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Studies on the Structure-Activity Relationships of Adrenergic β-Mimetic Benzylamine Derivatives. V.[1] 9-Aryl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinolines

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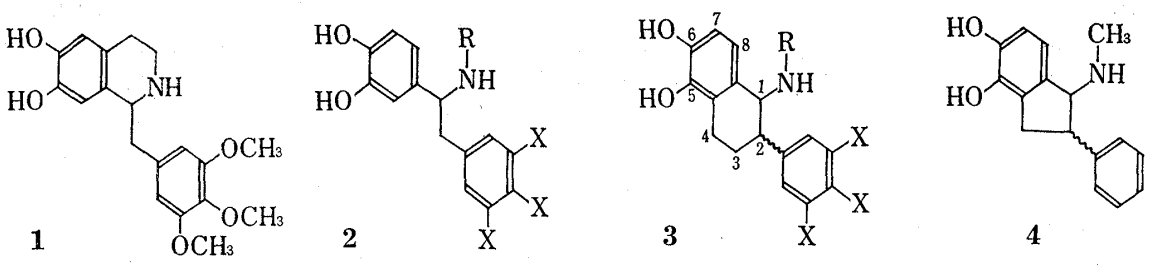
The synthesis and adrenergic β-mimetic activities of stereoisomeric 9-aryl-5,6-dihydroxy-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinolines (**5**), which should be regarded as constrained analogs of the benzylamine (**2**), the tetrahydronaphthalenes (**3**) and trimetoquinol (TMQ, **1**), are presented. Structure–activity relationships of these compounds were explained in terms of various spatial orientations of the functional groups in these molecules suggested by inspection of Dreiding model. The conformations of **3b**-*trans* and **5b**-*trans*, both of which are potent tracheal relaxants, are the type A orientation of the functional groups where the catechol and trimethoxyphenyl groups are approximately anti to each other. **5b**-*cis* which can not hold the type A orientation was only 1/130 as active as **5b**-*trans*. The spatial orientation of the functional groups in TMQ in the crystalline state was found to be the type A. These results may suggest that the conformation of TMQ required for manifesting its β_2-stimulating activity in the biophase is probably similar to that in the crystalline state. Contrary to the previous finding that **2** and **3b**-*trans* were active in both β_2 and β_1 adrenoceptors, **5b**-*trans* was found to possess high selectivity for β_2-adrenoceptors.

Keywords——hexahydrobenzo[*d*,*e*]quinoline deriv.; tetrahydronaphthalene deriv.; benzylamine deriv.; trimetoquinol; tracheal relaxing action; positive chronotropic action; adrenergic β-mimetic agent; structure–activity relationships

The adrenergic β-mimetic activity shown by the simple benzylamine derivative (BZA, **2**)[3] suggested that trimetoquinol (TMQ, **1**)[4] should be regarded as a conformationally constrained analog of **2**. The observation was followed by the finding that the tetrahydronaphthalenes (THN, **3**) and indans (**4**), other "bridged" versions of **2**, also possess β-activity.[1,5]

As a logical extension of these studies on β-stimulating agents structually related to TMQ, we have synthesized a hexahydrobenzo[*d*,*e*]quinoline derivative (BQ, **5**)[6] which might be looked upon as a relative of both THN (**3**) and TMQ (**1**). It was hoped that the reduced flexibility of **5** conferred by introduction of the new two carbon bridge between the nitrogen and catechol ring of THN (**3**) would increase activity and/or selectivity of β-mimetic actions. In addition, this reduced flexibility of **5**, hopefully, would provide a further insight into the steric aspects of the orientations of the catechol, nitrogen, and trimethoxyphenyl groups, which are three functional groups essential for eliciting β-mimetic activity.[3] Described herein are the synthesis of **5** and the structure-β-activity relationships of its stereoisomers as well as those of THN (**3**) examined in terms of the steric aspects of their functional groups.

1) Part IV: S. Yamamura, K. Oda, T. Mizoguchi, S. Saito, Y. Iwasawa, M. Ohashi, and A. Kiyomoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 3613 (1978).
2) Location: *2-2-50, Kawagishi, Toda, Saitama.*
3) Y. Iwasawa, M. Ohashi, S. Yamamura, S. Saito, and A. Kiyomoto, *Japan. J. Pharmacol.*, **26**, 133 (1976).
4) Y. Iwasawa and A. Kiyomoto, *Japan. J. Pharmacol.*, **17**, 143 (1967).
5) S. Yamamura, S. Saito, Y. Iwasawa, M. Ohashi, and A. Kiyomoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 3222 (1976).
6) A preliminary account of the synthesis and pharmacology of **5** has been presented. See ref. 7).
7) S. Yamamura, K. Oda, S. Saito, M. Yamazaki, Y. Iwasawa, A. Kiyomoto, and K. Abe, *Heterocycles*, **8**, 211 (1977).

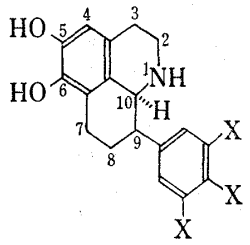


1 TMQ

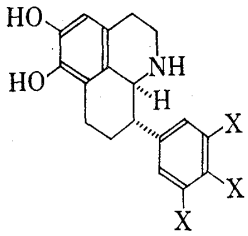
2b: R=CH_3, X=OCH_3

3b-*cis* : R=CH_3,X=OCH_3
3b-*trans* : R=CH_3,X=OCH_3

4



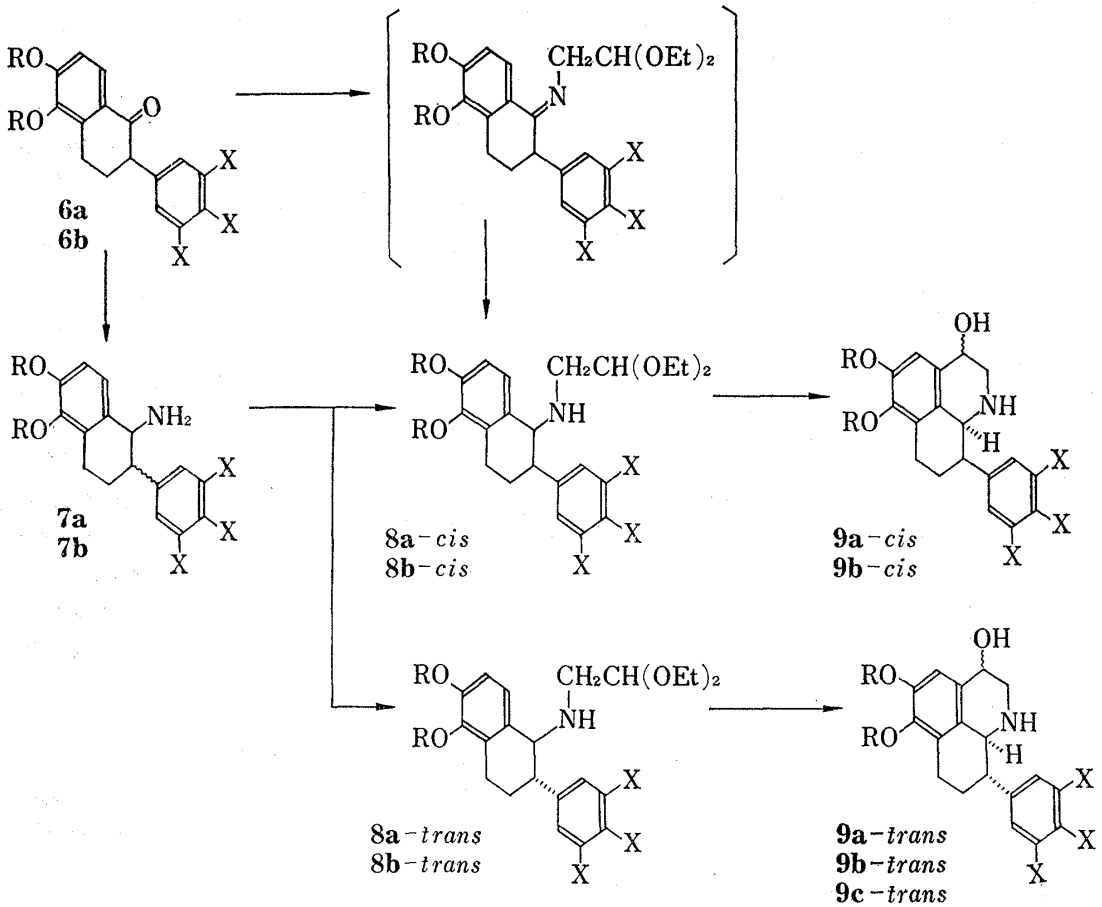
5a-*cis*
5b-*cis*



5a-*trans*
5b-*trans*

a: X=H
b: X=OCH_3
cis, *trans*: C_9–H and C_{10}–H in BQ
C_1–H and C_2–H in THN

Fig. 1



6a
6b

7a
7b

8a-*cis*
8b-*cis*

9a-*cis*
9b-*cis*

8a-*trans*
8b-*trans*

9a-*trans*
9b-*trans*
9c-*trans*

a: X=H, R=CH_3
b: X=OCH_3, R=CH_2Ph
c: X=H (epimer of **a**-*trans* at C_3), R=CH_3

