Chart 1, with retention of the configuration at C-24. The resulted alcohol forms 24*S* ketal derivatives such as 25-*O*-methylcimigenol (IV) and cimigenol (V) during the acid hydrolysis of I. On the other hand, when I was treated with alkali, deacetylation and subsequent hemiketal formation between 16-keto group and 23-alcohol occur first and then the hemiketal hydroxyl at C-16 attacks C-24 of the epoxide with inversion of its configuration. This reaction mechanism explains the formation of 24*R*-ketal derivative such as cimigol xyloside (III) from I on alkaline treatment.

Based on the above described evidence and discussion, we propose the structure (XII) (23*R*, 24*S*) for acetyl shengmanol. It seems noteworthy that acetyl shengmanol xyloside (I) is unstable even in the separation procedures from the plant material, and that I is readily convertible to cimigol xyloside (III) on alkaline treatment, and to cimigenol (V) during its acid hydrolysis. We consider that acetyl shengmanol (XII) is a precursor of cimigenol (V) and cimigol (VII) in *Cimicifuga japonica.*

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Studies on the Structure Activity Relationship of Adrenergic β-Mimetic Benzylamine Derivatives. II.[1] 1-Alkylamino-2-phenyl-1,2,3,4-tetrahydronaphthalenes

The synthesis and adrenergic activity of stereoisomeric 1-methylamino- and 1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalenes (IIa,b and IIIa,b), rigid structures related to the benzylamine derivatives (I), are presented. These compounds were found to possess direct β-stimulating activity both in the isolated tracheal and right atrial preparations of the guinea pigs. The structure-activity relationship in this series is described.

In the previous paper,[1] appropriately substituted benzylamine derivatives (I), fragmented derivatives of trimetoquinol (TMQ), were reported to be directly acting β-mimetics. In this series of compounds (I), the spatial arrangement of the nitrogen atom, the catechol and the trimethoxyphenyl group, which are necessary to manifest the β-mimetic actions, is flexible, while in TMQ the spatial relationship between the nitrogen atom and the catechol group is fixed.

In continuation of our study on the steric requirements for the manifestation of the β-mimetic actions, *cis*- and *trans*-isomers of 1-methylamino- and 1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (IIa, b and IIIa, b), conformationally more rigid compounds than the benzylamine derivatives (I), were synthesized and tested for their β-mimetic actions.

1) Y. Iwasawa, M. Ohashi, S. Yamamura, S. Saito, and A. Kiyomoto, *Japan, J. Pharmacol.*, **26**, 133 (1976).

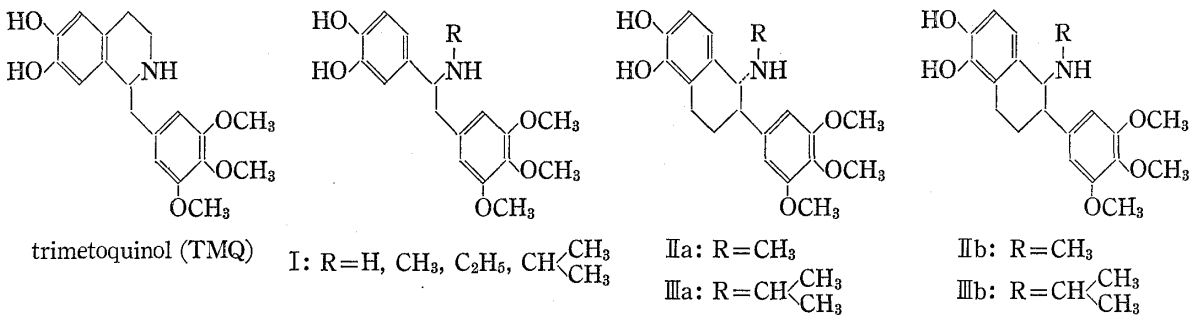

Fig. 1

Pharmacological studies were carried out in the isolated tracheal chains and the isolated right atrial preparations of the guinea pigs.

The isolated tracheal chain was prepared by the method described in the previous paper.[2] Cumulative dose-response curves of the test compounds obtained by increasing the concentrations by a factor of 3 were studied after contraction with histamine 2HCl (1×10^{-5} g/ml). Isoproterenol (ISO: 1×10^{-5} g/ml) was added to obtain the maximum relaxation response at the end of each experiment. Potencies of the compounds tested were expressed as pD_2.[3]

The spontaneous atrial rate was recorded on a polygraph (Nihon Koden) *via* a cardiotachography. Cumulative dose-response curves were obtained by increasing the concentrations by a factor of 10, and the chronotropic responses were expressed in terms of relative frequency to the initial rate just prior to the start of the cumulative drug addition.

