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

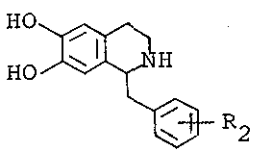
Shiro Yamamura*, Kuniyuki Oda, Seiichi Saito, Michio Yamazaki, Yoshio Iwasawa, Akio Kiyomoto, and Kyuji Abe

Biological and Chemical Research Laboratory,

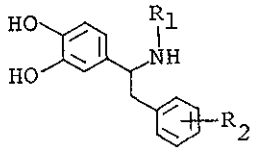
Tanabe Seiyaku Co., Ltd., Toda, Saitama, 335, Japan

The synthesis and adrenergic activity of stereoisomeric 5,6-dihydroxy-9-aryl-1H-2,3,7,8,9,10-hexahydrobenzo[d,e]quinolines (4a, 4b, 4'a, and 4'b), rigid structures related to the compounds (1, 2, and 3), are presented.

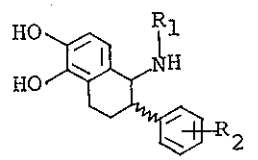
In our previous papers, it was reported that appropriately substituted tetrahydroisoquinoline (THI : 1)[2] and benzylamine (BZA : 2)[3] derivatives possessed adrenergic β-mimetic activity. Furthermore, tetrahydronaphthalenes (THN : 3)[1], a conformationally restricted molecule relative to the BZA (2), proved to have similar activity. In structures (2 and 3), it was shown that introduction of bulky substituents at the nitrogen adversely affected their mimetic activity[1),3)]. Therefore, it



1

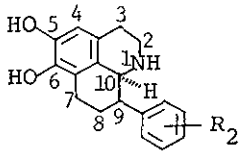


2

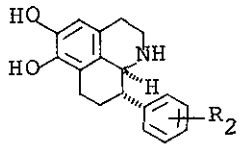


3

R_1=H, CH_3, C_2H_5, $CH(CH_3)_2$
R_2=H, 3,4,5-tri-OCH_3



4a
4'a



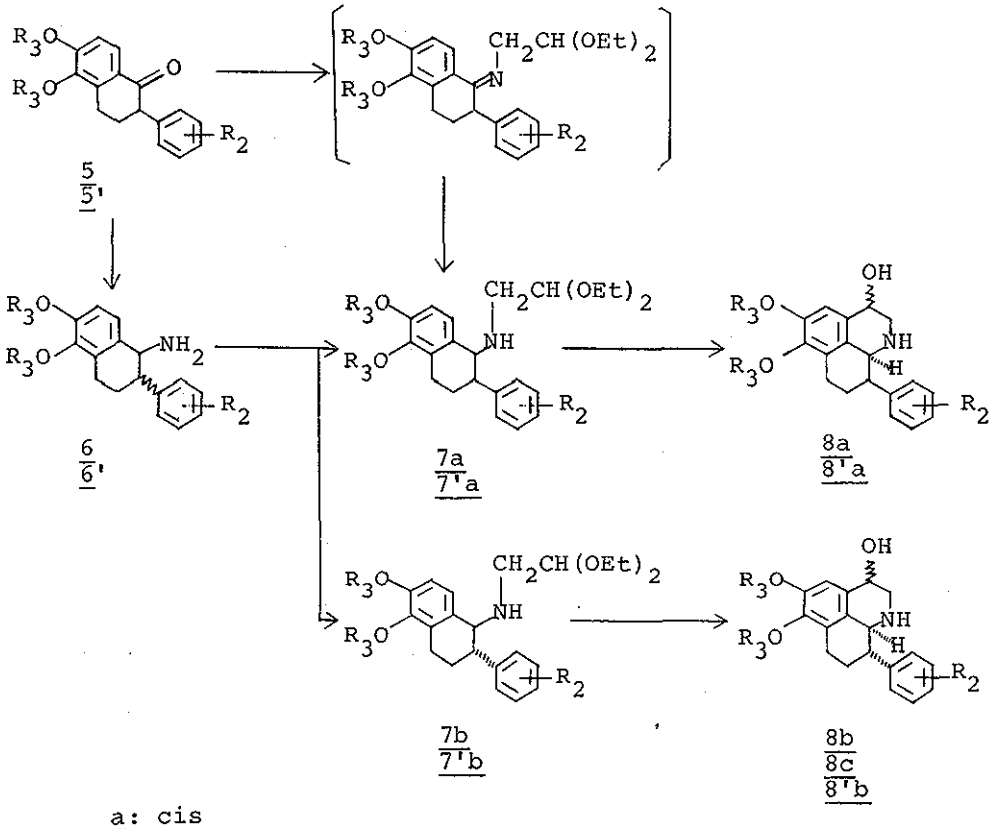
4b
4'b

a: cis (C_9-H and C_{10}-H)
b: trans (C_9-H and C_{10}-H)
': R_2=3,4,5-tri-OCH_3
without ': R_2=H

