$ acetal bonds. Hence an attention was given to these bands in the $1200\sim 800\text{ cm}^{-1}$ region for all compounds pre-

TABLE V. The Characteristic Bands in the $900\sim 800\text{ cm}^{-1}$ Region for Tetrahydro-1,3-oxazine^{a)}

Compd. No.	The Characteristic bands (cm^{-1})		
XIX	880	850	808
XX	880	858	838
XXI	880	850	815
XXII	879	846	803
XXV	880	842	805
XXVI	880	868	840
XXVII	885	870	845
XXIX	880	850	840
XXX	880	850	840

a) Compounds measured in liquid film.

7) Z. Eckstein, P. Gluziński, W. Hofman, T. Urbański: J. Chem. Soc., 1961, 489.

pared in the present paper. Unfortunately, the N-aralkylaminopropanols (VII~XVIII) showed several peaks in the 1150~1050 and 955~925 cm^{-1} , which made it difficult to assign the characteristic bands for the tetrahydro-1,3-oxazines in these regions. Some of these bands are assumed to originate in the methoxyl group⁸⁾ or aromatic ring.⁹⁾ However, the tetrahydro-1,3-oxazines showed, as indicated in Table V, three characteristic bands at 900~800 cm^{-1} , which were absent in the corresponding γ -aminoalcohols and 3-cinnamylideneamino-1-propanol. Although XI, XII, and XVI showed one or two bands at 900~800 cm^{-1} , presumably ascribed to the C-H bending vibration in aromatic ring⁹⁾ (XI : 835 cm^{-1} , XII : 880 and 810 cm^{-1} , XVI : 840 cm^{-1}), the corresponding tetrahydro-1,3-oxazines (XXIII, XXIV, and XXVIII) showed three or four absorption bands (XXIII : 880, 860, 830, and 810 cm^{-1} , XXIV : 878, 848, and 810 cm^{-1} , XXVIII : 882, 865, and 845 cm^{-1}). These bands were also observed in the free bases of 2-substituted tetrahydro-1,3-oxazines (I~VI) and in the hydrochlorides of 2- and 3-substituted tetrahydro-1,3-oxazines. The results support the conclusion of Eckstein, *et al.* that the bands in the 900~800 cm^{-1} region*⁵ are characteristic for tetrahydro-1,3-oxazine ring.

TABLE VI. Bronchodilator Activities of Some 2-Aralkyltetrahydro-1,3-oxazines, 3-Aralkylamino-1-propanols and 3-Aralkyltetrahydro-1,3-oxazines

Compd. No.	Effect on isolated tracheal smooth muscle of guinea pig ^{a)}		Effect on excised small intestine of guinea pig ^{b)}	
	anti-Ach. action	anti-Histamine action	anti-Ach. action	anti-Histamine action
I	—	—	1	10
II	—	1/2	1	10
III	1/5	1/5	2	10
IV	—	—	10	2
VII	2	1/2	4	2
VIII	1	2	40	40
IX	—	—	2	4
X	—	1	2	10
XI	2	2	20	40
XII	—	—	10	10
XIII	—	—	4	20
XIV	—	1/2	1	1
XVI	1	1	10	50
XVII	1	2	4	10
XVIII	1	4	10	20
XX	2	10	10	20
XXI	—	1/2	10	20
XXV	1	4	40	100
XXVI	10	20	20	100
XXVIII	20	40	50	100
XXIX	—	—	4	4
XXX	1	2	10	40
A ^{c)}	1	1	1	1
E ^{d)}	2	2	2	2

a) Relative potency to aminophylline (=1), measured by the minimal inhibitory concentration of aminophylline.

b) Relative potency to aminophylline (=1), measured by the minimal inhibitory concentration of aminophylline.

c) Aminophylline.

d) Ephedrine.

*⁵ Habermehl has recently stated that bands in the 900~800 cm^{-1} region are characteristic for oxazolidine ring. [G. Habermehl : Chem. Ber., **96**, 2029 (1963).]

8) L. H. Briggs, L. D. Colebrook, H. M. Fales, W. C. Wildman : Anal. Chem., **29**, 904 (1957).

9) L. J. Bellamy : "The Infra-red Spectra of Complex Molecules," 54 (1954), Methuen & Co., Ltd., London.

Pharmacological Results

The compounds subjected to biological screening and their bronchodilator activities are summarized in Table V. N-Cinnamyl derivatives (XXVI and XXVIII) were shown to possess much more potent bronchodilator activities than aminophylline. On the blood pressure of rabbits, these compounds had generally the decreasing effect, but in the case of I, II, and XXI, the decrease was followed by increase.

Experimental*6

Materials—Reagent grade of carbonyl compounds and 3-amino-1-propanol were distilled before use. Hydratropaldehyde (b.p.₂ 105~108°),¹⁰⁾ 2-methoxyhydratropaldehyde (b.p.₂ 105~108°),¹¹⁾ 4-methoxyhydratropaldehyde (b.p.₃ 106~108°),¹¹⁾ 2-methoxy-5-methylhydratropaldehyde (b.p._{1,5} 93~95°),¹¹⁾ phenylglyoxal (b.p.₃₅ 116~118°),¹²⁾ 2-methoxycinnamaldehyde (b.p.₁₀ 152~158°),¹³⁾ 4-methoxycinnamaldehyde (b.p.₆ 155~160°),¹³⁾ dihydrocinnamaldehyde (b.p.₃ 83~85°)¹⁴⁾ and diphenylacetaldehyde (b.p.₃ 139~141°)¹⁵⁾ were prepared according to the literatures, respectively.