Chart 1

Chemistry

Leuckart reactions of the tetralone derivatives (**6a** and **6b**)[1,5] with ammonium formate and formamide followed by hydrolysis with KOH gave diastereoisomeric mixtures of the amines (**7a**; 82% and **7b**; 79% yields), respectively (Chart 1). Since the separation of these mixture was difficult,[8] **7b** was allowed to react with bromoacetaldehyde diethyl acetal in the presence of K_2CO_3. The resulting mixture of the acetals was chromatographed over silica gel to give the *cis* isomer (**8b**-*cis*, 39%) and *trans* isomer (**8b**-*trans*, 40% yield). Similarly, the *cis* acetal (**8a**-*cis*, 34%) and *trans* isomer (**8a**-*trans*, 38% yield) resulted from **7a**.

Stereochemical assignments for these isomers were made from the coupling constants of their C_1 protons (**8b**-*cis*: $J_{1,2}$=4 Hz at δ 3.76, **8b**-*trans*: $J_{1,2}$=9 Hz at δ 4.05, and **8a**-*trans*: $J_{1,2}$=8 Hz at δ 4.09).[9] More conveniently, the *cis* acetals (**8a**-*cis* and **8b**-*cis*) resulted stereoselectively[1,5,10] from **6a** and **6b** by treatment with aminoacetaldehyde diethyl acetal followed by $NaBH_4$ reduction in 69% and 82% yields, respectively.

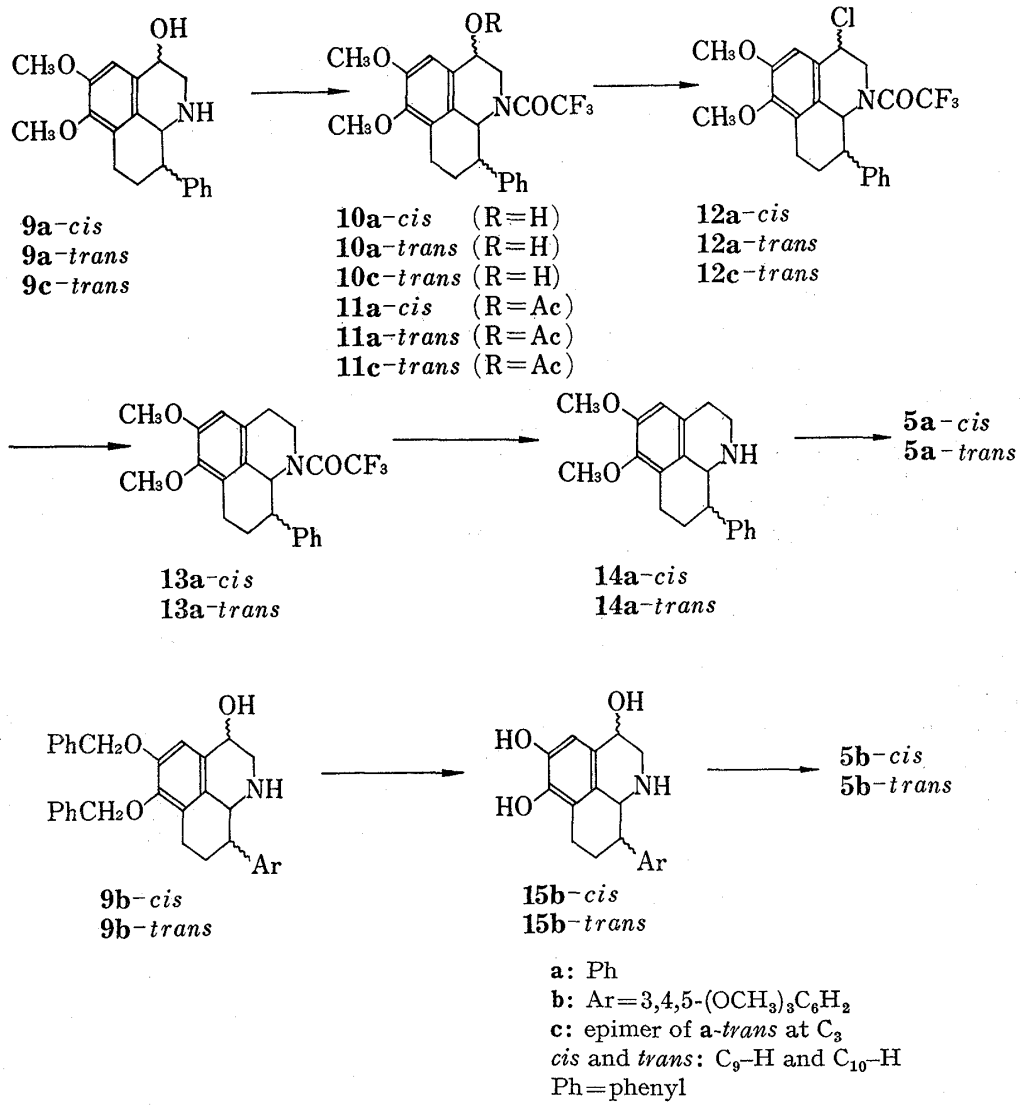


Chart 2

8) In case of **7b**, the diastereoisomers could be separated by repeated fractional recrystallization from MeOH. See Experimental Section.
9) The C_1-proton of **8a**-*cis* was not assignable due to its overlapping with other protons.
10) R. Sarges, *J. Org. Chem.*, **40**, 1216 (1975).

Cyclization of the acetals (**8a**-*cis*, **8b**-*cis*, and **8b**-*trans*) was effected by treatment with HCl in aq THF[11] to give the benzo[*d*,*e*]quinolines (**9a**-*cis*, 93%; **9b**-*cis*, 65%; and **9b**-*trans*, 71% yields), respectively. Similar treatment of **8a**-*trans* gave the two cyclized products (**9a**-*trans* and **9c**-*trans*), epimers of the C_3–OH, which were separated by column chromatography in 46% and 27% yields. The C_3 isomeric nature of **9a**-*trans* and **9c**-*trans* later became apparent by their conversion into the identical chloride (**12a**-*trans* and **12c**-*trans*) (*vide infra*). Table I gives the nuclear magnetic resonance (NMR) data of these isomers (**9a** and **9b**) and their derivatives (**10**, **11**, and **12**). The large coupling constants of the C_{10} protons ($J_{9,10}$= 11—12 Hz) were invariably observed for the *trans*[12] isomers compared with 6—8 Hz for those of their *cis*[12] counterparts. The stereochemistries of the C_3 substituents were tentatively assigned for quasi-axial or quasi-equatorial from the δ and J values of their C_4 and C_3 protons, respectively.[13]

Table I. Chemical Shifts and Coupling Constants[a]

Compd.	C_{10}–H	C_3–H	C_4–H
9a-*cis* (ax)[b]	4.10(d, J=6)	4.44(d,d, J=2, 2)	6.78
9a-*trans* (ax)	3.72(d, J=11)	4.46(d,d, J=2, 2)	6.86
9c-*trans* (eq)	3.7—3.9	4.80(d,d, J=8, 8)	6.98
9b-*cis* (ax)	4.16(d, J=6)	4.48(d,d, J=2, 2)	6.92
9b-*trans* (ax)	3.68(d, J=12)	4.50(d,d, J=2, 2)	7.00
10a-*cis* (eq)	5.13(d, J=6)	4.4—4.7(m)	7.01
10a-*trans* (eq)	5.36(d, J=11)	4.6—4.9(m)	7.04
10c-*trans* (ax)	5.41(d, J=11)	4.5—4.7(m)	6.80
11a-*cis* (eq)	5.16(d, J=7)	5.64(d,d, J=5, 11)	6.67
11a-*trans* (eq)	5.33(d, J=12)	5.84(d,d, J=5, 10)	6.68
11c-*trans* (ax)	5.56(d, J=12)	5.82(d,d, J=2, 2)	6.80
12a-*cis* (ax)	5.34(d, J=8)	4.81(d,d, J=2, 2)	6.69
12a-*trans* (ax)	5.56(d, J=11)	5.05(d,d, J=2, 2)	6.72
12c-*trans* (eq)	5.37(d, J=12)	5.03(d,d, J=5, 11)	7.05

a) These data (δ: ppm, J: Hz) were obtained with JEOL PS-100 instrument in $CDCl_3$ (6% (w/v), 26°).
b) Conformational assignment of C_3-substituents.