became of interest for us to synthesize hexahydrobenzo[d,e]-quinoline system (4 and 4')[4], which may be regarded as a relative of both THN (3) and THI (1). The introduction of the new two carbon bridge between the nitrogen and benzene ring of THN (3) in place of its N-substituent confers rigidity on the molecule and it was hoped that the reduced flexibility and differences in peripheral shape around the nitrogen would increase activity and specificity of the β-action.

Leuckart reaction of the tetralone derivatives (5 and 5')[1] with ammonium formate and formamide followed by hydrolysis with KOH in ethylene glycol and H_2O at 140° for 22 hr gave diastereoisomeric mixtures of the amines[5] (6: 82% and 6': 79% yields), respectively (Chart I). Since the separation of these mixtures was difficult[6], 6' was allowed to react with

bromoacetaldehyde diethyl acetal in the presence of K_2CO_3 in DMSO. The resulting mixture of the acetals was chromatographed over silica gel to give the cis isomer (7'a : mp 94-95°, 39%) and the trans isomer (7'b : mp 114-115°, 40% yield). Similarly, the cis acetal (7a : bp 150-200°/0.2 mmHg, 34%) and the trans isomer (7b : mp 71-73°, 38% yield) resulted from 6. Stereochemical assignments for these isomers were made from the coupling constants of their C_1 protons[1] (7'a : $J_{1,2}$=4 Hz at δ 3.76,



5 / 5'

6 / 6'

7a / 7'a

8a / 8'a

7b / 7'b

8b / 8c / 8'b

a: cis
b: trans
c: trans (epimer of b at C_3)
': R_2=3,4,5-tri-OCH_3, R_3=$PhCH_2$
without ': R_2=H, R_3=CH_3

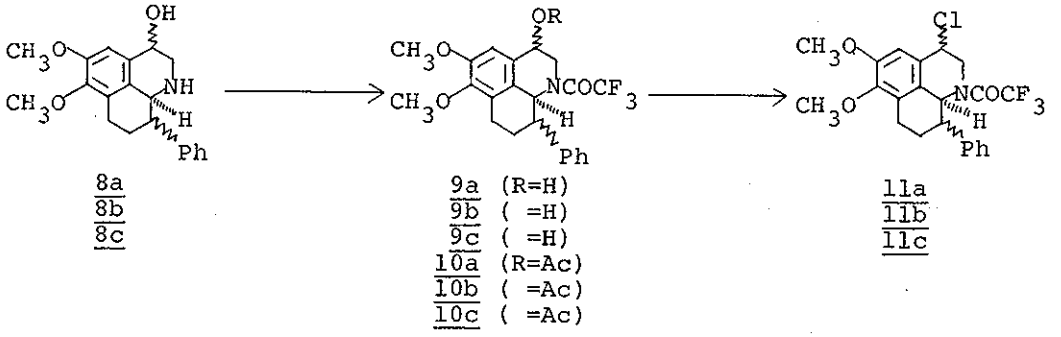
Chart I

7'b : $J_{1,2}$=9 Hz at δ4.05, and 7b : $J_{1,2}$=8 Hz at δ4.09)[7]. Alternatively and more conveniently, the cis acetals (7a and 7'a) resulted stereoselectively[1,8] from 5 and 5' by treatment with aminoacetaldehyde diethyl acetal followed by $NaBH_4$ reduction in 69% and 82% yields, respectively.

Cyclization of the acetals (7a, 7'a, and 7'b) was effected by treatment with HCl in aq THF[9] to give the benzo[d,e]-quinolines, 8a (HCl salt, mp 216-218° (dec), 93%), 8'a (HCl salt, mp 195-197°, 65%), and 8'b (HCl salt, mp 240-242.5°, 71% yield), respectively. Similar treatment of 7b gave the two cyclized products (8b mp 149-150.5° and 8c, mp 171-172.5°), epimers of the C_3-OH, which were separated by column chromatography in 46% and 27% yields. The C_3 isomeric nature of 8b and 8c later became apparent by their transformations (vide infra). Table I gives the NMR data of these isomers (8 and 8') and their derivatives (9, 10, and 11). The large coupling constants of the C_{10} protons ($J_{9,10}$=11-12 Hz) were invariably observed for the trans isomers compared with 6-8 Hz for those of their cis[10] counterparts. Regarding the stereochemistry of the C_3 substituents in these derivatives, conformational assignments (quasi-axial or quasi-equatorial) were tentatively made from the δ and J values of their C_4 and C_3-protons, respectively[11]. However, definitive conclusions including their configurational assignments must await further experimental results[12].