General Procedure for 2-Aralkyltetrahydro-1,3-oxazines (I~VI) (Table I)—A mixture of 0.1 mole of the carbonyl compound, 0.12 mole of 3-amino-1-propanol, 0.05 mole of anhydrous potassium carbonate and 200 ml. of dry benzene was heated under reflux in a flask fitted with a Dean Stark apparatus until no more water separated (2~3 hr.). Potassium carbonate was filtered off. The filtrate was washed with water and dried over anhydrous magnesium sulfate. Benzene was removed and the residual oil was purified by fractional distillation under reduced pressure.

3-Aralkylamino-1-propanols (VII~XVIII) (Table II). i) **Reductive Amination with Sodium Borohydride (Method A)**—To a mixture of 0.1 mole of the carbonyl compound and 0.12 mole of 3-amino-1-propanol in 100 ml. of methanol was added a solution of 0.08 mole of sodium borohydride in 50 ml. of methanol with stirring at 20°, and stirring was continued for 1 hr. Almost part of methanol was removed from the reaction mixture and dilute hydrochloric acid was added to the residue with ice-cooling. After the organic substance separated was removed by shaking with ether, the water layer was strongly basified with a sodium hydroxide solution. The separated oily base was extracted with ether, the extract was washed with water and dried over magnesium sulfate. After removal of the solvent, the residue was distilled under reduced pressure.

ii) **Reductive Amination of VII, IX~XII and XVIII by Hydrogenation (Method B)**—A solution of 0.05 mole of the carbonyl compound and 0.06 mole of 3-amino-1-propanol in 60 ml. of ethanol was hydrogenated over platinum oxide at room temperature and atmospheric pressure. The uptake of hydrogen ceased after about 3 hr. The solution was filtered, concentrated *in vacuo* and the residual oil was distilled.

iii) **Hydrogenolysis of I and VI (Method C)**—A solution of 0.02 mole of I or VI in 40 ml. of ethanol was hydrogenated over 0.2 g. of platinum oxide at room temperature and atmospheric pressure. The catalyst was removed by filtration and the filtrate was treated as usual.

General Procedure for 3-Aralkyltetrahydro-1,3-oxazines (XIX~XXX) (Table III)—These compounds were prepared from 0.1 mole of 3-aralkylamino-1-propanols and 0.12 mole of 37% formaldehyde without potassium carbonate in a similar manner to that employed for 2-substituted tetrahydro-1,3-oxazines, and purified through distillation.

3-Cinnamylideneamino-1-propanol (XXXI)—A mixture of 6.6 g. (0.05 mole) of cinnamaldehyde, 4.0 g. (0.053 mole) of 3-amino-1-propanol and 100 ml. of benzene was heated under reflux in a flask fitted with a Dean Stark apparatus for 3 hr. The solution was concentrated and the residue distilled to give a yellow oil, b.p.₂ 165~168°, 5.8 g. (61%). n_D^{20} : 1.6082, d_4^{20} : 1.0489, MR: 58.54 (theor. 58.07). IR $\nu_{\text{max}}^{\text{liquid}}$ cm⁻¹: 1670, 1638, but no absorption in the 800~900 cm⁻¹ region. The picrate melted at 123~124°. Anal. Calcd. for C₁₈H₁₈O₈N₄: C, 51.76; H, 4.34; N, 13.39. Found: C, 51.72; H, 4.46; N, 13.30.

Pharmacological Methods—i) Effect on strips of isolated guinea pig's trachea: The isolated guinea pig's trachea was cut spirally and suspended in an aerated Locke solution kept at 27°. Change in tonus of the preparation was recorded on a smoked paper kymograph. Because the compounds tested were

*6 All melting points are corrected.

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13) M. Scholz, A. Wiedmann: Ber., 36, 853 (1905).

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15) E. Fischer, H. Hoffa: *Ibid.*, 31, 1989 (1898).

inactive in themselves, the minimal concentrations of these compounds to relax the contractions of the preparation evoked by acetylcholine (5×10^{-6}) and histamine (5×10^{-6}) were searched, by which their relative potencies to aminophylline were measured. The minimal concentrations of aminophylline to inhibit the above concentrations of acetylcholine and of histamine were found to be similar and about $5 \times 10^{-3} \sim 5 \times 10^{-4}$.

ii) Effect on blood pressure of rabbits : Rabbits (2.5~3.0 kg.) were anesthetized with urethane 1.0 g./kg. (intraperitoneal injection) and the compounds injected into ear vein. The blood pressure was recorded kymographically.

iii) Effect on isolated guinea pig's intestine : Contraction of the guinea pig's small intestine was recorded kymographically by the Magnus method. The minimal concentrations to inhibit the contractions by acetylcholine and histamine were searched for each of the test compounds (inactive in themselves) and their relative potencies to aminophylline (=1) were measured. The minimal concentrations to inhibit the above contractions by acetylcholine and by histamine were found to be similar and about $2 \times 10^{-4} \sim 5 \times 10^{-4}$. The compounds tested were applied with the pretreatment method.

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Summary

A number of 2-aralkyltetrahydro-1,3-oxazines, 3-aralkylamino-1-propanols and 3-aralkyltetrahydro-1,3-oxazines were prepared and their pharmacological activities tested. Some compounds belonging to the last two groups showed higher bronchodilator activities than aminophylline and even than ephedrine. The structures of tetrahydro-1,3-oxazines prepared were also discussed.

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