1-Alkylamino-2-trimethoxyphenyl-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene derivatives (IIa, b and IIIa, b) were prepared as illustrated in Chart 1. Treatment of V[4] with sodium hydride in DMF, followed by heating with IV at 120° for 32 hr gave VI, which was hydrolyzed with KOH in ethylene glycol at 150° for 27 hr to the carboxylic acid (VII) (mp 72—74°, 67.3% yield). VII was cyclized to the tetralone derivative (VIII) (mp 158—160°, 77.7% yield) by treatment with trifluoroacetic anhydride[5] in benzene at 60° for 2 hr. Leuckart reaction of VIII in formamide at 160° for 6 hr afforded a mixture of the two stereoisomers (IX) (mp 170—173°, 83.4% yield) which was then reduced with diborane in THF, followed by column chromatography, to provide Xa (*trans* isomer, mp 132—134°, 53% yield) and Xb (*cis* isomer, mp 118—119°, 34% yield). Stereochemical assignments for these isomers were made from the coupling constants of their C_1-protons (Xa, $J_{1,2}=8$ Hz; Xb, $J_{1,2}=4$ Hz). The *cis* isomer (Xb) was alternatively obtained according to a method reported by R. Sarges[6] in the stereoselective synthesis of *cis*-1-methylamino-2-phenyl-1,2,3,4-tetrahydronaphthalenes. Thus, reaction of VIII with monomethylamine in the presence of titanium tetrachloride ($TiCl_4$) and subsequent reduction of the resulting imine (XI) with $NaBH_4$ in methanol gave exclusively Xb (77% yield). This fact also supported the stereochemistry of Xb.

On the other hand, the synthesis of N-isopropyl analogues was carried out from the primary amines (XII) which was obtained in 81% yield by hydrolysis of IX with KOH in ethylene glycol at 120° for 44 hr. The solution of XII in acetone was stirred in the presence of molecular sieves at room temperature for several days to afford the imine (XIII). Reduction of XIII with $NaBH_4$ in methanol, followed by column chromatography of the resulting mixture of the two stereoisomeric amines, furnished XIVa·HCl (*trans* isomers, mp 142—144°, 48% yield) and XIVb·HCl (*cis* isomer, mp 202—204°, 39% yield). The latter compound XIVb

2) Y. Iwasawa, M. Ohashi, S. Yamamura, S. Saito, and A. Kiyomoto, *Japan J. Pharmacol.*, **25**, 525 (1975).
3) J.M. Van Rossum, *Archs. int. Pharmacodyn. Ther.*, **143**, 299 (1963).
4) Satisfactory analytical, infrared and nuclear magnetic resonance data have been obtained for all compounds in this paper.
5) R.J. Ferrier and J.M. Tedder, *J. Chem. Soc.*, **1957**, 1435.
6) R. Sarges, *J. Org. Chem.*, **40**, 1216 (1975).