An unexpected difficulty arose when direct conversion of the carbinols (**9a**-*cis*, **9a**-*trans*, and **9c**-*trans*) into **14a**-*cis* and **14a**-*trans* was attempted (Chart 2). They resisted any attempt to effect reductive removal of their C_3–OH; hydrogenation using 10% Pd–C, colloidal Pd, or PtO_2 under a variety of conditions all gave unchanged starting material. Conversion of these carbinols to **14a**-*cis* and **14a**-*trans* *via* their chlorides was, therefore, examined next. Treatment of **9a**-*cis*, **9a**-*trans*, and **9c**-*trans* with trifluoroacetic anhydride in pyridine afforded their respective amides (**10a**-*cis*, **10a**-*trans*, and **10c**-*trans*) in 80%, 93%, and quantitative yields, respectively. Chlorination of **10a**-*cis* and **10a**-*trans* with thionyl chloride and pyridine in ether gave the corresponding chlorides (**12a**-*cis* and **12a**-*trans*) in quantitative yields. On the other hand, similar treatment of **10c**-*trans*, the C_3 epimer of **10a**-*trans*, afforded the two isomeric chlorides (**12a**-*trans* and **12c**-*trans*) in 44% and 28% yields, respectively. **12a**-*trans* proved identical with the sample obtained from **10a**-*trans*. Hydrogenolysis of the chlorides (**12a**-*cis* and **12a**-*trans*) with 10% Pd–C in isopropanol proceeded smoothly to give **13a**-*cis* (65%) and **13a**-*trans* (88% yield), which in turn were hydrolysed with KOH in aq EtOH to

11) *a*) J.M. Bobbitt and J.C. Sin, *J. Org. Chem.*, **33**, 856 (1968); *b*) J.M. Bobbitt, A.S. Steinfeld, K.H. Weisgraber, and S. Dutta, *J. Org. Chem.*, **34**, 2478 (1969).
12) *cis* and *trans* designation in these 9-aryl-benzo[*d*,*e*]quinolines represents that the protons of the C_9 and C_{10} are *cis* and *trans*, respectively.
13) *a*) E. Schreier, *Helv. Chim. Acta*, **46**, 75 (1963); *b*) *Idem*, *ibid.*, **47**, 1529 (1964).

give quantitative yields of **14a**-*cis* and **14a**-*trans*, respectively. Demethylation of the HBr salts of **14a**-*cis* and **14a**-*trans* with boron tribromide in CH_2Cl_2 gave the desired catechols (**5a**-*cis* and **5a**-*trans*) in 84% and 90% yields, respectively.

Hydrogenolysis of the carbinols (**9b**-*cis* and **9b**-*trans*) with 10% Pd–C in aq EtOH gave the debenzylated products (**15b**-*cis* and **15b**-*trans*) in 88% and 82% yields without affecting their C_3–OH groups. In contrast with the methoxy derivatives described above, hydrogenolysis of these catechols (**15b**-*cis* and **15b**-*trans*) using PtO_2 in EtOH containing HCl[14] proceeded without difficulty to give the desired compounds (**5b**-*cis* and **5b**-*trans*) in 58% and 61% yields, respectively.

Pharmacology and Discussion

In Table II are given the tracheal relaxing activity (β_2-stimulating activity) of the benzo[*d*,*e*]quinoline derivatives (**5**) determined in the isolated tracheal chain preparation of guinea pigs by the method described previously.[3] Comparative data for BZA (**2b**) and THN (**3b**) are also included.

Table II. Tracheal Relaxing Activity

Compd. tested	$pD_2 \pm$ S.E.M.[a]	% relaxation at 3×10^{-4} M
5a-*trans*	3.92±0.14	
5b-*trans*	6.03±0.10	
5a-*cis*	<3.5	21±3
5b-*cis*	4.14±0.18	
15b-*trans*	<3.5	40±3
15b-*cis*	<3.5	27±4
BZA (**2b**)	5.98±0.05	
THN (**3b**-*trans*)	6.31±0.08	
THN (**3b**-*cis*)	5.33±0.16	
TMQ (**1**)	8.81±0.12	

a) Each value represents the mean of more than 6 experiments±S.E.M. pD_2 values defined as $-\log ED_{50}$.

The order of the tracheal relaxing activity observed in this series of compounds was **5b**-*trans*>**5b**-*cis*>**5a**-*trans*>**15b**-*trans*>**15b**-*cis*>**5a**-*cis*. The dose response curves of these compounds shifted dose-dependently parallel to the right by propranolol.

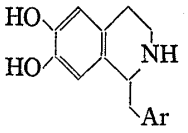
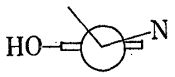
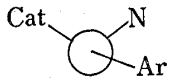
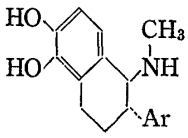
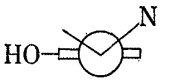
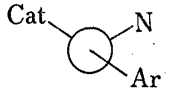
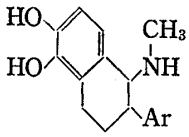
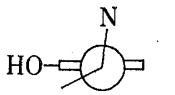
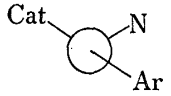
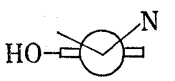
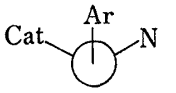
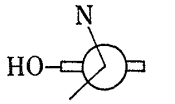
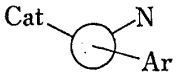
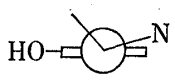
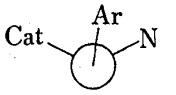
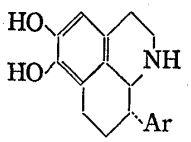
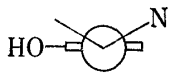
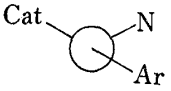
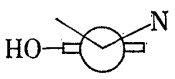
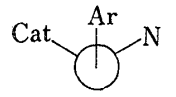
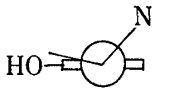
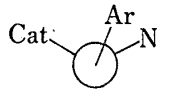
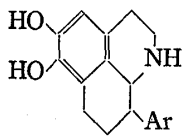
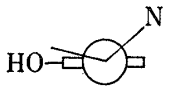
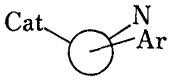
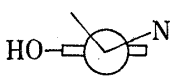
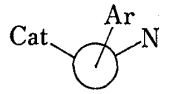
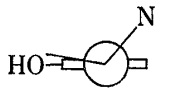
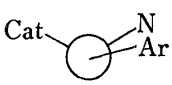
Like the previous case of BZA (**2**)[3] and THN (**3**),[1] replacement of a phenyl by a trimethoxyphenyl group conferred a remarkable increase in the activity. Introduction of a hydroxy group at C_3 in this series (**15b**-*cis* and **15b**-*trans*) adversely affected the tracheal relaxing activity.

Comparison of the pairs of stereoisomers (**5a**, **5b**, and **15b**) showed that the *trans* isomers (**5a**-*trans*, **5b**-*trans*, and **15b**-*trans*) are much more active than their *cis* counterparts. This tendency is apparently in parallel to our previous observations with THN (**3**).[1,5] However, comparison of the pairs of stereoisomers of THN (**3**) and BQ (**5**) in a more quantitative manner revealed that the potency ratio of the stereoisomers differs markedly in these two series of compounds. Thus, in the THN series, **3b**-*cis* was found to be about one-tenth as active as **3b**-*trans*. While, in the BQ series, **5b**-*cis* was only 1/130 as active as **5b**-*trans*. Since the activity of **5b**-*trans* is approximately equal to that of **3b**-*trans*, note should be taken of the much reduced activity occasioned by **5b**-*cis*.

The structure–activity relationships of these compounds were explained in terms of the various spatial orientations of the nitrogen, catechol, and trimethoxyphenyl groups adopted by these molecules. Table III shows the Newman projections of the stereoisomers of THN

14) I. Noguchi and D.B. Maclean, *Can. J. Chem.*, 53, 125 (1975).