An unexpected difficulty arose when direct conversion of the carbinols (8a, 8b, and 8c) into 13a and 13b was attempted (Chart II). They resisted any attempt to effect the reductive

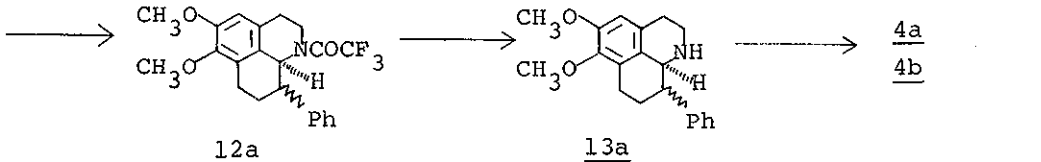
removal of their C_3-OH; hydrogenation using 10% Pd-C, colloidal Pd, or PtO_2 under a variety of conditions all gave unchanged starting material. Conversion of these carbinols to 13a and 13b via their chlorides was, therefore, examined next. Treatment of 8a, 8b, and 8c with trifluoroacetic anhydride in pyridine afforded their respective amides, 9a (mp 163-164°,



8a
8b
8c

9a (R=H)
9b (=H)
9c (=H)
10a (R=Ac)
10b (=Ac)
10c (=Ac)

11a
11b
11c

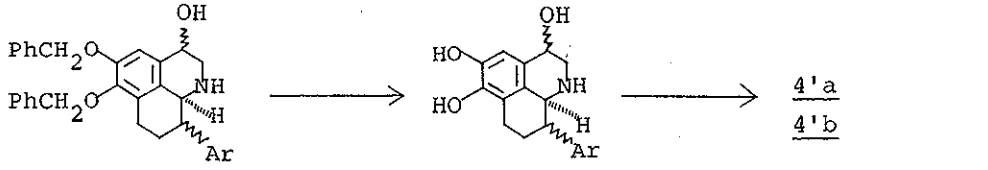


12a
12b

13a
13b

4a
4b

a: cis
b: trans
c: trans (epimer of b at C_3)



8'a
8'b

14'a
14'b

4'a
4'b

a: cis
b: trans
Ar=3,4,5-tri-$OCH_3 \cdot C_6H_2$

Chart II

Table I. Chemical Shifts and Coupling constants[a)]

Compd.	C_{10}-H	C_3-H	C_4-H
8a (cis[b)], ax[c)]	4.10(d, J=6)	4.44(d, d, J=2, 2)	6.78
8b (trans, ax)	3.72(d, J=11)	4.46(d, d, J=2, 2)	6.86
8c (trans, eq)	3.7-3.9	4.80(d, d, J=8, 8)	6.98
8'a (cis, ax)	4.16(d, J=6)	4.48(d, d, J=2, 2)	6.92
8'b (trans, ax)	3.68(d, J=12)	4.50(d, d, J=2, 2)	7.00
9a (cis, eq)	5.13(d, J=6)	4.4-4.7(m)	7.01
9b (trans, eq)	5.36(d, J=11)	4.6-4.9(m)	7.04
9c (trans, ax)	5.41(d, J=11)	4.5-4.7(m)	6.80
10a (cis, eq)	5.16(d, J=7)	5.64(d, d, J=5,11)	6.67
10b (trans, eq)	5.33(d, J=12)	5.84(d, d, J=5,10)	6.68
10c (trans, ax)	5.56(d, J=12)	5.82(d, d, J=2, 2)	6.80
11a (cis, ax)	5.34(d, J=8)	4.81(d, d, J=2, 2)	6.69
11b (trans, ax)	5.56(d, J=11)	5.05(d, d, J=2, 2)	6.72
11c (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°C).
b) Stereoisomers of C_9 and C_{10} protons
c) Conformational assignment of C_3-substituents