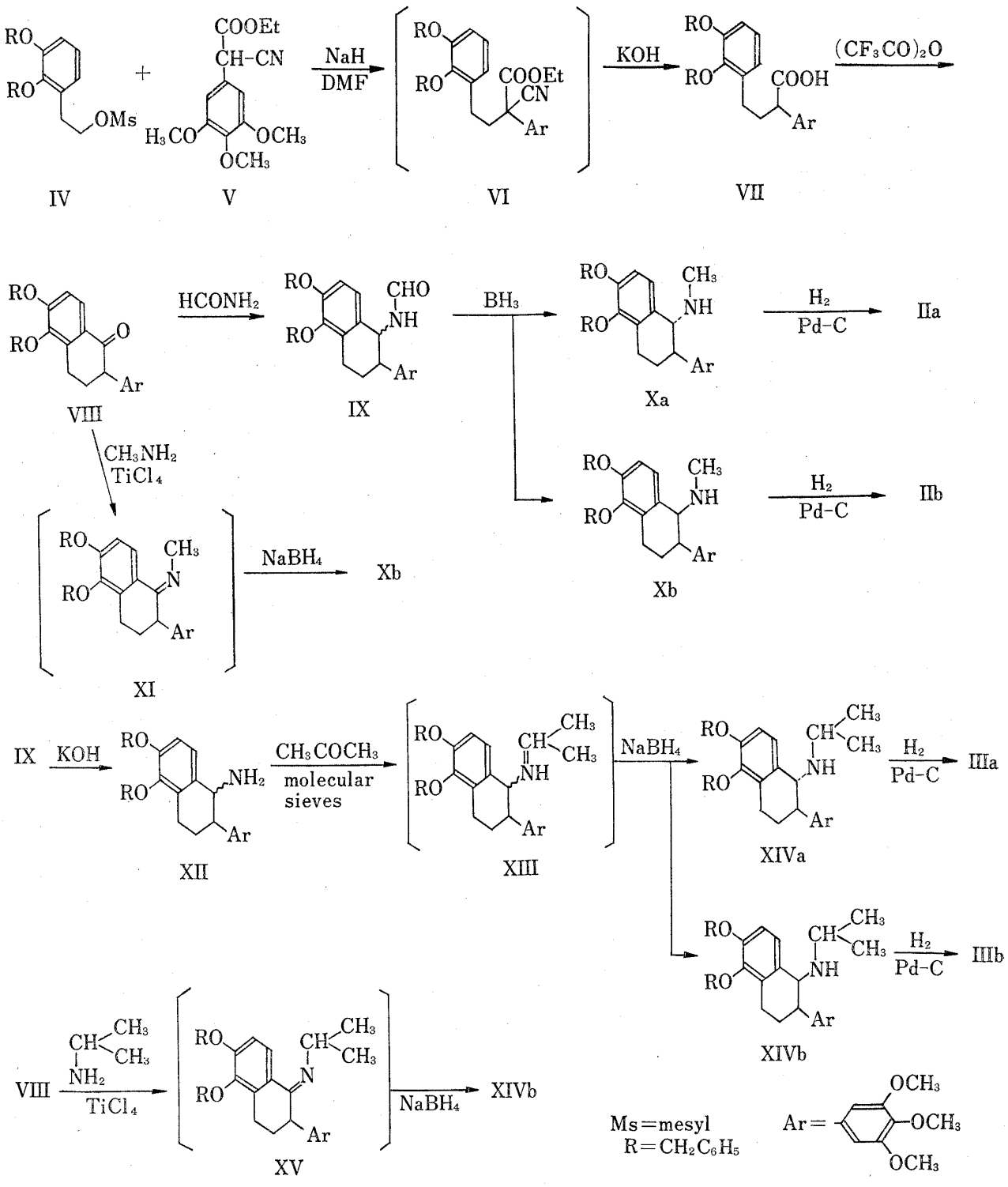

Chart 1

was obtained also from VIII in 86.2% yield by a procedure similar to that described for the *cis* N-methyl relative (Xb) (isopropylamine-$NaBH_4$). Hydrogenolysis of Xa, b and XIVa, b using 10% palladium on charcoal gave the desired compounds IIa·HCl (mp 173—176°, 94% yield), IIb·HCl (mp 172—174°, 62.7% yield), IIIa·HCl (mp 140—143°, 75% yield), and IIIb·HCl (mp 114—119°, 50.7% yield), respectively.

The bronchodilating and positive chronotropic actions were shown in Fig. 2 and 3. As shown in Fig. 2, the order of tracheal relaxing activity observed was *trans*-N-methyl (IIa)> *cis*-N-methyl (IIb)>*trans*-N-isopropyl (IIIa)>*cis*-N-isopropyl (IIIb). Regardless of configu-

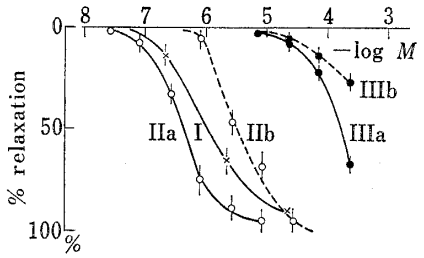

Fig. 2. Dose-response Curves for the Tracheal Relaxing Action

Chemical structures are shown in Fig. 1. Each point represents the mean of more than 6 experiments ± S.E.M. I: R=CH_3

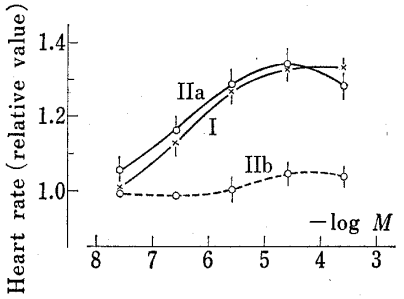

Fig. 3. Dose-response Curves for the Positive Chronotropic Action

The ordinate represents the relative frequency to the initial heart rate prior to the start of the cumulative drug addition. Each point represents the mean of more than 6 experiments ± S.E.M. I: R=CH_3

ration, N-methyl derivatives were more active than N-isopropyl ones. This relationship between substituents on the N atom and the activity was the same as that observed in the benzylamine series (I).[1)]

With regard to stereoisomers, the *trans* isomers were more active than their *cis* counterparts. The *trans*-N-methyl compound (IIa: $pD_2=6.31\pm0.08$) was the most active tracheal relaxing compound tested, which was approximately ten times as active as the *cis* isomer (IIb: $pD_2=5.33\pm0.06$) and about two times as active as I (R=CH_3), the most active compound in the benzylamine derivatives tested.[1)] These dose-response curves shifted dose-dependently parallel to the right by propranolol.

The positive chronotropic action of IIa was approximately equal to I (R=CH_3), while IIb was almost inactive (Fig. 3).

These results may suggest that the spatial arrangement of the catechol, the trimethoxyphenyl group and the N atom in IIa would be more suitable to interact with the β-adrenoceptor than that in IIb and the benzylamine derivatives.

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