TABLE III. Newman Projections viewed along C_α–C_γ and C_β–C_α Bonds

Compd.	Isomerism	Structure	Conformation[a]		C_α–C_γ	C_β–C_α[b]	
TMQ (1)							type A
THN (3)	*trans*		3-*trans*	C_α–N eq C_β–Ar ax B: chair			type A
	cis		3-*cis*-1	C_α–N ax C_β–Ar eq B: chair			type A
			3-*cis*-2	C_α–N eq C_β–Ar ax B: chair			type B
			3-*cis*-3	C_α–N ax C_β–Ar eq B: boat			type A
			3-*cis*-4	C_α–N eq C_β–Ar ax B: boat			type B
BQ (5)	*trans*		5-*trans*	C_α–N eq C_β–Ar eq B: chair C: chair			type A
			5-*cis*-1	C_α–N eq C_β–Ar ax B: chair C: boat			type B
			5-*cis*-2	C_α–N eq C_β–Ar ax B: chair C: boat			type B
	cis		5-*cis*-3	C_α–N ax C_β–Ar eq B: chair C: boat			type C
			5-*cis*-4	C_α–N eq C_β–Ar ax B: boat C: chair			type B
			5-*cis*-5	C_α–N eq C_β–Ar ax B: boat C: boat			type C

a) A=catechol ring, B=hydroaromatic ring, C=piperidine ring.
b) Cat=catechol ring, Ar=C_6H_5 or $C_6H_2(OCH_3)_3$.

(3) and BQ (5) suggested by inspection of Dreiding model.[15] The projection of the C_α–C_γ[16] bond and C_β–C_α[16] bond of the compounds are given in the first and second columns of Table III, respectively. The latter represents the spatial orientation of the three functional groups.

Since 3-*cis* and 5-*cis* are rather flexible molecules, they should be able to assume such various conformations as shown in Table III (3-*cis*-1—3-*cis*-4 and 5-*cis*-1—5-*cis*-5). By comparing these two sets of conformers, it becomes evident that the type A orientation of the functional groups, in which the catechol and trimethoxyphenyl groups are approximately anti to each other, cannot be adopted by 5-*cis*. On the other hand, two of possible conformers of 3-*cis*, *i.e.*, 3-*cis*-1 and 3-*cis*-3, bearing a quasi-axial C_α–N bond can hold this orientation.

Hence, the type A orientation can be, at least in part, adopted by 3-*cis*. The much reduced activity of 5b-*cis* when compared with 3b-*cis* thus appears to be caused by the fact that 5b-*cis* can not hold the type A orientation of the functional groups.

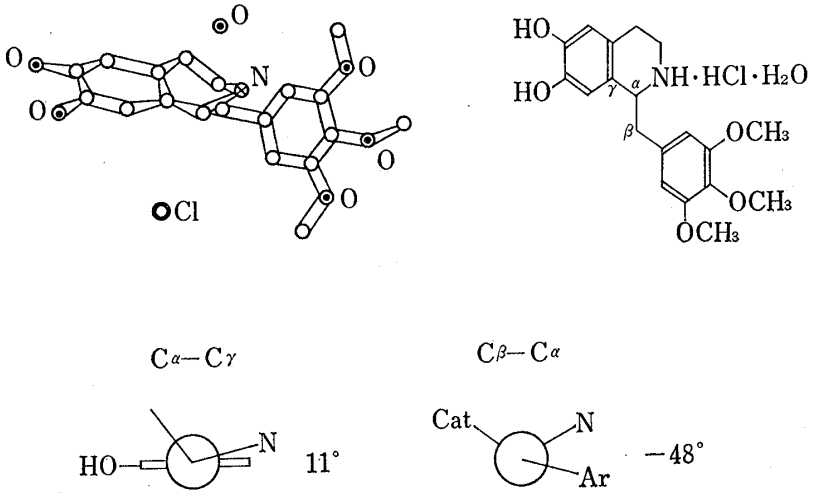


Fig. 2. Perspective drawing of TMQ from the X-Ray Study and Newman Projections viewed along C_α–C_γ and C_β–C_α Bonds

The importance of this orientation of the functional groups in conferring β_2-stimulating activity becomes more evident, when one examines the conformations of 3b-*trans* and 5b-*trans*, both of which are potent tracheal relaxants. It is reasonably expected that the most stable conformation of the hydroaromatic rings of 3b-*trans* and 5b-*trans* is half-chair form, in which the C_α–N bond and trimethoxyphenyl group are diequatorial. Thus both 3b- and 5b-*trans* isomers hold almost entirely type A orientations of the functional groups.

The conformation of the hydrochloride of TMQ determined from the X-ray study[17] is given in Fig. 2. From this figure and the

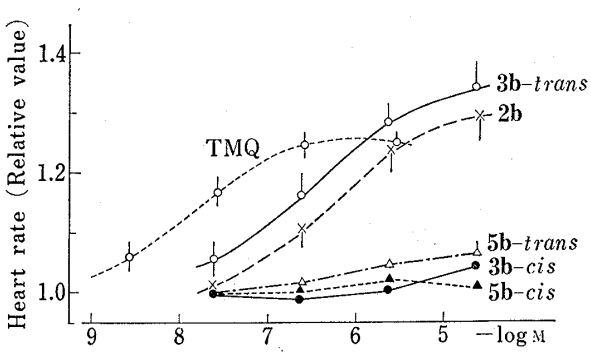


Fig. 3. Dose-response Curves for the Positive Chronotropic Action

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.

15) Although 3 and 5 are tested as the racemates, the projections represents one of the two enantiomers for convenience.
16) The C_α represents the tertiary carbon bearing nitrogen atom. The C_β designates the carbon bearing a trimethoxyphenyl group and the C_γ represents the aromatic carbon attached to C_α. See Table III.
17) Details of this study will be appeared elsewhere by T. Date, *et al.*

projections given in Table III, it is evident that the spatial orientation of the three functional groups in TMQ in the crystalline state is type A and quite similar to those of **3b**-*trans* and **5b**-*trans*. These results may suggest that the conformation of TMQ required for manifesting its β_2-stimulating activity in biophase is probably similar to that in the crystalline state. In summary, the results so far available suggest that the *anti* orientation of the catechol and trimethoxyphenyl groups is at least one of important factors in conferring β_2-stimulating activity.

Figure 3 shows the positive chronotropic activity (β_1-stimulating action) of the BQ derivatives (**5**) in guinea pigs in comparison with those of BZA (**2**) and THN (**3**). Interestingly, neither **5b**-*trans* nor **5b**-*cis* exhibits appreciable β_1-activity up to 3×10^{-5} mole concentration. Contrary to the previous finding that **2b** and **3b**-*trans* are active in both β_2 and β_1 adrenoceptors, **5b**-*trans* was thus found to possess high β_2-selectivity.

Experimental

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrophotometer. NMR spectra were determined on a JEOL PS-100 instrument in $CDCl_3$ (containing tetramethylsilane at δ 0.00 as an internal standard), unless otherwise specified. Coupling constants (J) are given in Hz and the following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were measured on a Hitachi RMS-4 mass spectrometer. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out *in vacuo*.

1-Amino-5,6-dibenzyloxy-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (7b)——A mixture of **6b** (12 g) and ammonium formate (4 g) in formamide (120 ml) was stirred at 170—175° for 6 hr. The mixture was poured onto ice-water, extracted with $CHCl_3$, washed with H_2O, and evaporated to give a residue. A mixture of this residue, KOH (24 g), H_2O (50 ml) and ethylene glycol (150 ml) was refluxed for 22 hr. The mixture was poured onto ice-water and extracted with $CHCl_3$. Evaporation of the dried extracts gave, after recrystallization from EtOH, 9.5 g, (79%) of **7b** as a mixture of two stereoisomers, mp 139—141°. *Anal.* Calcd. for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.43; H, 6.86; N, 2.66.