80% yield), 9b (mp 167-168.5°, 93% yield), and 9c (mp 178-179°, quantitative yield). Chlorination of 9a and 9b with thionyl chloride and pyridine in Et_2O gave the corresponding chlorides (11a, mp 142-143° and 11b, mp 185-186.5° (dec)) in quantitative yields. On the other hand, similar treatment of 9c, the C_3 epimer of 9b, afforded the two isomeric chlorides,

11b (44% yield) and 11c (mp 168-170° (dec), 28% yield). 11b proved identical with the sample obtained from 9b. Thus, the diastereoisomers (9b and 9c) markedly differed in their substitution reaction, the stereochemical course of which will be discussed in a later paper together with the configurational assignment of their OH groups. Hydrogenolysis of the chlorides (11a and 11b) with 10% Pd-C in isopropanol proceeded smoothly to give 12a (mp 95-96°, 65%) and 12b (mp 142-143.5°, 88% yield), which in turn were hydrolysed with KOH in aq EtOH to give quantitative yields of 13a (mp 108-109°) and 13b (mp 149-150.5°), respectively. Demethylation of the HBr salts of 13a and 13b with boron tribromide in CH_2Cl_2 gave the desired catechols, 4a (HBr salt: mp 261-262° (dec), 84%) and 4b (HBr salt: mp 282-283° (dec), 90% yield).

Hydrogenolysis of the carbinols (8'a and 8'b) with 10% Pd-C in aq EtOH gave the debenzylated products (14'a·HCl salt; mp 224-227° (dec), 88%, and 14'b·HCl salt; mp 241-244° (dec), 82% yield) without affecting their C_3-OH groups. In contrast with the methoxy derivatives described above, however, hydrogenolysis of these catechols (14'a and 14'b) using PtO_2 in EtOH containing HCl[13] proceeded without difficulty to give the desired compounds, 4'a (HCl salt; mp 243-245° (dec), 58%) and 4'b (HCl salt; mp 261-264° (dec), 61% yield).

The compounds prepared were tested for their trachea-relaxing activity by the usual method[2] (Table II). The order of the trachea-relaxing activity in this series was 4'b > 4'a > 4b > 4a > 14'b > 14'a. The trans compounds (4b and 4'b) were much

Table II. Tracheal relaxing activity

Compd.	N[a)]	pD_2[b)]
4b	6	3.92 ± 0.14
4'b	8	6.03 ± 0.10
4a	6	<3.5 (21 ± 3%)[c)]
4'a	8	4.14 ± 0.18
14'b	8	<3.5 (40 ± 3%)[c)]
14'a	8	<3.5 (27 ± 4%)[c)]

a) No. of experiments
b) Negative log molar concentration which produced 50% relaxation.
c) %-Relaxation at about 3×10^{-4}M

more active than their cis counterparts (4a and 4'a) in agreement with our previous results obtained with the THN derivatives (3)[1].

Acknowledgement We wish to thank Drs. T. Mizoguchi and M. Takeda for their support.

References and Notes

1) S. Yamamura, S. Saito, Y. Iwasawa, M. Ohashi, and A. Kiyomoto, Chem. Pharm. Bull., 1976, 24, 3222.
2) Y. Iwasawa and A. Kiyomoto, Japan. J. Pharmacol., 1967, 17, 143.

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

4) The series (') represents the compounds having 3,4,5-trimethoxy as substituents (R_2), and the one without (') represents the parent compounds (R_2=H).

5) Satisfactory analytical, infrared and nuclear magnetic resonance data have been obtained for all compounds in this paper.

6) In case of 6', the diastereoisomers could be separated by repeated fractional recrystallization from MeOH (cis isomer; 156-157°, C_1-proton : $J_{1,2}$=4 Hz at δ 4.11. trans isomer; mp 130-131°, C_1-proton : $J_{1,2}$=9 Hz at δ 4.05).

7) The C_1-proton of cis 7a was not assignable due to its overlapping with other protons.

8) R. Sarges, J. Org. Chem., 1975, 40, 1216.

9) a) J. M. Bobbitt and J. C. Sin, J. Org. Chem., 1968, 33, 856. b) J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgraber, and S. Dutta, J. Org. Chem., 1969, 34, 2478.

10) 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.

11) a) E. Schreier, Helv. Chim. Acta, 1963, 46, 75. b) ibid., 1964, 47, 1529.

12) These experiments including X-ray study will be reported in a later communication.

13) I. Noguchi and D. B. Maclean, Can. J. Chem., 1975, 53, 125.

Received, 20th July, 1977