Fractional recrystallization of **7b**: A mixture of two stereoisomers (**7b**, 500 mg) was recrystallized from MeOH (32 ml). Filtration gave 260 mg of colorless plates (*cis* isomer enriched base). Recrystallization from MeOH (20 ml) was repeated six times to give 30 mg of **7b**-*cis* as colorless plates, mp 156—157°. NMR: 1.18 (2H, s, NH_2, disappeared on addition of D_2O), 3.87 (9H, s, $3\times OCH_3$), 4.11 (1H, d, J=4, $-\dot{C}H-N$), 5.06, 5.15 (4H, each s, $2\times CH_2Ph$), 6.48 (2H, s, Ar–H), 6.88 (1H, d, J=9, Ar–H), 7.02 (1H, d, J=9, Ar–H), 7.2—7.5 (10H, m, $2\times C_6H_5$). *Anal.* Calcd. for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.43; H, 6.82; N, 2.60. The mother liquor (*trans* isomer enriched base) of the first recrystallization from MeOH was evaporated, recrystallized six times from MeOH (6 ml) to give 30 mg of **7b**-*trans* as colorless needles, mp 130—131°. NMR: 1.47 (2H, s, NH_2), 3.88 (9H, s, $3\times OCH_3$), 4.05 (1H, d, J=9, $-\dot{C}H-N$), 5.05, 5.17 (4H, each s, $2\times CH_2Ph$), 6.48 (2H, s, Ar–H), 6.95 (1H, d, J=9, Ar–H), 7.2—7.5 (11H, m, Ar–H). *Anal.* Calcd. for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.36; H, 6.87; N, 2.44.

1-Amino-5,6-dimethoxy-2-phenyl-1,2,3,4-tetrahydronaphthalene (7a)——A mixture of **6a** (15.6 g), ammonium formate (8.7 g) and formamide (400 ml) was stirred at 180° for 18 hr. The mixture was poured onto ice-water, extracted with $CHCl_3$, washed with H_2O, and evaporated to give a residue. A mixture of this residue, KOH (11 g), ethylene glycol (600 ml), and H_2O (70 ml) was refluxed for 17 hr. The mixture was diluted with H_2O and extracted with ether. The ether solution was extracted with 10% HCl. The acidic aqueous layer was basified with 10% NaOH and extracted with $CHCl_3$. Evapotioran of the dried extracts gave 13 g (82%) of **7a** as a mixture of two stereoisomers. Granules from isopropyl ether, mp 108—110°. Mass Spectrum m/e: 283 (M^+). *Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.02; H, 7.48; N, 4.85.

***cis* and *trans*-5,6-Dibenzyloxy-1-(2,2-diethoxyethyl)amino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (8b-*cis* and 8b-*trans*)**——A mixture of **7b** (2.3 g), K_2CO_3 (6.1 g), bromoacetaldehyde diethylacetal (1.3 g), and DMSO (50 ml) was stirred at 70° for 38 hr. The mixture was poured onto ice-water and extracted with AcOEt. Evaporation of the dried extracts gave a mixture of two stereoisomers (**8b**-*cis* and **8b**-*trans*) as an oil which was chromatographed over silica gel (90 g) and eluted with C_6H_6–AcOEt (6: 1). The first part of the eluate gave 1.1 g (39%) of **8b**-*cis* as colorless needles, mp 94—95° (from isopropyl ether). Mass Spectrum m/e: 641 (M^+). NMR: 1.04, 1.11 (6H, each t, J=8, $2\times OCH_2\underline{C}H_3$), 3.76 (1H, d, J=4, $-\dot{C}H-N$), 3.85 (9H, s, $3\times OCH_3$), 4.41 (1H, t, J=6, $-CH(OEt)_2$), 5.06, 5.15 (4H, each s, $2\times OCH_2Ph$), 6.53 (2H, s, Ar–H), 6.85, 6.99 (2H, each d, J=8, Ar–H), 7.2—7.6 (10H, m, $2\times C_6H_5$). *Anal.* Calcd. for $C_{39}H_{47}NO_7$: C, 72.98; H, 7.38; N, 2.18. Found: C, 72.81; H, 7.33; N, 2.08. The following elution gave 1.13 g (40%) of **8b**-*trans* as colorless needles, mp 114—115° (from isopropyl ether). Mass Spectrum m/e: 641 (M^+). NMR: 1.10,

1.16 (6H, each t, J=8, 2×$OCH_2C\underline{H}_3$), 3.84 (6H, s, 2×OCH_3), 3.86 (3H, s, OCH_3), 4.05 (1H, d, J=9, -C$\underline{H}$-N), 4.49 (1H, t, J=6, -CH$(OEt)_2$), 5.03, 5.16 (4H, each s, 2×OCH_2Ph), 6.43 (2H, s, Ar-H), 6.91 (1H, d, J=8, Ar-H), 7.2—7.6 (11H, m, Ar-H). *Anal.* Calcd. for $C_{39}H_{47}NO_7$: C, 72.98; H, 7.38; N, 2.18. Found: C, 72.92; H, 7.24; N, 2.19.

***cis* and *trans*-1-(2,2-Diethoxyethyl)amino-5,6-dimethoxy-2-phenyl-1,2,3,4-tetrahydronaphthalene (8a-*cis* and 8a-*trans*)**——A mixture of **7a** (16.6 g), bromoacetaldehyde diethylacetal (12.7 g), triethylamine (8.9 g), and DMF (200 ml) was stirred at 70° for 48 hr. The mixture was concentrated, taked in AcOEt, and washed with H_2O. Evaporation of the dried AcOEt gave an oil which was chromatographed over silica gel (500 g) and eluted with $CHCl_3$–AcOEt (30: 1). The first part of the elution gave 8.0 g (34%) of **8a**-*cis* as an oil, $bp_{0.2}$ 150—200°. Mass Spectrum *m/e*: 399 (M^+). NMR: 0.97, 1.08 (6H, each t, J=7, 2×$OCH_2C\underline{H}_3$), 3.85, 3.87 (6H, each s, 2×OCH_3), 4.38 (1H, t, J=7, -C$\underline{H}$$(OEt)_2$), 6.79, 7.04 (2H, each d, J=8, Ar-$\underline{H}$), 7.34 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.58; H, 8.19; N, 3.50.

The second part of the eluate gave 8.8 g (38%) of **8a**-*trans* as needles, mp 71—73° (from *n*-hexane). Mass Spectrum *m/e*: 399 (M^+). NMR: 1.08, 1.13 (6H, each t, J=7, 2×$OCH_2C\underline{H}_3$), 3.81, 3.87 (6H, each s, 2×OCH_3), 4.09 (1H, d, J=8, -C$\underline{H}$-N), 4.44 (1H, t, J=6, -C$\underline{H}$$(OEt)_2$), 6.85 (1H, d, J=9, Ar-H), 7.30 (5H, s, C_6H_5), 7.2—7.5 (1H, m, Ar-H). *Anal.* Calcd. for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.48; H, 8.24; N, 3.60.

From the third part of the eluate, 1.6 g (10%) of the starting material (**7a**) was recovered.

***cis*-5,6-Dibenzyloxy-1-(2,2-diethoxyethyl)amino-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene (8b-*cis*)**——A mixture of the tetralone (**6b**) (3 g) and aminoacetaldehyde diethylacetal (15 ml) was refluxed for 64 hr. Evaporation of the mixture left crude imine as an oil which was taken in MeOH (40 ml) and treated with $NaBH_4$ (1.1 g) for 3 hr. After decomposition of excess $NaBH_4$ by the addition of H_2O, the mixture was concentrated, and extracted with C_6H_6. Evaporation of the dried extracts left an oily residue which was chromatographed over silica gel. Elution with $CHCl_3$–MeOH (10: 1) gave, after crystallization from isopropyl ether, 3.0 g (82%) of **8b**-*cis* as colorless needless, mp 94—95°. This compound was identified with the sample (from the first part of the eluate on chromatography) previously obtained from the amine (**7b**) (IR, mixed mp, and TLC).

***cis*-1-(2,2-Diethoxyethyl)amino-5,6-dimethoxy-2-phenyl-1,2,3,4-tetrahydronaphthalene (8a-*cis*)**——A mixture of the tetralone (**6a**) (4.4 g) and aminoacetaldehyde diethylacetal (22 ml) was refluxed for 20 hr. Evaporation of the mixture left crude imine as an oil which was taken in MeOH (20 ml) and treated with $NaBH_4$ (0.6 g) for 1 hr. The mixture was worked up in the same manner as that described above to give 4.3 g (69%) of **8a**-*cis* as an oil. This compound was identified with the sample (from the first part of the eluate on chromatography) previously obtained from the amine (**7a**) (IR and TLC).

[9*β*,10*α*H]-5,6-Dibenzyloxy-3-hydroxy-9-(3,4,5-trimethoxyphenyl)-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (9b-*cis*) Hydrochloride——To a solution of **8b**-*cis* (1.3 g) in THF (5 ml) was added 8 N HCl (10 ml) and the mixture was stirred at room temperature for 4 hr. The mixture was poured onto ice-water, basified with 10% NaOH, and extracted with $CHCl_3$. Evaporation of the dried extracts gave an oil which was chromatographed over silica gel (50 g). Elution with $CHCl_3$–MeOH (30: 1) gave, after conversion to the hydrochloride, 0.8 g of **9b**-*cis*·HCl as colorless prisms, mp 195—197° (from AcOEt). Mass Spectrum *m/e* 567 (M^+). NMR (free base in $CDCl_3$): 3.60 (6H, s, 2×OCH_3), 3.79 (3H, s, OCH_3), 4.16 (1H, d, J=6, -C$\underline{H}$-N), 4.48 (1H, d.d, J=2 and 2, -C$\underline{H}$-OH), 5.02, 5.18 (4H, each s, 2×CH_2Ph), 6.18 (2H, s, Ar-H), 6.92 (1H, s, Ar-H), 7.2—7.6 (10H, m). *Anal.* Calcd. for $C_{35}H_{37}NO_6$·HCl: C, 69.58; H, 6.34; N, 2.32; Cl, 5.87. Found: C, 69.41; H, 6.52; N, 2.46; Cl, 5.83.

[9*α*,10*α*H]-5,6-Dibenzyloxy-3-hydroxy-9-(3,4,5-trimethoxyphenyl)-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (9b-*trans*) Hydrochloride——To a solution of **8b**-*trans* (1.0 g) in THF (10 ml) was added 8 N HCl (18 ml) and the mixture was stirred at room temperature for 14 hr. The mixture was poured onto ice-water. The precipitate was collected and recrystallized from MeOH–ether to give 0.69 g (71%) of **9b**-*trans*·HCl as colorless needles, mp 240—242.5 (dec.). Mass Spectrum *m/e* 567 (M^+). NMR (free base in $CDCl_3$): 3.68 (1H, d, J=12, -C$\underline{H}$-N), 3.90 (9H, s, 3×OCH_3), 4.50 (1H, d.d, J=2 and 2, -C$\underline{H}$-OH), 5.06, 5.18 (4H, each s, 2×CH_2Ph), 6.53 (2H, s, Ar-H), 7.00 (1H, s, Ar-H), 7.2—7.6 (10H, m, 2×C_6H_5). *Anal.* Calcd. for $C_{35}H_{37}NO_6$·HCl·H_2O: C, 67.56; H, 6.48; N, 2.25; Cl, 5.70. Found: C, 67.80; H, 6.29; N, 2.24; Cl, 5.95.

[9*β*,10*α*H]-3-Hydroxy-5,6-dimethoxy-9-phenyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (9a-*cis*)——A mixture of **8a**-*cis* (4.3 g) and 8 N HCl (35 ml) was stirred at room temperature for 19 hr. The precipitate was collected by filtration to give 3.6 g (93%) of **9a**-*cis*·HCl. Needles from EtOH, mp 216—218° (dec.). *Anal.* Calcd. for $C_{20}H_{23}NO_3$·HCl·H_2O: C, 63.23; H, 6.90; N, 3.69; Cl, 9.33. Found: C, 63.38; H, 7.05; N, 3.60; Cl, 9.11. The HCl salt was converted to the free base with 10% NaOH. Prisms from isopropyl alcohol, mp 202—204°. Mass Spectrum *m/e*: 325 (M^+). NMR: 3.80, 3.90 (6H, each s, 2×OCH_3), 4.10 (1H, d, J=6, -C$\underline{H}$-N), 4.44 (1H, d.d, J=2 and 2, -C$\underline{H}$-OH), 6.78 (1H, s, Ar-H), 6.9—7.3 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.67; H, 7.40; N, 4.23.

[9*α*,10*α*H]-3-Hydroxy-5,6-dimethoxy-9-phenyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (9a-*trans* and 9c-*trans*: Epimers of the C_3-OH)——A mixture of **8a**-*trans* (8.8 g), 8 N HCl (70 ml), and THF (15 ml) was stirred at room temperature for 14 hr. The mixture was basified with 10% NaOH, concentrated, and extracted with $CHCl_3$. Evaporation of the dried extracts gave a residue which was chromatographed over

silica gel (350 g) and eluted with $CHCl_3$–MeOH (100: 1). The first part of the elution gave 3.3 g (46%) of **9a**-*trans*. Prisms from isopropyl alcohol, mp 149.0—150.5°. Mass Spectrum *m/e*: 325 (M^+) NMR: 3.72 (1H, d, $J=11$, –CH–N), 3.83, 3.88 (6H, each s, $2\times OCH_3$), 4.46 (1H, d.d, $J=2$ and 2, –CH–OH) 6.86 (1H, s, Ar–H), 7.29 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.82; H, 7.20; N, 4.30. The second part of the elution gave 1.9 g (27%) of **9c**-*trans*, epimer of **9a**-*trans* at the C_3–OH. Needles from isopropyl alcohol, mp 171.0—172.5°. Mass Spectrum *m/e*: 325 (M^+). NMR: 3.82, 3.86 (6H, each s, $2\times OCH_3$), 3.7—3.9 (1H, m, –CH–N), 4.80 (1H, d.d, $J=8$ and 8, –CH–OH), 6.98 (1H, s, Ar–H), 7.30 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.82; H, 7.20; N, 4.30.

[9*β*,10*α*H]-3-Hydroxy-5,6-dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (10a-*cis*)——To a mixture of **9a**-*cis*·HCl (3.6 g) and pyridine (20 ml) was added trifluoroacetic anhydride (2.8 ml) under ice-cooling. The mixture was stirred at room temperature for 4 hr and extracted with $CHCl_3$. The extracts were washed with aq. $NaHCO_3$, 10% HCl and H_2O, successively. Evaporation of the dried extracts gave a residue which was chromatographed over silica gel (200 g) and eluted with $CHCl_3$. Evaporation of the eluate gave 3.6 g (80%) of **10a**-*cis*. Leaflets from isopropyl ether, mp 163—164°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 421 (M^+). NMR: 3.88, 3.92 (6H, each s, $2\times OCH_3$), 4.4—4.7 (1H, m, –CH–OH), 5.13 (1H, d, $J=6$, –CH–N), 6.6—6.8 (2H, m, Ar–H), 7.01 (1H, s, Ar–H), 7.1—7.2 (3H, m, Ar–H). *Anal.* Calcd. for $C_{22}H_{22}F_3NO_4$: C, 62.70; H, 5.26; N, 3.32. Found: C, 62.65; H, 5.43; N, 3.32. Acetate (**11a**-*cis*) was prepared from **10a**-*cis* with Ac_2O-pyridine in the usual manner. Neeldes from isopropyl alcohol, mp 193—194°. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1690 (CO). Mass Spectrum *m/e*: 463 (M^+). *Anal.* Calcd. for $C_{24}H_{24}F_3NO_5$: C, 62.19; H, 5.22; N, 3.02. Found: C, 62.15; H, 5.27; N, 3.08.

[9*α*,10*α*H]-3-Hydroxy-5,6-dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (10a-*trans*)——To a solution of **9a**-*trans* (2.0 g) in pyridine (10 ml) was added trifluoroacetic anhydride (2.2 ml) under ice-cooling. The mixture was worked up in the same manner as that described above to give 2.4 g (93%) of **10a**-*trans*. Needles from isopropyl ether, mp 167.0—168.5°. IR ν_{max}^{Nujol} cm^{-1}: 1710 (CO). Mass Spectrum *m/e*: 421 (M^+). NMR: 3.84, 3.90 (6H, each s, $2\times OCH_3$), 4.6—4.9 (1H, m, –CH–OH), 5.36 (1H, d, $J=11$, –CH–N), 7.04 (1H, s, Ar–H), 7.25 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{22}F_3NO_4$: C, 62.70; H, 5.26; N, 3.32. Found: C, 62.79; H, 5.32; N, 3.28.

Acetate (**11a**-*trans*) was prepared from **10a**-*trans* with Ac_2O-pyridine in the usual manner. Needles from isopropyl ether, mp 127—128°. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1690 (CO). Mass Spectrum *m/e*: 463 (M^+). *Anal.* Calcd. for $C_{24}H_{24}F_3NO_5$: C, 62.19; H, 5.22; N, 3.02. Found: C, 62.07; H, 5.38; N, 3.11.

[9*α*,10*α*H]-3-Hydroxy-5,6-dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (10c-*trans*, Epimer of 10a-*trans* at the C_3-OH)——To a solution of **9c**-*trans* (0.1 g) in pyridine (1 ml) was added trifluoroacetic anhydride (0.1 ml) under ice-cooling. The mixture was worked up in the same manner as that described above to give 0.13 g (quant.) of **10c**-*trans*. Needles from isopropyl alcohol, mp 178—179°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 421 (M^+). NMR: 3.87, 3.92 (6H, each s, $2\times OCH_3$), 4.5—4.7 (1H, m, –CH–OH), 5.41 (1H, d, $J=11$, –CH–N), 6.80 (1H, s, Ar–H), 7.20 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{22}F_3NO_4$: C, 62.70; H, 5.26; N, 3.32. Found: C, 62.74; H, 5.39; N, 3.39.

Acetate (**11c**-*trans*) was prepared from **10c**-*trans* with Ac_2O pyridine in the usual manner. Needles from isopropyl ether, mp 152—153°. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1690 (CO). Mass Spectrum *m/e*: 463 (M^+). *Anal.* Calcd. for $C_{24}H_{24}F_3NO_5$: C, 62.19; H, 5.22; N, 3.02. Found: C, 62.29; H, 5.34; N, 3.06.

[9*β*,10*α*H]-3-Chloro-5,6-dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (12a-*cis*)——To a mixture of **10a**-*cis* (2.6 g), pyridine (0.2 ml) and ether (30 ml) was added $SOCl_2$ (0.9 ml) under ice-cooling. The mixture was stirred at room temperature for 2 hr and then extracted with AcOEt. The extracts were washed with saturated $NaHCO_3$, 10% HCl, and H_2O, successively. Evaporation of the dried extracts gave 2.7 g (quant.) of **12a**-*cis*. Needles from *n*-hexane, mp 142—143°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 439 (M^+). NMR; 3.90, 3.93 (6H, each s, $2\times OCH_3$), 4.81 (1H, d.d, $J=2$ and 2, –CH–OH), 5.34 (1H, d, $J=8$, –CH–N), 6.69 (1H, s, Ar–H), 6.6—6.7 (2H, m, Ar–H), 7.0—7.3 (3H, m, Ar–H). *Anal.* Calcd. for $C_{22}H_{21}ClF_3NO_3$: C, 60.07; H, 4.81; N, 3.19; Cl, 8.06. Found: C, 59.90; H, 4.84; N, 3.18; Cl, 7.82.

[9*α*,10*α*H]-3-Chloro-5,6-dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (12a-*trans*)——To a mixture of **10a**-*trans* (2.6 g), pyridine (0.2 ml) and THF (50 ml) was added $SOCl_2$ (0.9 ml) under ice-cooling. The mixture was worked up in the same manner as that described above to give 2.7 g (99%) of **12a**-*trans*. Needles from isopropyl ether, mp 185.0—186.5 (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 439 (M^+). NMR: 3.84, 3.88 (6H, each s, $2\times OCH_3$), 5.05 (1H, d.d, $J=2$ and 2, –CH–OH), 5.56 (1H, d, $J=11$, –CH–N), 6.72 (1H, s, Ar–H), 7.23 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{21}ClF_3NO_3$: C, 60.07; H, 4.81; N, 3.19; Cl, 8.06. Found: C, 60.11; H, 4.83; N, 3.25; Cl, 8.54.

Chlorination of 10c-*trans* with Thionyl Chloride: [9*α*,10*α*H]-3-Chloro-5,6-dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (12a-*trans* and 12c-*trans*, Epimers of the C_3-Cl)——To a mixture of **10c**-*trans* (0.2 g), pyridine (0.1 ml) and THF (3 ml) was added $SOCl_2$ (0.2 ml) under ice-cooling and the mixture was stirred at room temperature for 45 min. The mixture was evaporated and extracted with AcOEt. The extracts were washed with 10% HCl, saturated $NaHCO_3$ and H_2O, successively. Evaporation of the dried extracts gave, after fractional recrystallization from isopropyl ether, 78 mg (44%) of **12a**-*trans* as needles, mp 185.0—186.5 (dec.). This compound was identified with the sample previously

obtained from **10a**-*trans* (IR, mixed mp, and TLC). The powder part on recrystallization from isopropyl ether gave 49 mg (28%) of **12c**-*trans* (the upper fraction on TLC compared with **12a**-*trans*) as granules, mp 168—170° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 439 (M^+). NMR: 3.86, 3.92 (6H, each s, $2\times OCH_3$), 5.03 (1H, d.d, $J=5$ and 11, –CH–Cl), 5.37 (1H, d, $J=12$, –CH–N), 7.05 (1H, s, Ar–H), 7.26 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{21}ClF_3NO_3$: C, 60.07; H, 4.81; N, 3.19; Cl, 8.06. Found: C, 59.72; H, 4.82; N, 3.13; Cl, 7.98.

[9*β*,10*α*H]-5,6-Dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (13a-*cis*)——A solution of **12a**-*cis* (2.7 g) in isopropyl alcohol (100 ml) was subjected to catalytic reduction over 10% Pd–C (1.4 g) under ordinary temperature and pressure. After removal of the catalyst by filtration, the filtrate was evaporated, taken in AcOEt, and washed with saturated $NaHCO_3$ and H_2O. Evaporation of the dried AcOEt gave a residue which was chromatographed over silica gel (100 g) and eluted with $CHCl_3$. Evaporation of the eluate gave 1.6 g (65%) of **13a**-*cis*. Pillars from *n*-hexane, mp 95—96°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 405 (M^+). NMR: 3.88, 3.91 (6H, each s, $2\times OCH_3$), 5.22 (1H, d, $J=7$, –CH–N), 6.54 (1H, s, Ar–H), 6.7—6.9 (2H, m, Ar–H), 7.0—7.3 (3H, m, Ar–H). *Anal.* Calcd. for $C_{22}H_{22}F_3NO_3$: C, 65.17; H, 5.47; N, 3.46. Found: C, 64.96; H, 5.44; N, 3.48.

[9*α*,10*α*H]-5,6-Dimethoxy-9-phenyl-1-trifluoroacetyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (13a-*trans*)——A solution of **12a**-*trans* (2.7 g) in isopropyl alcohol (100 ml) and THF (30 ml) was subjected to catalytic reduction over 10% Pd–C (1.4 g) under ordinary temperature and pressure. The mixture was worked up in the same manner described above to give 2.2 g (88%) of **13a**-*trans*. Needles from isopropyl ether, mp 142.0—134.5°. IR ν_{max}^{Nujol} cm^{-1}: 1690 (CO). Mass Spectrum *m/e*: 405 (M^+). NMR: 3.86, 3.90 (6H, each s, $2\times OCH_3$), 5.47 (1H, d, $J=11$, –CH–N), 6.60 (1H, s, Ar–H), 7.29 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{22}H_{22}F_3NO_3$: C, 65.17; H, 5.47; N, 3.46. Found: C, 65.21; H, 5.42; N, 3.37.

[9*β*,10*α*H]-5,6-Dimethoxy-9-phenyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (14a-*cis*)——A mixture of **13a**-*cis* (1.5 g), KOH (0.9 g), H_2O (4 ml) and EtOH (40 ml) was refluxed for 3 hr. The mixture was evaporated, taken in $CHCl_3$, and washed with H_2O. Evaporation of the dried $CHCl_3$ gave, after recrystallization from isopropyl ether, 1.1 g (quant.) of **14a**-*cis* as needles, mp 108—109°. Mass Spectrum *m/e*: 309 (M^+). NMR: 3.84, 3.93 (6H, each s, $2\times OCH_3$), 4.23 (1H, d, $J=6$, –CH–N), 6.61 (1H, s, Ar–H), 7.0—7.1 (2H, m, Ar–H), 7.1—7.3 (3H, m, Ar–H). *Anal.* Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.57; H, 7.51; N, 4.55.

[9*α*,10*α*-H]-5,6-Dimethoxy-9-phenyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (14a-*trans*)——A mixture of **13a**-*trans* (2.0 g), KOH (1.3 g), H_2O (5 ml) and EtOH (50 ml) was refluxed for 2 hr. The mixture was worked up in the same manner as that described above to give 1.5 g (quant.) of **14a**-*trans*. Pillars from isopropyl alcohol, mp 149.0—150.5°. Mass Spectrum *m/e*: 309 (M^+). NMR: 3.84, 3.88 (6H, each s, $2\times OCH_3$), 3.8—3.9 (1H, m, –CH–N), 6.57 (1H, s, Ar–H), 7.33 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.67; H, 7.55; N, 4.54.

[9*β*,10*α*H]-5,6-Dihydroxy-9-phenyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (5a-*cis*) Hydrobromide——To a mixture of **14a**-*cis*·HBr [prepared from its free base (1.0 g)] and CH_2Cl_2 (40 ml) was added BBr_3 (1.6 ml) at −70° under N_2 and the mixture was stirred at room temperature for 1 hr. The mixture was decomposed by addition of MeOH and evaporated. Recrystallization from EtOH gave 0.9 g (84%) of **5a**-*cis*·HBr as needles, mp 261—262° (dec.). Mass Spectrum *m/e*: 281 (M^+). NMR (**5a**-*cis*·HBr in d_6-DMSO): 6.64 (1H, s, Ar–H), 6.9—7.5 (5H, m, C_6H_5), 7.6—8.5 and 9.2—9.9 (4H, each m, $2\times OH$ and NH_2, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{18}H_{19}NO_2\cdot HBr$: C, 59.67; H, 5.56; N, 3.87; Br, 22.06. Found: C, 59.53; H, 5.70; N, 3.91; Br, 21.98.

[9*α*,10*α*H]-5,6-Dihydroxy-9-phenyl-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]-quinoline (5a-*trans*) Hydrobromide——To a mixture of **14a**-*trans*·HBr [prepared from its free base (1.4 g)] and CH_2Cl_2 (40 ml) was added BBr_3 (2.1 ml) at −70° under N_2. The mixture was worked up in the same manner as that described above to give 1.4 g (90%) of **5a**-*trans*·HBr. Needles from EtOH, mp 282—283° (dec.). Mass Spectrum *m/e*: 281 (M^+). NMR (**5a**-*trans*·HBr in d_6-DMSO): 4.53 (1H, d, $J=11$, –CH–N), 6.62 (1H, s, Ar–H), 7.45 (5H, s, C_6H_5), 7.7—8.6 and 9.0—9.7 (4H, each m, $2\times OH$ and NH_2, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{18}H_{19}NO_2\cdot HBr$: C, 59.67; H, 5.56; N, 3.87; Br, 22.06. Found: C, 59.88; H, 5.66; N, 3.88; Br, 21.83.

[9*β*,10*α*H]-3,5,6-Trihydroxy-9-(3,4,5-trimethoxyphenyl)-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (15b-*cis*) Hydrochloride——A solution of **9b**-*cis*·HCl (0.3 g) in EtOH (40 ml) was hydrogenated over 10% Pd–C (0.3 g) at room temperature. The catalyst was filtered off and the filtrate was evaporated. Recrystallization from MeOH–ether gave 170 mg (88%) of **15b**-*cis*·HCl as colorless prisms, mp 224—227°. NMR (**15b**-*cis*·HCl in d_6-DMSO): 3.60 (6H, s, $2\times OCH_3$), 3.64 (3H, s, OCH_3), 4.5—4.8 (2H, m, –CH–OH and –CH–N), 6.46 (2H, s, Ar–H), 6.84 (1H, s, Ar–H). *Anal.* Calcd. for $C_{21}H_{25}NO_6\cdot HCl$: C, 59.50; H, 6.18; N, 3.30; Cl, 8.36. Found: C, 59.45; H, 6.32; N, 3.42; Cl, 8.22. Peracetylate of **15b**-*cis* [prepared from **15b**-*cis*·HCl with Ac_2O–pyridine in the usual manner]: Colorless prisms from ether, mp 127—130°. IR ν_{max}^{Nujol} cm^{-1}: 1780 (Ar–OCOCH$_3$), 1745 (aliph-OCOCH$_3$), 1650 (NHCO). Mass Spectrum *m/e*: 555 (M^+). NMR: 2.12, 2.18, 2.32, 2.36 (12H, each s, $4\times COCH_3$), 3.60 (6H, s, $2\times OCH_3$), 3.76 (3H, s, OCH_3), 5.2—5.8 (2H, m, –CH–N and –CH–O), 5.95 (2H, s, Ar–H), 7.30 (1H, s, Ar–H). *Anal.* Calcd. for $C_{29}H_{33}NO_{10}\cdot 1/2(C_2H_5)_2O$: C, 62.82; H, 6.46; N, 2.36. Found: C, 62.77; H, 6.47; N, 2.41.

[9α,10αH]-3,5,6-Trihydroxy-9-(3,4,5-trimethoxyphenyl)-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (15b-*trans*) Hydrochloride——A solution of **9b**-*trans*·HCl (260 mg) in EtOH (130 ml) and H_2O (13 ml) was hydrogenated over 10% Pd–C (200 mg) at room temperature. The catalyst was filtered off and the filtrate was evaporated. Recrystallization from MeOH–ether gave 150 mg (82%) of **15b**-*trans*·HCl as colorless prisms, mp 241—244° (dec.). NMR (**15b**-*trans*·HCl in d_6-DMSO): 3.72 (3H, s, OCH_3), 3.84 (6H, each s, $2\times OCH_3$), 4.39 (1H, d, $J=10$, –CH–N), 4.66 (1H, m, –CH–OH), 5.8 (1H, m, –CH–OH, disappeared on addition of D_2O), 6.78 (2H, s, Ar–H), 6.83 (1H, s, Ar–H), 7.9, 8.6 (2H, each broad s, $2\times OH$, disappeared on addition of D_2O), 9.5 (2H, broad s, NH_2, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{21}H_{25}NO_6\cdot HCl$: C, 59.50; H, 6.18; N, 3.30; Cl, 8.36. Found: C, 59.19; H, 6.30; N, 3.05; Cl, 8.11.

[9β,10αH]-5,6-Dihydroxy-9-(3,4,5-trimethoxyphenyl)-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (5b-*cis*) Hydrochloride——A mixture of **15b**-*cis*·HCl (0.83 g), PtO_2 (0.2 g), EtOH (350 ml) and 25% HCl–EtOH (110 ml) was hydrogenated under ordinary temperature and pressure. The catalyst was filtered off and washed with MeOH. The combined filtrate was evaporated. Recrystallization from MeOH gave 0.46 g (58%) of **5b**-*trans*·HCl as colorless needles, mp 243—245° (dec.). NMR (**5b**-*cis*·HCl in d_6-DMSO): 3.60 (6H, s, $2\times OCH_3$), 3.64 (3H, s, OCH_3), 4.58 (1H, broad s, –CH–N, appeared as doublet ($J=6$) on addition of D_2O), 6.40 (2H, s, Ar–H), 6.58 (1H, s, Ar–H), 7.5—10.2 (4H, m, $2\times OH$ and NH_2, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{21}H_{25}NO_5\cdot HCl$: C, 61.83; H, 6.43; N, 3.43; Cl, 8.69. Found: C, 61.75; H, 6.54; N, 3.37; Cl, 8.36. Peracetylate of **5b**-*cis* [prepared from **5b**-*cis*·HCl with Ac_2O–pyridine in the usual manner]: Colorless needles from $CHCl_3$–ether, mp 190—192°. IR ν_{max}^{Nujol} cm^{-1}: 1770 (Ar–$OCOCH_3$), 1640 (NHCO). Mass Spectrum *m/e*: 497 (M^+). *Anal.* Calcd. for $C_{27}H_{31}NO_8$: C, 65.18; H, 6.28; N, 2.82. Found: C, 65.01; H, 6.39; N, 2.88.

[9α,10αH]-5,6-Dihydroxy-9-(3,4,5-trimethoxyphenyl)-1H-2,3,7,8,9,10-hexahydrobenzo[*d*,*e*]quinoline (5b-*trans*) Hydrochloride——A mixture of **15b**-*trans*·HCl (180 mg), PtO_2 (60 mg), EtOH (100 ml), 25% HCl–EtOH (50 ml) was hydrogenated under ordinary temperature and pressure. The catalyst was filtered off and the filtrate was evaporated. Recrystallization from MeOH–ether gave 105 mg (61%) of **5b**-*trans*·HCl as colorless prisms, mp 261—264 (dec.). NMR (**5b**-*trans*·HCl in d_6-DMSO): 3.70 (3H, s, OCH_3), 3.82 (6H, s, $2\times OCH_3$), 4.47 (1H, d, $J=12$, –CH–N), 6.57 (1H, s, Ar–H) 6.76 (2H, s, Ar–H), 7.9, 8.4 (2H, each broad s, $2\times OH$, disappeared on addition of D_2O). *Anal.* Calcd. for $C_{21}H_{25}NO_5\cdot HCl\cdot 1/4H_2O$: C, 61.16; H, 6.48; N, 3.40; Cl, 8.60. Found: C, 61.01; H, 6.49; N, 3.17; Cl, 8.38.

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